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WPA Secretariat
Geneva University Psychiatric Hospital, 2 Chemin du Petit Bel-Air, 1226 Thônex, Geneva, Switzerland. Phone: +41223055737; Fax: +41223055735; E-mail: wpasecretariat@wpanet.org.

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Office of the Editor – Department of Psychiatry, University of Campania "L. Vanvitelli", Largo Madonna delle Grazie, 80138 Naples, Italy. Phone: +390815666502; Fax: +390815666523; E-mail: mario.maj@unicampania.it.

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Agency and well-being

The 20th century history of psychiatry and clinical psychology was characterized by initial major successes in understanding and treating mental disorders. This was in recent decades followed by a frustrating plateau, particularly concerning common conditions such as depression and anxiety[1]. I wrote four editions of *Abnormal Psychology* over the last forty years, and I found that both psychotherapy and pharmacotherapy showed little change beyond the plateau of 60% efficacy, often versus a placebo efficacy of around 40%. This just might be the upper limit of what treating mental disorders can aspire to[2].

While massive investment has been directed toward repairing damage within a disease model of human functioning, the preoccupation with pathology neglects the flourishing individual and the thriving community. One crucial insight emerging from psychological science is that mental health is more than the mere absence of mental illness; it is defined by the *presence of positive psychological strengths*. Central among these is *agency*, defined as the psychological state of believing "I can accomplish my goals"[3]. Understanding and enhancing agency is rapidly becoming indispensable for a psychiatry dedicated not just to relieving suffering, but to building optimal well-being.

The conceptual origins of agency in psychological science trace back directly to the study of its absence: *learned helplessness*[4,5]. Early laboratory work demonstrated that the experience of uncontrollable negative events led to a state of passivity, exhibiting eight of the nine symptoms required for a diagnosis of unipolar depression. This line of research, initiated in the 1960s, challenged existing behavioral and Freudian paradigms, both of which denied the importance of conscious mental states. It instead revealed the causal power of the *mindset of agentic beliefs*: the belief that one is helpless produces depression and undermines trying, whereas the belief that one can succeed spurs action[2].

This discovery coincided with the broader cognitive revolution, which solidified agency as a core psychological construct[3]. Agency is now rigorously understood as having three fundamental components that drive action and thereby ignite human progress:

- *Efficacy*, i.e. the belief that *you, yourself, can bring about the goal you desire* in the here and now. This psychological state is a proximal driver of *trying*, particularly of innovative action.
- *Optimism*, i.e. projecting that efficacy into the future, often the far-future, believing that bad events are temporary, local and controllable. This fosters *persistence*. Optimistic future-mindedness is a causal factor in the prevention of depression and in cardiac health[2]. At the societal level, it is a major causal factor in human progress.
- *Imagination*: the range and richness of plausible goals contemplated in the future marks the freedom that an individual experiences, and it fuels *creativity*. Human action is thus conceived as primarily being *drawn into the future*, through prospection (simulating possible futures), rather than being driven by the past[6].

The traditional focus of psychiatry, often motivated by reimbursement guidelines tied to the DSM and ICD, centers on treating discrete disorders. This model views mental health (a euphemism) simply as the absence of mental disorders. However, the psychological analysis of agency requires a shift in focus from remediating negative states (moving from, for example, negative ten to negative five on an illness scale) toward building positive psychological assets (moving from negative two to positive three and beyond on a well-being scale)[6].

This approach recognizes that the absence of mental illness does not remotely guarantee the presence of *well-being*[7]. I conceive of well-being as having five components: Positive Emotion, Engagement, Relationships, Meaning and Mattering, and Accomplishment (PERMA)[2]. The ultimate goal of treatment should not merely be symptom relief but enabling clients to thrive, maximizing their potential to be agents in their own lives and thereby increasing PERMA.

Crucially, the concept of agency has evolved from abstract theory into a rigorously measurable, quantifiable construct, presenting new tools for psychiatric research and clinical practice. Traditional tools such as the Attributional Style Questionnaire (ASQ), developed in 1982, quantified an individual's pessimistic or optimistic explanatory style. This led directly to the Content Analysis of Verbatim Explanations (CAVE) technique, which allowed researchers to infer psychological states from spontaneous verbatim materials. This technique is now critical for historical and big data research in which subjects do not take questionnaires and may even be long dead[2].

The advent of big data and artificial intelligence (AI) has revolutionized agency measurement, providing unprecedented scale and nuance. Researchers now compile vast corpuses of billions of words from books, newspapers and social media to track the frequency of agentic lexicons (words connoting efficacy, optimism and imagination) across history and cultures[3]. The newest computational methods utilize large language models (LLMs), such as ChatGPT-5, not only to generate validated lexicons but also to analyze context, determining whether groups or individuals are being presented as *actors* (taking action) or *objects* (being acted upon). This capacity allows for real-time, population-level assessment of psychological states such as optimism and well-being, complementing or even replacing traditional questionnaires[3].

The relevance of agency is now seen in current clinical applications. Positive psychotherapy (PPT), a manualized form of cognitive-behavioral therapy, explicitly focuses on fostering the three components of agency (efficacy, optimism and imagination), alongside the PERMA model, to achieve durable mental health. Studies have shown PPT to be effective, often performing better than traditional treatment-as-usual for depression[8].

Furthermore, AI promises to act as a profound extension of personal agency, offering new avenues for tailored interventions. AI tools can analyze client's thoughts to rapidly generate accurate life history and personalized coaching plans, assisting therapists in

focusing treatment on enhancing efficacy, persistence, and goal setting[9].

The framework of agency pushes psychiatric thinking beyond the limitations of reducing the symptoms of illness toward a science and practice dedicated to optimizing well-being. By focusing on *prospection*, the capacity to simulate and choose among possible futures, clinicians can address the full spectrum of human experience, shifting from treating patients as passive recipients of past history or biological forces, to empowering them as conscious agents shaping their own destinies[6].

As psychological science has abandoned the historical blind spots that neglected conscious thought, happiness and free will, agency now stands as a central concept enabling a more complete and hopeful approach to human well-being.

Martin E.P. Seligman
Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA

1. Hyman SE. Sci Transl Med 2012;4:155cm11.
2. Seligman M. Flourish. New York: Free Press, 2011.
3. Seligman M. Agency: the psychological history of progress. New York: Simon & Schuster, 2026.
4. Seligman M. Helplessness: on depression, development, and death. San Francisco: Freeman, 1975.
5. Baratta M, Seligman M, Maier S. Front Psychiatry 2023;14:1170417.
6. Seligman M, Railton P, Baumeister R et al. Homo prospectus. New York: Oxford University Press, 2016.
7. Jeste D, Palmer B (eds). Positive psychiatry: a clinical handbook. Washington: American Psychiatric Publishing, 2015.
8. Rashid T, Seligman M. Positive psychotherapy: clinician manual. New York: Oxford University Press, 2018.
9. Blyler A, Seligman M. J Posit Psychol 2023;19:579-91.

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The burnout paradox

In today's volatile work environment, health care professionals face a paradox. They are driven by compassion and purpose, yet they increasingly feel depleted by the very work that once gave meaning to their lives. Hospitals and clinics are becoming pressure cookers of digital alerts, administrative overload, and emotional strain. Artificial intelligence promises efficiency but also accelerates the pace of decision-making. Patients, armed with online information, arrive with heightened expectations. Meanwhile, smartphones nudge doctors to work around the clock, eroding the boundaries between professional and personal life. The result is a culture of perpetual availability – a cognitive and emotional "always-on" state that keeps the mind engaged long after the workday ends.

Working hard is not inherently harmful. Fatigue after a demanding day is natural and, when followed by sufficient recovery, harmless. Short-term fatigue is the body's way of signaling that energy reserves need replenishment. Engaging in restorative activities – spending time with loved ones, exercising, reading, or simply taking a walk – promotes psychological detachment and relaxation, two essential recovery experiences[1]. These experiences replenish lost energetic resources and restore motivation and focus for the next day. However, when recovery is consistently postponed, short-term fatigue accumulates into chronic exhaustion. Over weeks or months, this unrelieved strain can evolve into burnout – a state of physical, emotional and cognitive depletion that no amount of weekend rest can repair[2]. The body remains in a state of heightened arousal, stress hormones stay elevated, and the capacity for empathy and complex decision-making erodes.

Burnout is not simply fatigue. In the ICD-11, the World Health Organization (WHO) defines burnout as a syndrome resulting from chronic workplace stress that has not been successfully managed, characterized by three interrelated dimensions: chronic exhaustion, a cynical or detached attitude toward work and clients, and reduced professional efficacy – often manifesting in difficulties concentrating, remembering details, and processing information efficiently.

Although the WHO does not classify burnout as a medical disorder, several European countries recognize it as an occupational disease under specific legal or compensation frameworks. Regardless of classification, the consequences are serious. Burnout increases the risk of anxiety, depression, musculoskeletal pain, type 2 diabetes mellitus, and cardiovascular disease[3]. For health care professionals, the toll is particularly heavy: burnout erodes empathy, precision, and cognitive control – the very capacities that ensure safe and compassionate care. Here lies the paradox: those who care the most often recover the least and, in doing so, undermine both their well-being and the quality of care they deliver.

Consider a psychiatrist who cannot seem to switch off. Even at home, her patients remain in her thoughts. At first, her exhaustion feels like a badge of dedication. But, over time, she becomes impatient, forgetful and self-critical. Instead of slowing down, she pushes herself harder, chasing an impossible balance. Her experience reflects that of countless clinicians worldwide: the more depleted they become, the less able they are to engage in the recovery and proactive behaviors that could protect them.

The Job Demands-Resources theory[4] offers a framework for understanding why burnout emerges, and how it can be prevented. Job demands such as high workload, emotionally intense interactions, and cognitive overload consume energy and effort. Job resources – social support, autonomy, feedback, opportunities for learning – help employees meet these demands and stimulate engagement. When demands exceed available resources, strain accumulates. But when resources are sufficient, they can transform pressure into motivation and growth. Organizations that design jobs with this balance in mind can promote sustainable performance. In health care, this means structuring teams so that clini-

cians have autonomy, time for reflection, collegial support, and clear priorities. Resources not only buffer against stress but also fuel work engagement – defined as vigor, dedication, and absorption in work[5].

While leaders and human resource policies play a vital role, employees themselves are not passive recipients of job design. They can actively shape their work through job crafting – the proactive process of optimizing one's job demands and resources[6]. Employees who craft their jobs seek new challenges, build social connections, and adjust tasks to align better with their strengths and values. Over time, this improves person-job fit, meaning and engagement[7]. A related concept, playful work design, involves approaching routine or difficult tasks with curiosity and enjoyment – introducing small elements of fun or challenge that transform monotonous work into a source of energy[4]. Both strategies enable employees to stay motivated even in demanding environments such as hospitals, where stress is unavoidable.

Yet, the very state of burnout undermines these protective behaviors. When stress accumulates and energy resources are depleted, employees become less capable of engaging in recovery and less likely to craft their jobs[8]. They enter a loss cycle: high demands lead to fatigue, which impairs self-regulation and leads to more errors, conflicts and misunderstandings – each of which generates new demands. Exhaustion, cynicism, and cognitive depletion make it difficult to seek help or learn from mistakes. Moreover, burned-out individuals are often perceived as draining rather than inspiring, and colleagues may unconsciously distance themselves, further reducing social support. The workplace becomes emotionally impoverished.

A special case of this paradox is workaholism – the compulsive drive to work excessively hard and the inability to disengage[9]. Workaholics rarely rest; they see recovery as wasted time. When they do craft their jobs, they tend to increase their challenges rather than seek social support or reduce demands. This self-defeating strategy accelerates burnout. Moreover, the workaholic pattern extends beyond work into the home. Overinvolvement at work creates home demands – neglected relationships, conflict, and emotional distance – and erodes home resources such as intimacy and support. Stress then spills back into work, creating a vicious cycle across life domains. What begins as dedication ends in depletion.

How can we resolve the burnout paradox? Prevention must begin with systemic awareness. Organizations need to monitor workloads, allow sufficient recovery time, and ensure access to resources such as mentorship, social support, and professional development. Leaders play a crucial role in modeling healthy boundaries – leaving on time, disconnecting after work, and showing that recovery is not a luxury but a responsibility. But organizational action alone is insufficient. Professionals must also learn to self-monitor and regulate their energy. Simple strategies – brief detachment during breaks, mindfulness, or even micro-moments of playfulness – can interrupt the stress cycle. Training programs that teach job crafting and self-reflection can help clinicians identify and shape their own job demands and resources before exhaustion sets in. The combination of top-down and bottom-up approaches – organizational redesign and individual self-regulation – is the most effective safeguard against chronic strain[4,6].

Among health care professionals, psychiatrists face particular vulnerability. Despite their expertise in emotional regulation and resilience, many struggle to apply these principles to themselves. This paradox is profound: those trained to alleviate emotional suffering often internalize it instead – directing empathy outward but seldom inward. To sustain the capacity to care for others, clinicians must also care for their own psychological resources – protecting rest, nurturing connection, and practicing the same compassion they prescribe.

Ultimately, the burnout paradox reminds us that exhaustion is not a badge of honor but a warning signal. Recovery is not indulgence – it is maintenance. By redesigning work and empowering professionals to manage their own demands and resources, burnout can shift from an endpoint to a turning point – a catalyst for renewal. When organizations and individuals align around sustainable performance, health care can return to its essence: a place where compassion, competence and vitality coexist – for both patients and those who heal them.

Arnold B. Bakker
Center of Excellence for Positive Organizational Psychology, Erasmus University Rotterdam, Rotterman, The Netherlands; School of Management, Human Resource Management, University of Vaasa, Vaasa, Finland; School of Economics and Business, University of Ljubljana, Ljubljana, Slovenia

1. Sonnentag S, Cheng BH, Parker SL. Annu Rev Organ Psychol Organ Behav 2022;9:33-60.
2. Demerouti E, Bakker AB. Work Stress 2025;39:153-61.
3. Salvagioni DAJ, Melanda FN, Mesas AE et al. PLoS One 2017;12:e0185781.
4. Bakker AB, Demerouti E, Sanz-Vergel A. Annu Rev Organ Psychol Organ Behav 2023;10:25-53.
5. Schaufeli WB, Bakker AB. In: Ruch W, Bakker AB, Tay L et al (eds). Handbook of positive psychology assessment. Göttingen: Hogrefe, 2023:273-98.
6. Demerouti E. Annu Rev Organ Psychol Organ Behav 2026;13:195-220.
7. Oprea BT, Barzin L, Vîrgă D et al. Eur J Work Organ Psychol 2019;28:723-41.
8. Bakker AB, De Vries JD. Anxiety Stress Coping 2021;34:1-21.
9. Schaufeli WB, Taris TW, Bakker AB. In: Burke RJ, Cooper CL (eds). The long work hours culture: causes, consequences and choices. Bingley: Emerald, 2008:203-26.

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Social cohesion, social capital and mental health: current evidence and future research directions

Ichiro Kawachi

Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Social cohesion is defined as the sense of belonging, solidarity and shared values within a group. Although the terms "social capital" and "social cohesion" are sometimes used interchangeably, strictly speaking the former refers to the resources embedded in social relations – such as trust and norms of cooperation – which then create social cohesion. Social cohesion has been studied as a predictor of mental health in residential communities, schools and workplaces. Taking a life-course perspective, this paper reviews the empirical evidence linking social cohesion to common mental disorders, psychosis, suicidality and substance misuse. Consistent evidence is found for a protective association between social cohesion and common mental disorders, suicidality and substance misuse. Findings are mixed for psychosis. Hypothetical pathways explaining the link between social cohesion and mental health include that: a) living in a cohesive community promotes neighborly interactions which may reduce residents' risk of becoming socially isolated; b) social cohesion buffers the deleterious effects of adversity; and c) social cohesion lowers crime and increases safety perceptions. Important gaps remain in the literature, including the need for improved measurement (greater consistency in the use of indicators to measure social cohesion, developing measures to capture bridging social capital, and enhancing the validity of multi-item instruments via application of item-response theory); the need to strengthen causal inference; and the need for participatory intervention studies that demonstrate how social cohesion can be intentionally generated, and for whom it can be beneficial. Investing in the strengthening of social cohesion represents an asset-based approach to mental health promotion. In contrast to a deficits-based approach (such as efforts targeting loneliness or social isolation), increased attention to social cohesion can be viewed as targeting an upstream driver of both social isolation and loneliness, as well as an independent determinant of population mental health.

Key words: Social cohesion, social capital, common mental disorders, psychosis, suicidality, substance misuse, life-course perspective, residential communities, schools, workplaces

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Research on the social determinants of mental health has devoted the bulk of its efforts toward identifying risk factors that contribute to mental illness, such as socioeconomic disadvantage, early life adversity, ethnoracial discrimination, loneliness and social isolation[1]. The identification of risk factors characterizes what has been called a "deficit" model of mental health[2].

While these efforts have helped to target interventions towards those who are at greatest risk, there is growing recognition of the fact that addressing deficits alone may not suffice to achieve good mental health. For example, even if interventions could be successfully deployed to screen, identify and treat individuals who suffer from loneliness and social isolation, they would only alleviate suffering in the "tail" of the population distribution of risk for poor mental health[3].

What is additionally needed is a strategy that would seek to shift the population distribution of social connectedness in a healthier direction[4]. That is, we need to devote increased attention to factors that promote mental well-being in the whole population, not just individuals who are at highest risk of mental illness. Instead of (or more precisely, in addition to) directing resources toward lonely and socially isolated individuals, the target of our interventions should be strengthening social connections within communities, or even the whole of society.

A salutogenic approach to mental health promotion would involve the identification of community assets, in contrast to the identification of risk factors or deficits. The World Health Organization (WHO) defines health assets as "any factor (or resource) which enhances the ability of individuals, groups, communities, populations, social systems and/or institutions to maintain and sustain health and well-being, and to help to reduce health inequities"[5].

Just as assets are not simply the absence of deficits, the assets-based model of health promotion is not mutually exclusive to a deficits-based model. Indeed, most communities are characterized by the simultaneous presence of both assets and deficits. For example, significant variations are found in levels of social cohesion across communities that look similar with respect to their level of deficits, e.g., levels of deprivation[1].

Therefore, a comprehensive approach to mental health promotion in the population seeks to: a) advance the measurement of health assets within communities; b) understand the mechanisms through which health assets promote mental well-being in the population; and c) develop interventions at scale that can strengthen community health assets. The specific focus of this paper is on social cohesion as an example of a health asset[6].

SOCIAL CAPITAL AND SOCIAL COHESION: DEFINITIONS

When individuals draw upon their social network to obtain assistance, we call it "social support". In daily life, people look to their friends and family to receive tangible support – for example, cash loans to tide them over an emergency, or help with transportation and childcare to attend a clinic. These types of instrumental assistance can be considered part of the "social capital" possessed by individuals[7]. The formal definition of social capital is "the resources to which individuals and groups have access through their social networks"[8].

The extensive evidence linking social support – as a resource that individuals access through their social networks – to mental

and physical health outcomes has been recently reviewed in this journal[3]. Hence, this paper will not cover this topic further. Instead, the focus of the present paper is on social capital as a group attribute; namely, the resources that members of a group are able to access as a result of belonging to that group[9]. In turn, a group can be defined by any collective of individuals; for example, neighbors who live in the same community, students who attend the same school, or employees who work in the same company.

Although the terms "social capital" and "social cohesion" are frequently used interchangeably[10], strictly speaking "social capital" should be used to refer to the building blocks – i.e., the resources embedded in social relations – which then create "social cohesion" within a group. The forms of social capital (i.e., the building blocks) which create social cohesion include trusting relationships between members of the group, as well as the presence of norms of mutual assistance and cooperation within the group[11]. High levels of trust and norms of cooperation create a sense of belonging and solidarity.

A community – e.g., a neighborhood, school or workplace – endowed with high levels of trust and norms of cooperation, and a strong sense of belonging, can be said to be a "cohesive" community. Trust and norms of cooperation – even though they seem less tangible compared to cash loans or help with transportation and childcare – are nevertheless examples of resources available to members of the collective, and no less important in having the potential to promote and protect the health of members.

A review from 2005[12] noted that the concept of social capital was being used in the literature as an "umbrella term" embracing a set of disparate phenomena, ranging from social cohesion to social support, social integration and/or social participation. This loose usage of terminology continues to be practiced to this day. Wherever possible, I will reserve the use of the term "social capital" to refer to the resources embedded in social relations, while "social cohesion" will be used to refer to the solidarity and sense of belonging created by the presence of high stocks of social capital within the group.

The question is sometimes asked of why trust and norms of cooperation are viewed as resources. The answer is that they catalyze social exchange and enable the group to engage in collective action for the benefit of members. Trust is a kind of moral resource that emerges and accumulates as a result of repeated interactions, such as members of a community performing small favors for each other or volunteering to perform actions for the benefit of the collective[13]. Without trust, it is difficult for a group to establish norms of cooperation. For example, studies have shown that the "greening" of vacant lots (planting trees, cleaning litter) in urban neighborhoods can improve the mental health of residents[14]. A resident of a neighborhood who volunteers to donate an afternoon each year to plant trees and clean litter in his/her neighborhood performs the service because he/she trusts that others in the community will join these efforts and will not just sit at home benefiting from prosocial actions without doing their part (the "free rider" problem). In turn, once it is established, the norm of cooperation is instrumental for mobilizing other types of collective action, such as petitioning local government to request funding for further resources (e.g., purchasing seedlings and equipment). The result is strengthening of the shared belief that the group can work together to achieve a goal, or what is called "collective efficacy"[15]. In short, without social capital – i.e., the resources such as shared trust between members of a group – there can be no social cohesion.

MEASUREMENT OF SOCIAL COHESION

Social cohesion has been studied in different settings, such as neighborhoods[16], schools[17] and workplaces[18]. A systematic review of instruments to measure neighborhood social cohesion[19] found that, in 70% of studies, measurements were derived from two previously validated scales: the 1988 instrument developed by Buckner[20], and the 1997 instrument developed in the Project on Human Development in Chicago Neighborhoods[21]. Individual items on the Chicago scale inquire about the strength of trust between residents, norms of cooperation ("people around here are willing to help their neighbors"), sense of belonging ("this is a close-knit neighborhood"), and shared values.

Responses to the instrument are then typically aggregated to the neighborhood level to represent a group characteristic, i.e., the average level of social cohesion in the neighborhood where the respondents live. The rationale for aggregating individual responses is twofold: the first is to circumvent the problem that an individual respondent's perception of social cohesion in his/her neighborhood may be biased by (unobserved) personal characteristics. For example, an individual suffering from clinical depression is more likely to have a negative view of his/her community. This can lead to the problem of "common method bias", when both independent and dependent variables are measured within a survey using the same response technique, i.e. self report. The problem is mitigated by aggregating individual responses up to the level of their neighborhood such that the assessment of social cohesion is less likely to be influenced by any particular individual's biased perceptions of his/her environment.

The second reason for survey response aggregation is because social cohesion is a collective force which is hypothesized to exert a contextual influence on the health of individuals. That is, social cohesion is not an individual attribute, but rather a property of the group. Identifying the contextual influence of social cohesion on health is typically accomplished by multi-level modeling, in which we simultaneously regress a health outcome (e.g., depressive symptoms) on both the individual's perception of social cohesion (level 1) as well as the community-aggregated levels of social cohesion (level 2). An important goal of multi-level analysis is to tease out whether an association between social cohesion and mental health outcomes arises as a result of individuals with prosocial attitudes being clustered in communities with social cohesion (a compositional effect), or whether living in a socially cohesive community promotes mental health over and above individual characteristics (a contextual effect). The question of interest is: could a misanthropic individual who is suspicious and mistrustful of other people still benefit from living in a community where residents express high trust toward each other? An analogy can be drawn

with herd immunity, where the behavior of other people in the collective (e.g., being immunized against an infectious disease) can lower the risk of infection for an unvaccinated individual.

Limitations in the measurement of social cohesion

Before proceeding to review the empirical evidence on social cohesion and mental health, we need to call out two common limitations of published studies.

The first limitation is the widespread use of proxy indicators to measure social cohesion[22]. This issue stems from the use of secondary survey data that were not intentionally designed to measure social cohesion. A systematic review of studies between 2007 and 2018 summarized the most frequently measured indicators of social cohesion and social capital[23]. These indicators, ranked from most to least frequently used, include trust, participation, social support, social networks, reciprocity, satisfaction with the environment, voting, helpfulness, collective efficacy, volunteerism, crime, and control. Many of these indicators are either antecedents of social capital (such as social networks) or the downstream consequences of social capital (such as rates of crime). For example, the tendency to equate social cohesion with the absence of community "bads" (such as crime) has prompted the criticism that the measurement of social cohesion suffers from a tautology – if the community does not exhibit deficits, then it must be because it is endowed with high stocks of social capital.

The uncritical use of proxy indicators may account for some of the inconsistencies in findings noted across systematic reviews of social cohesion and health (discussed below). More rigorous attention to the issue of measurement would enhance our understanding of the causal mechanisms through which social cohesion affects mental health. For example, the use of proxy indicators such as voting behavior can be problematic, given that electoral participation is driven by many other factors besides social cohesion, such as attempts at voter suppression in many US electoral precincts with high prevalence of Black and Hispanic voters. Hence, low rates of voting may not be a valid reflection of the true levels of social cohesion within a community.

A second limitation in the literature is the widespread use of individual perceptions of social cohesion instead of aggregated measures. Broadly speaking, two types of studies have been conducted in the mental health field: a) studies that correlate individual perceptions of community social cohesion with mental health outcomes, and b) multi-level studies that correlate community-aggregated measures of social cohesion with individual mental health outcomes. The former type of study is frequently seen when data were not collected in a way to permit multi-level analysis, i.e., multistage cluster sampling of a sufficient number of individuals nested within different neighborhoods to permit reliable estimation of neighborhood-level social cohesion. As mentioned earlier, studies of individual perceptions of neighborhood social cohesion are prone to the common method bias, especially when the outcome is mental health.

The challenge of common method bias can be present even in multi-level studies. For example, in a multi-level, prospective study of large nationally representative samples from 14 European countries, the UK and the US[24], the researchers operationalized neighborhood social cohesion using two items inquiring about "feeling part of the area" (sense of belonging) and "receiving help from others in times of trouble". The critical point to note is that, even though the analysis was conducted using a multi-level framework (32,531 adults nested within 16 countries), the data were not clustered at the neighborhood level, so that the study is actually about individual perceptions of neighborhood social cohesion. The results showed that perceived lack of neighborhood social cohesion was significantly associated with increased risk of depression (odds ratio, OR=1.76). The authors attempted to address reverse causality by removing individuals with depression at baseline. Nevertheless, we cannot completely rule out common method bias, i.e., biased ratings of neighborhoods by individuals suffering from subclinical depressed mood[24].

EVIDENCE ON NEIGHBORHOOD SOCIAL COHESION AND MENTAL HEALTH

Common mental disorders

A systematic review of the literature up to 2015[25] concluded that there was sufficient evidence supporting social capital as a protective factor in reducing the risk of common mental disorders. Although the goal of the systematic review was to focus on social capital, the studies included in the review featured a mix of indicators of social cohesion (such as sense of belonging to the community and getting along with neighbors) and indicators of social capital (such as trust). The review identified 31 cross-sectional and 8 cohort studies focusing on community social capital/social cohesion and common mental disorders. Studies were further classified according to: a) whether they used "cognitive" indicators (such as residents' perceptions of trust and norms of reciprocity within their community), or behavioral indicators (such as whether people voted, volunteered or participated in social organizations); and b) whether social capital/social cohesion was analyzed as an individual perception or as an aggregated community characteristic. Of the 39 studies which analyzed social capital/social cohesion as an individual perception, 32 (27 cross-sectional and 5 longitudinal) reported a statistically significant protective association with common mental disorders. The review also found that seven of nine studies of community-level cognitive social capital/social cohesion reported a protective association with common mental disorders.

A notable conclusion drawn by the review – which echoed the conclusions from an earlier review[26] – was that behavioral indicators of social capital (voting, volunteering and social participation) were less consistently associated with common mental disorders compared to cognitive indicators. Almost half of the studies using indicators of individual behaviors found no association with common mental disorders. The results for community-aggregated measures of behavioral social capital were similarly null, with 8

of the 11 studies (9 cross-sectional and 2 longitudinal) finding no association with common mental disorders. However, caution is warranted in interpreting these findings, because – as already discussed – behaviors such as voting and volunteering are best viewed as proxies for social capital, so that it is unclear whether these studies provided an appropriate test of the association between social cohesion and mental health.

One important study which appeared to have been overlooked by the 2015 systematic review is the longitudinal, multi-level Caerphilly Health and Social Needs Cohort Study[27]. A strength of this study was that it used a neighborhood social cohesion scale which was ecometrically validated[28]. Ecometrics refers to the technique of integrating item-response theory with hierarchical modelling to validate self-reported neighborhood characteristics[29]. Ecometric validation allows the researcher to decompose whether the variability in area-level measures of neighborhood cohesion is reflective of the neighborhood environments *per se*, or a function of the characteristics of individuals living in the neighborhoods. In the Caerphilly Health and Social Needs Cohort Study, ecometrically validated assessments of neighborhood cohesion were then modeled at both the individual and neighborhood levels. After controlling for individual level covariates, the study found that, compared to low social cohesion neighborhoods, both medium and high cohesion neighborhoods were significantly associated with an improvement in mental health during a 7-year follow-up, measured by the Mental Health Inventory (MHI-5) subscale of the Short Form Health Survey 36 (SF-36) questionnaire. The average improvement in MHI-5 scores of +1.70 points (95% CI: 0.24 to 3.17) among residents of high cohesion neighborhoods was of greater magnitude than the decline in mental health experienced by residents in deprived neighborhoods (–1.08, 95% CI: –2.01 to –0.14)[27].

Additional studies published after the 2015 systematic review[25] were summarized in a more recent systematic review[16]. For the most part, these studies support earlier evidence, finding that neighborhood social capital (or more accurately, cohesion) is linked to better mental health[30-32]. Nonetheless, some important challenges remain, as identified by an umbrella review of social capital and health (i.e., a systematic review of twenty systematic reviews)[33]. Chief among them is the pervasive heterogeneity in the conceptualization and measurement of social capital (and social cohesion) across studies. The problem veers from studies that used distant proxies to capture social capital, to those that used indicators that are too narrow, such as the Canadian General Social Survey, which used a single survey item on "sense of community belonging" to stand for social capital[34].

Even though sense of community belonging is inarguably a component of social cohesion, it is unclear – when it is used as a single item – the extent to which it overlaps with other constructs such as "loneliness". No doubt the practice of using proxy indicators and single item measures reflects the underlying problem of limited space on surveys. But, just as nutritional epidemiologists would not attempt to measure "diet" using a single item, we cannot expect to advance the field by the continuing practice of loose measurement. As a result, our understanding of which elements of social cohesion we should be targeting for intervention has been held back, as well as an appreciation of the complex heterogeneity in the association between social cohesion and health, i.e., the question of for whom is cohesion beneficial and for whom it is harmful.

Suicidality

A robust correlation exists between social connectedness – as an individual attribute – and reduced risk of suicide[35,36]. However, fewer studies have examined the relationship between neighborhood social cohesion and suicidality. Community social cohesion could theoretically reduce the occurrence of suicide by enforcing norms against self-harm and fostering a sense of purpose and belonging[37]. Ever since Durkheim[38], it has been something of a shibboleth that social cohesion protects against the risk of suicide. Although some doubts have been raised about Durkheim's original claims[39], multi-level studies from Korea[40] and Japan[41] do find a correlation between neighborhood social cohesion and reduced risk of suicide ideation. However, these studies were cross-sectional, so that we cannot entirely rule out reverse causation, even though the risk of this bias was mitigated by the fact that the exposure (social cohesion) was based on individual responses aggregated to the level of the neighborhood.

A concept adjacent to social cohesion is collective efficacy, defined as the combination of neighborhood social cohesion and informal social control, i.e., the ability of residents to intervene when they witness antisocial behavior[15,21]. According to theory, the capacity of the community to influence adolescents' suicidal behaviors rests not just on the existence of close ties between parents and youth, but also on expectations for intergenerational support and supervision of youth by local adults in the neighborhood. A multi-level analysis from the Project on Human Development in Chicago Neighborhoods[42] tested this theory, but found no main effect of neighborhood collective efficacy on adolescent suicide attempts. However, there was a significant cross-level interaction in multi-level models. Specifically, collective efficacy interacted with family attachment and support, such that, as neighborhood collective efficacy increased, it potentiated the protective effect of family attachment on adolescent suicide attempts.

The correlation between neighborhood collective efficacy and suicide ideation was similarly examined in a multi-level study among South Korean adolescents[43], in which the authors found a main effect of collective efficacy: higher levels were protectively associated with adolescent suicidal ideation (OR=0.49, $p<0.001$), even after controlling for other neighborhood characteristics such as concentrated poverty, divorce rate, and residential instability.

Psychosis

The theoretical mechanisms linking neighborhood social cohesion to psychosis are less clear than for common mental disorders. In theory, residents of cohesive neighborhoods may be more likely to intervene to refer neighbors for treatment who are observed

to be suffering from symptoms of psychosis[44]. This could reduce the severity of illness but also increase the incidence of disease through higher case detection. At the same time, cohesive communities might be more effective in preventing access to illicit substances, which is a known risk factor for psychotic illness.

Studies linking social cohesion to psychosis remain sparse. A scoping review[44] on the topic identified 12 studies, of which seven focused on risk of psychotic disorders or symptoms of psychosis, three focused on the course of psychotic illness, and two on both. The literature presents mixed findings, with some studies suggesting a protective effect of higher social cohesion on psychosis risk[45,46], others finding null associations[47], yet others reporting nonlinear associations[48,49], or protective associations only in some subgroups – e.g., people with a family history of psychosis[50]. Based on this sparse and conflicting evidence, the review found that firm conclusions could not be drawn about the role of social cohesion on incidence of psychotic disorders, prognosis or severity of symptoms[44]. The review cited also weaknesses in measurement, with voting being the most commonly used proxy indicator for social capital.

A comment on the magnitude of effect sizes reported in the literature

The effect sizes linking neighborhood social cohesion to mental health outcomes have been criticized by some researchers as being "small", implying that it is not worth addressing social cohesion as a target of intervention[51]. However, it would be unexpected and surprising if an ecological variable had a large effect on an individual's health status. An individual-level risk factor (such as social isolation) typically doubles the risk of depression[3], but ecological variables such as neighborhood social cohesion are seldom associated with risk ratios that are greater than 1.5 – so-called "weak" associations in epidemiology.

A 2020 meta-analysis[51] found robust associations between social cohesion and mental health outcomes. The association was found to be stronger than for physical health outcomes, such as mortality or chronic diseases. Furthermore, the associations were strongest for indicators of social cohesion such as social trust and perceived reciprocity. However, the authors also noted that the effect sizes were "consistently very small" and that "the small effects that we estimate cast doubt on recent initiatives to promote health through social capital such as those by the WHO, the Organization for Economic Co-operation and Development (OECD), and US Healthy People 2020"[51]. However, as the eminent epidemiologist R. Doll cautioned: "Weak associations showing odds ratios of less than (say) three to one are often due to chance, bias, or confounding; but if they are causal and relate to common diseases and agents that are prevalent in the community, they may be important for the public health and more important than strong associations with agents that occur only rarely"[52].

Stated differently, effect sizes alone are not a sufficient guide to public health action. To give an analogy from the field of environmental epidemiology, an increase in mean air temperature from the 75th to the 99th percentile in 620 cities from 36 countries was associated with an average 8.9% (95% CI: 7.1-10.7) increase in daily mortality[53]. This corresponds to a risk ratio of 1.089, which some people might consider "very small". Yet, if exposures are sufficiently widespread, this can translate to a significant burden on population health, warranting action to mitigate the consequences of climate change. Large effect sizes (risk ratios greater than 2) – such as those reported for social isolation and depressive illness – apply to the 20% of population who are classified as socially isolated[54]. By contrast, the "weak" average effects for low neighborhood cohesion apply to all of the residents who live in such areas.

PATHWAYS LINKING NEIGHBORHOOD SOCIAL COHESION TO MENTAL HEALTH

Four distinct pathways, or mechanisms, have been hypothesized to link neighborhood social cohesion to mental health outcomes.

Pathway 1: Living in a cohesive neighborhood promotes neighborly interactions which may reduce residents' risk of becoming socially isolated

The hypothesis that living in a cohesive neighborhood lowers risk of social isolation was tested by the National Health and Aging Trend Study[55] in a 11-year follow-up of people aged 65 and older. Neighborhood social cohesion was measured with a 3-item scale that asked respondents to what extent they agreed with the following statements: "In the community where you live: 1) people know each other well; 2) people are willing to help each other; and 3) people can be trusted". The outcome of social isolation was measured by four indicators: marital/partner status, family and friend contact, religious attendance, and club participation. Controlling for socio-demographic and health covariates, higher levels of neighborhood social cohesion were longitudinally associated with lower odds of social isolation. Over time, a one-unit increase in the level of neighborhood social cohesion was associated with 56% lower odds of overall social isolation.

Given that extensive literature documents social isolation as a risk factor for poor mental and physical health[3], these results suggest a potential pathway to explain how living in a less cohesive neighborhood could adversely impact mental health via the increase of social isolation over time. A limitation of the study, however, is that both ratings of neighborhood social cohesion and social isolation were obtained from the same individuals, so that we cannot exclude the possibility that people who were already on a trajectory of declining social contacts were more likely to perceive their neighborhoods as being unfriendly. A more compelling design would be a multi-level study that examines the contextual influence of neighborhood social cohesion on individual trajectories of social isolation.

Pathway 2: Neighborhood social cohesion reduces crime and increases safety perceptions

In the field of urban criminology, social disorganization theory posits that neighborhoods suffering from a disrupted or weakened system of friendship or kinship networks are hampered in their ability to realize the common values of residents and to maintain effective social controls[56]. Neighborhood social cohesion (which is the opposite of social disorganization) is robustly correlated with reduced rates of crime and increased perceptions of safety[21]. This is achieved as a result of the collective efficacy of residents to prevent the occurrence of crime via their ability to intervene when antisocial behavior is witnessed on the streets, such as when teenagers are engaged in acts of vandalism. In turn, neighborhood crime is strongly correlated with mental health. A systematic review of 63 studies[57] which looked at associations between neighborhood crime and residents' mental health found significantly increased risks for depression, psychological distress, anxiety, and psychosis.

An important pathway through which neighborhood perceptions of safety can affect mental health is by promoting physical activity among residents. Neighborhood social cohesion is correlated with higher levels of physical activity[58,59], partly because cohesion promotes perceptions of safety. However, no studies have mapped the chain of causation running from a) neighborhood cohesion to safety perceptions, b) safety perceptions to physical activity behaviors, and c) physical activity to mental health. A recent systematic review identified only five studies that addressed the link between exposure to neighborhood violence and physical activity[60]; none of them examined the role of neighborhood social cohesion as an upstream driver of safety perceptions and physical activity. Perceptions of neighborhood safety are likely to play a significant role in the willingness of children and older adults to exercise or play outdoors. In particular, childhood is a critical developmental period when individuals acquire life-long habits of physical activity, suggesting that growing up in a cohesive and safe neighborhood may have lasting consequences for individual trajectories of mental health through this channel.

Pathway 3: Neighborhood social cohesion buffers the effects of adversity on mental health

Neighborhood social cohesion can also influence mental health by moderating – or "buffering" – the effects of stressful life events. For example, widowhood and living alone are both linked to increased risk of depression[61,62]. A nationwide prospective, multilevel study in Japan[63] examined whether community-level social capital could ameliorate the adverse impact of widowhood and living alone on depressive symptoms. Neighborhood social cohesion was subdivided into two components: cognitive indicators of social capital, including trust of neighbors and norms of reciprocity; and a behavioral indicator derived by averaging the level of people's engagement in community organizations. Widowhood in the past 12 months, in combination with living alone, was associated with a significant worsening of depressive symptoms among men, measured by the Geriatric Depression Scale (β=1.67; 95% CI: 1.38-1.95). The study found that community-level civic participation buffered the association between recent widowhood/living alone and depressive symptoms among men, though not among women[63].

Neighborhood social cohesion was also found to buffer the association between stressful life events and mental health in a nationally representative sample of Canadian adolescents[64]. Associations of stressful life events with depression and anxiety were significantly attenuated among adolescents living in cohesive communities (OR=0.98 for those living in highly cohesive neighborhoods vs. OR=3.11 for those living in low cohesion neighborhoods). Neighborhood cohesion similarly buffered the effects of stressful life events on suicidal ideation and aggression/conduct disorder[64].

Beyond stressful life events, neighborhood social cohesion was found to buffer the association between socioeconomic deprivation and poor mental health. In the UK Household Longitudinal Study linked to census data[65], the presence of local friendship networks buffered the relationship between socioeconomic deprivation and mental health: young adolescents living in neighborhoods with a higher percentage of friends reported better mental health, and this relationship was strongest in neighborhoods of greater deprivation. Similar findings were reported in the Caerphilly Health and Social Needs Cohort Study[27], where living in the most deprived neighborhoods was associated with decline in mental health over time, but the extent of deterioration was significantly attenuated for residents in cohesive neighborhoods. The predicted change in mental health (based on SF-36 MHI-5 scores) over 7 years was calculated for the 10th and 90th centiles of the household income distribution. The gap between income groups was –2.8 points (i.e., declining mental health) in low social cohesion neighborhoods and +1.1 points in high cohesion neighborhoods, yielding a difference between the groups of 3.9 points (95% CI: 0.2-7.6), which is a clinically meaningful difference in MHI-5 scores[27].

Pathway 4: Neighborhood social cohesion buffers the deleterious mental health consequences of disasters and public health emergencies

Disasters represent a special circumstance in which the protective effects of neighborhood social cohesion have been studied extensively in recent years. They deserve separate discussion here, especially since their frequency has been increasing over time, driven by the effects of climate change (heat waves, wildfires, hurricanes/typhoons) as well as patterns of human settlement in disaster-prone areas[66]. It has been argued that the stock of social capital in communities constitutes a type of "informal insurance" that people rely upon during acute crises[67]. Cohesive communities are quicker to mobilize assistance to victims, before even first responders have reached the scene, and long before formal mechanisms of insurance become available to assist in recovery. During the recovery phase of disasters, socially cohesive communities are more effective in giving "voice" to the needs of the community.

Residents of tightly-knit communities are also less likely to "exit" from disaster-stricken areas and more motivated to remain behind to assist in reconstruction[67]. In short, community resilience to disaster hinges not just on investments in physical infrastructure (e.g., reinforcing building codes to make habitations more earthquake-resistant), but also on strengthening the fabric of social connections in communities[68].

The mental health impacts of disaster-related experiences have been widely documented[69]. Psychological trauma stemming from the loss of loved ones, property damage, and disruption of employment are associated with increased risks of post-traumatic stress disorder (PTSD), depression, and anxiety disorder[70-72]. A growing number of studies have documented that pre-disaster social cohesion can immunize victims against developing mental disorders in the aftermath of traumatic experiences[73]. In a tsunami-affected area after the 2011 Great East Japan Earthquake, it was found that approximately 11% of residents developed severe PTSD symptoms[74]. That risk was reduced by 23% for participants who lived in communities with high levels of social cohesion preceding the disaster. The protective association held after controlling for differences in depressive symptoms at baseline, as well as for the type of traumatic experiences during the disaster (loss of loved ones, housing damage, and interruption of access to health care)[74].

The COVID-19 pandemic is an example of a public health crisis which caused widespread psychological distress and mental illness symptoms (depression, anxiety, post-traumatic stress symptoms)[75]. Besides the effects of economic recession, the imposition of infection control measures – such as lockdowns, mobility restrictions, and social distancing – also increased the prevalence of loneliness and social isolation, particularly among population subgroups such as women with dependent children[76]. Interestingly, communities with higher levels of social cohesion were more likely to comply with mobility restrictions (reflecting strong norms of cooperation)[77] and, as a result, declines in social connectedness were proportionally greater in cohesive communities[78]. A trade-off was therefore seen between a community's ability to control the spread of infection and the ability of individual residents to maintain in-person social contacts. Nevertheless, cohesive communities proved to be more resilient in the sense of being better equipped to buffer the negative consequences of shelter-in-place directives on the mental health of residents[79].

How can a cohesive community provide an effective buffer against the deleterious consequences of lockdown policies on mental health? During the normal course of our daily lives, the benefits of living in a cohesive community may not be noticed by most people. That is, during normal times, most of us "get by" with the social support that we receive from our personal social networks. The actions of our neighbors matter less to our mental health. Yet, as soon as a crisis occurs, social cohesion "kicks in" when we are forced to rely on the assistance of other members of the community, especially when resources in our own personal networks become quickly depleted and everyone we know is overwhelmed[80].

A vivid illustration of this mechanism comes from a case study in Unnan city (population 36,000) in Shimane Prefecture, Japan[81-83]. At the beginning of the pandemic, some residents voluntarily took upon themselves extra responsibilities to check on the welfare of older neighbors who were living alone. For example, postal workers would perform welfare checks and pass along information to the city's community health and social workers. Or community nurses voluntarily visited rural people's houses and provided transport to local community centers or clinics. However, as the pandemic wore on, neither the informal assistance provided by community volunteers nor the level of formal assistance provided by local government sufficed to meet the needs of isolated older residents. Eventually new forms of social capital emerged, taking the form of informal assemblies where a mix of residents, social work professionals, and local government officials gathered together to solve problems brought up by townspeople; for example, organizing a system of volunteer transport for disabled residents to drive to the grocery store. The ability of cohesive communities to spontaneously organize mutual aid in the teeth of crisis has been described elsewhere as well[84].

To conclude, there is sufficiently strong evidence of the role of social cohesion in disaster resilience to support efforts to map existing levels of social capital in areas that are at risk of disaster. Mapping and strengthening the social capital of communities should be an integral part of the process of disaster planning and preparedness[73].

SOCIAL COHESION AND MENTAL HEALTH ACROSS THE LIFE COURSE

The seminal review by Almedom[12] was the first to call attention to the need to adopt a life-course perspective as a route to understanding the different contexts in which social cohesion matters for people's mental health. For example, the mental health of children and adolescents, as well as older citizens, might be more closely tied to the social environment of residential neighborhoods, where they spend a substantial portion of their lives, compared to working-age adults for whom workplace social cohesion matters more. Neighborhood social cohesion may be more critical to families with young children compared to younger adults without dependents. The school social environment, specifically in the form of school social cohesion, may be particularly important for the emotional development, socialization and trajectories of substance misuse in adolescents, and so on. We turn to summarize what is known about the influence of social cohesion in different settings on people at different stages of the life course.

Adolescents and young adults

Common mental disorders

A recent review[85] identified 42 studies focused on the association between neighborhood social cohesion and adolescent depression and anxiety (age range 12-18 years), including two systematic reviews, 13 longitudinal studies and 27 cross-sectional

studies. The review concluded that there is sufficient evidence to support neighborhood social cohesion as a protective factor against adolescent depression.

However, similarly to other reviews of social cohesion, considerable heterogeneity was found in how the concept was operationalized across different studies. Seven indicators of neighborhood social cohesion were identified: a) positive relationships with peers in a local area; b) perceived safety of the neighborhood; c) sense of belonging to the neighborhood; d) perceived trust, availability of social support, norms of cooperation; e) shared values in the neighborhood; f) features of the built environment promoting social interaction; and g) social participation, including participation of adolescents in structured after-school activities. As mentioned earlier, some of these elements – e.g., crime and safety, features of built environment – ought to be considered as either antecedents or consequences of social cohesion. The review was limited to studies examining depression and anxiety as the outcome.

The relationship of a broader set of adolescent mental well-being outcomes to neighborhood cohesion was examined in a prospective analysis of the US Add Health Study, using an outcome-wide approach[86]. One advantage of this approach[87] is that authors were able to look comprehensively across 38 separate outcomes, including indicators of mental health, physical health, health behaviors, psychological well-being, social factors, and civic and prosocial behavior. By controlling for perceived neighborhood social cohesion in the pre-baseline wave as well as for an extensive range of potential confounders and outcomes, the analyses focused on the potential cumulative effects that perceived neighborhood social cohesion in the past had on health/well-being. The results showed that perceived neighborhood social cohesion was associated with adolescent mental health outcomes (depressive symptoms, suicidal ideation, perceived stress) a decade later, as well as with a broader set of outcomes, including psychological well-being (happiness, optimism), social outcomes (loneliness, romantic relationship quality, satisfaction with parenting), and prosocial behavior (volunteering). By contrast, perceived neighborhood cohesion in adolescence was not associated with physical health outcomes in adulthood.

Psychosis

Far fewer studies have examined the longitudinal association between neighborhood social cohesion and psychosis symptoms in an adolescent population[88,89]. In the Environmental Risk Longitudinal Twin Study, a nationally-representative cohort of UK-born twins, neighborhood social cohesion was measured by the 5-item instrument from the Project on Human Development in Chicago Neighborhoods[21], obtained from an independent postal survey of over 5,000 residents living alongside the children in the study. Children were interviewed about psychotic symptoms at age 12. Analyses were adjusted for important family-level confounders, including socioeconomic status, psychiatric history, and maternal psychosis. The study found that higher neighborhood social cohesion was significantly protective for psychotic symptoms at age 12 (OR=0.76, 95% CI: 0.65-0.89)[88].

By contrast, analysis of longitudinal data from the Avon Longitudinal Study of Parents and Children[89] yielded null findings. In this birth cohort of nearly 14,000 children, neighborhood social cohesion and trust were rated by the mothers of children during pregnancy, at 8 months postpartum, and when the child was approximately 2, 3, 5, 7 and 10 years old. Latent class growth modeling was used to examine trajectories of childhood exposure to neighborhood social cohesion. Logistic regression was then used to examine the association between these trajectories and psychotic experiences when the children were 13 and 18 years of age, adjusting for maternal psychopathology, participant socioeconomic characteristics, and area-level deprivation. At 13 and 18 years of age, 11.4% and 7.7% of children respectively had experienced suspected or definite psychotic symptoms. However, neighborhood social cohesion was not significantly correlated with psychosis at either age 13 or 18 years[89].

In summary, the mixed findings linking neighborhood social cohesion to adolescent psychosis echo the conclusions from the studies in adult populations[44].

Social cohesion in schools

Compared with residential communities, an arguably more influential context for the mental well-being of children is the schools they attend. As the primary place where children and adolescents interact with peers and teachers[90], the school environment may be more important than neighborhood contexts in shaping their development, health and behaviors. School social cohesion is manifested by the intangible prosocial resources derived from a child's social networks, which include social norms within peer groups as well as expectations of parents and teachers[91].

An example of a validated 8-item School Trust and Social Cohesion scale (Cronbach alpha = 0.81), developed in an adolescent sample of Japanese schoolchildren, includes items that tap into the child's sense of belonging to the school, the presence of trusting relations between students, and mutual support between students[92]. Individual responses are then aggregated to the level of the school and entered into a multi-level model to examine the association of school social cohesion with child health outcomes.

Based on a version of this instrument, a study of elementary school and junior high school students (aged from 9 to 15 years) in Japan found that both individual perceptions of school social cohesion and aggregated school cohesion were significantly protectively associated with symptoms reported by children on the Depression Self-Rating Scale[93]. The study also found an intriguing difference in the comparative importance of neighborhood versus school social cohesion according to educational stage. Specifically, school social cohesion was more strongly linked to depressive symptoms among older junior high students compared to younger elementary school students. By contrast, the mental health of elementary school students was more strongly related to neighborhood cohesion and safety. This seems to suggest that the effects of social cohesion vary by the child's developmental stage. Younger children are more strong-

ly affected by the social environment in their homes[94] and in their neighborhoods, whereas, as they grow older, children fall progressively into the social orbit of school peers.

An important pathway through which school social cohesion protects adolescents' mental health is by buffering the deleterious effects of socioeconomic disadvantage at home. A multi-level analysis of data from two municipalities in Denmark[95] found that the OR for daily emotional distress symptoms was 1.89 (95% CI: 1.25-2.86) among children from low socioeconomic backgrounds compared to high socioeconomic backgrounds (assessed by parental occupational class), whereas in school classrooms characterized by high and moderate trust, there were no statistically significant differences in emotional symptoms between pupils from high and low socioeconomic backgrounds.

School social cohesion and substance use/misuse

Substance use/misuse is an especially relevant outcome for school social cohesion, given that adolescence is a critical stage in the life course for initiation into tobacco, alcohol, and illicit drug use. The longitudinal association between school social cohesion and adolescent tobacco use was examined in the Healthy Passages Longitudinal Study of Adolescent Health[96], based in three US cities. An innovation in this study was that it sought to tease out the influence of school versus neighborhood environments through the use of cross-classified multi-level models[97]. School social cohesion – independently of the effects of neighborhood context – was protectively associated with cigarette smoking in grade 10. Each standard deviation increment in school average social cohesion in grade 5 was associated with an OR of 0.86 (95% CI: 0.75-0.98) for smoking in grade 10[96].

Studies have also examined the association between school cohesion and adolescent alcohol use. A cross-sectional study of 3,291 students in grades 10 through 12 cross-nested in 51 public high schools and 107 neighborhoods was conducted in two prefectures of Japan[98]. Social cohesion was measured in both schools and neighborhoods using the instrument from the Project on Human Development in Chicago Neighborhoods[21]. The results showed significant variation in alcohol use between schools but not between neighborhoods. After adjusting for covariates, school cohesion was protectively associated with alcohol drinking (OR for each standard deviation from the mean: 0.61; 95% CI: 0.49-0.75), whereas neighborhood cohesion was not associated with alcohol consumption[98].

Working aged adults

Workplace social cohesion and mental health

When we turn to working aged adults, the workplace is the social environment in which people spend substantial portions of their waking day. It stands to reason that mental health for working aged adults may be more closely tied to workplace social cohesion than to social cohesion in their neighborhoods. Workplace social cohesion refers to a strong sense of connection, trust and shared purpose among employees within a company.

A cohesive workplace is hypothesized to protect the mental health of employees through multiple pathways, including buffering the deleterious effects of job stress[99,100], job insecurity[101] and work-family conflicts[102]; enhancing job satisfaction[103] and worker engagement[104,105]; and reducing employee turnover[106,107], incidence of workplace bullying[108], and burnout[109].

The concepts of workplace social capital and social cohesion are often used interchangeably. But, as clarified earlier, social capital should be used to refer to network-derived resources (such as trust and norms of cooperation) which then create a cohesive workplace where employees express a high sense of belonging and solidarity. Measurement scales for workplace "social capital" are often a mix of items inquiring about the resources embedded in workplace social relations (such as trust, norms of cooperation) as well as the cohesion that they create (shared sense of purpose and sense of belonging).

Psychometrically validated instruments to measure workplace social cohesion and social capital have been developed[110-113]. An example of a validated instrument to measure workplace social capital was used in the Finnish Public Sector Cohort Study[110]. The items in the scale tap into workers' sense of belonging and solidarity, norms of cooperation, and trust between employees and supervisors (Cronbach alpha = 0.87).

Using this instrument, the association between workplace social cohesion and depression was examined in a cohort of 33,577 public sector employees in Finland, who had no recent history of antidepressant treatment and who reported no history of physician-diagnosed depression at baseline[114]. The outcome was assessed with two indicators: recorded purchases of antidepressants and new-onset depression diagnosed by a physician in the follow-up survey 3-4 years later. Multi-level logistic regression analysis found that the odds of antidepressant treatment and physician-diagnosed depression were 20-50% higher for employees reporting low perceived workplace social capital compared to those reporting high social capital. The association between perceived social capital and depression was attenuated, but remained statistically significant, after adjustment for multiple covariates as well as baseline psychological distress (a proxy for undiagnosed mental health problems)[114].

Three additional multi-level studies have examined workplace cohesion and mental health outcomes. The first study examined 2,796 employees clustered in 35 workplaces (government agencies, manufacturing worksites, and service companies) located in Shanghai, China[115]. Low individual perceptions of workplace social cohesion were linearly correlated with poor mental health, measured by the Chinese language version of the WHO Five Well-Being Index (WHO-5). Controlling for individual perceptions, low social cohesion (aggregated to the level of the workplace) was not consistently correlated with mental health, with only the 2nd quartile group showing a significant association with poor mental health

(OR=1.63, 95% CI: 1.05-2.53)[115].

A second study from Japan[116] examined 1,944 male and 786 female employees in two manufacturing worksites. In this 2-year prospective, multi-level study, workplace social cohesion was measured using a validated six-item instrument, while the outcome was assessed by the Kessler Psychological Distress Scale (K6). The study found that each standard deviation increment in work unit-level social cohesion was associated with a 0.69 point improvement in K6 scores (95% CI: –1.12 to –0.26)[116].

The third study analyzed longitudinal data from the WHALE (Well-being in Hospital Employees) cohort study[117] to examine the association between workplace social cohesion and incident purchases of psychotropic medications (antidepressants and anxiolytics/hypnotics/sedatives). The study population comprised 21,711 employees nested within 2,283 work units in the Capital Region of Denmark. Workplace social cohesion was assessed by eight items (covering trust, fairness and worker collaboration), and individual responses were aggregated up to the level of each work unit. Using two-level mixed-effects survival models, and adjusting for individual-level perceptions of workplace social capital, the study found that low work-unit social cohesion was associated with higher purchases of overall psychotropic medications in a dose-response manner (low-versus-high: hazard ratio, HR=1.32, 95% CI: 1.05-1.65), although this effect was attenuated after adjusting for individual-level workplace social capital (HR=1.14, 95% CI: 0.88-1.46). When the outcome was restricted to purchases of antidepressants, low work-unit social cohesion was associated with increased risk (HR=1.78, 95% CI: 1.16-2.73) even after adjusting for individual-level workplace social capital (HR=1.69, 95% CI: 1.05-2.73)[117].

Additional studies have examined the correlation between individual reports of workplace social cohesion and mental health symptoms in employees[118,119], but in each instance the associations were based on individual perceptions, so that common method bias could not be ruled out.

One study that sought to strengthen causal inference is the fixed effects analysis conducted by Tsuboya et al[120]. The authors analyzed a sample of 6,387 men and 1,825 women employed in 12 private companies in Japan. Questionnaires inquiring about workplace social cohesion, job strain and effort-reward imbalance were administered at baseline. At 1-year follow-up, social cohesion and K6 were assessed again, and the authors regressed changes in K6 psychological distress scores on changes in workplace social cohesion. They found that, after adjusting for baseline demographic characteristics and workplace-related factors (including job strain and effort-reward imbalance), increased workplace social cohesion between waves was associated with reduced psychological distress (β=–0.23, $p<0.0001$). A protective association was found in both men and women, in all age groups, and among employees with high or low baseline mental health. The association was stronger among those who reported higher stress at baseline[120].

Taken together, these studies suggest that strengthening social cohesion in the workplace setting may be a promising avenue for promoting the mental health of working-aged adults (a theme we will return to in the section on Interventions).

Older adults

Upon retirement from the workforce, many people begin to experience the onset of functional limitations that restrict their mobility, so that their neighborhoods begin to take on a larger significance in their ability to access social capital[121]. Arguably, no age group relies as much as older people on the capacity of social connections or community resources to maintain health[122].

A qualitative study[123] examined the reasons why neighborhood social cohesion matters for the mental health of people as they age. Cohesive communities are more likely to facilitate opportunities for residents to participate in social activities through informal and formal channels. Meaningful social activities are crucial for mental health, because they enhance older adults' sense of belonging, feelings of being needed and appreciated, as well as added purpose in everyday life and having something to plan for and look forward to[123]. Engagement in social activities do not substitute for the importance of lifelong friendships, but they can mitigate the shrinkage of social contacts as people age.

Volunteering is a prototypical example of a meaningful social activity associated with improved mental health, at least in observational studies[124]. It may seem tautological to claim that social cohesion facilitates acts of volunteering, given that voluntarism is often incorporated into the measurement of social cohesion. However, as argued earlier, it is a conceptual error to equate social cohesion with volunteering. Rather, volunteering is an *outcome* of social cohesion as opposed to an integral component of it. It has been argued[125] that "a community in which individuals volunteer is not intrinsically cohesive. However, socially cohesive societies may be more likely to elicit volunteering and assistance to others within a neighborhood".

The reciprocal is also likely to hold, i.e., acts of volunteering may promote feelings of identity and togetherness. This idea was tested in two large-scale and longitudinal social surveys in the UK: the Understanding Society Household Longitudinal Study and the Beyond Us and Them project[125]. Using a cross-lagged longitudinal model, a secondary analysis of these surveys found significant associations between social cohesion and subsequent volunteering, and vice versa. That is, people who perceived their neighborhoods as more cohesive were more likely to volunteer at later time points, and people who volunteered were more likely to feel socially cohesive later in time[125].

A 2013 systematic review[126] identified eleven studies concluding that social capital/social cohesion is correlated with mental well-being in older adults. Additional studies since that review have added to the evidence base linking community social cohesion to the mental health of the elderly[127,128], with some highlighting urban-rural differences[129,130], and others pointing to perceived cohesion as a mediator of perceived neighborhood quality and mental health[131,132]. An outcome-wide analysis based in the Health and Retirement Study found that perceived neighborhood cohesion was associated with reduced risks of a range of mental well-being outcomes among older adults, including depression, hopelessness, negative affect, and loneliness[133].

FUTURE DIRECTIONS OF RESEARCH ON SOCIAL COHESION AND MENTAL HEALTH

The review of current evidence on social cohesion and mental health reveals some gaps in the literature. In particular, there is a need to improve the measurement of social cohesion, and to implement stronger designs – e.g., quasi-experimental – to strengthen causal inference.

Improving measurement

Establishing measurement invariance

An emerging area for improving the measurement of social cohesion is by testing for differential item functioning (DIF), based on item-response theory[134]. DIF examines how items in a scale are related to a latent construct and whether this relationship differs across groups such as different racial groups. Villalonga-Olives et al[135] sought to examine whether there is DIF in measures of social capital according to race, using data from respondents to the Southeastern Pennsylvania Household Health Survey. They found evidence for DIF across several items, indicating measurement error. Conditional on the same level of social capital, White individuals, compared to Black ones, were more likely to respond "agree" or "strongly agree" to questions such as "people in my neighborhood are willing to help their neighbors" and "people in the neighborhood can be trusted". The presence of DIF suggests that the wording of items may not be meaningful for some groups of respondents, or that some key concepts of the item are understood differently by different groups.

An implication of DIF is that differences in levels of social cohesion between Black and White communities may be an artefact of bias introduced by the choice of items to measure the construct. Gilbert et al[136] have argued that the measurement of social cohesion is often based on cultural assumptions tested in mainstream White America. They call for further refinement of social cohesion measures incorporating indicators that are historically and culturally relevant to Black communities.

Bonding versus bridging social capital

Social cohesion research has been criticized for paying insufficient heed to power relations in society which structure people's opportunities to accumulate resources via social connections[137]. For example, community social cohesion is sometimes found to be a stronger predictor of mental health in socioeconomically advantaged compared to deprived neighborhoods. This point was underscored in a study which examined the association between community attachment (an indicator of social cohesion) and child behavioral problems across a socioeconomically diverse set of neighborhoods in Baltimore, Maryland[138]. Attachment to community was assessed using a multi-item scale comprised of two subscales (general sense of community and how well the respondent knew his/her neighbors). In wealthy neighborhoods, children of parents who reported knowing few of their neighbors had higher levels of internalizing problems, such as anxiety and depression, compared to those who knew many of their neighbors. But the opposite was found in poor neighborhoods: children whose parents reported knowing few of the neighbors had lower levels of internalizing problems compared to those who knew many of their neighbors. The cautionary lesson drawn by the authors is that the same indicator of social cohesion may vary in its association with mental health depending on the social context. One implication is that, before concluding that social cohesion is less effective in poor neighborhoods, researchers should take into account differences in the type of social capital available to different communities.

One distinction that is frequently mentioned, but less often measured, is between bonding social capital and bridging social capital. Bonding social capital refers to connections between members of a network who are similar to each other with respect to social class, race/ethnicity, and other attributes. By contrast, bridging social capital is defined by the connections between individuals who are dissimilar (or heterogeneous) with respect to socioeconomic and other characteristics[139]. Bridging social capital can link people to resources, information and norms of behavior that may not be available within their own social network.

A systematic review of 23 studies that examined bridging social capital in public health settings[140] found considerable variation in its operationalization and measurement. While most instruments attempt to tap heterogeneity in people's social connections (e.g., knowing someone who is outside one's neighborhood or profession), there is as yet no standard formulation, and few studies have formally conducted psychometric testing of instruments. Therefore, there is scope to develop a validated instrument in future studies. One promising avenue would be to develop scales that are more precisely targeted to specific populations – for example, immigrants.

A consistent finding across studies is that immigrants in the US access mental health services at much lower rates than non-immigrants[141]. Reasons for this disparity are rooted in structural issues, such as undocumented status, fear of deportation, lack of insurance, high cost and inaccessibility of services, as well as language barriers. As a result, immigrants are forced to turn to their sources of bonding social capital (family, friends) for assistance.

A study of Chinese immigrants in Japan found that bonding social capital (defined as social connections with co-ethnic residents) was directly associated with mental well-being, while bridging social capital (defined as social connections with native-born residents) indirectly improved immigrants' psychological well-being by improving their economic mobility[142]. Measurement of social capital in immigrants should, therefore, include questions that inquire about the ability of individuals to access valued resources outside of their own social milieu, e.g. whether a migrant to a foreign country is able to call upon others who have familiarity with immigration bureaucracies, or whether an unemployed person is acquainted with people who have knowledge about job opportunities[140].

Strengthening causal inference

Besides improving measurement, causal inference would be advanced by strengthening study designs. Everybody acknowledges that interpretation of cross-sectional data is hampered by the threat of reverse causality. However, it is important to be reminded that even longitudinal designs cannot completely rule out reverse causation. To the extent that the baseline assessment of social cohesion in longitudinal studies is affected by unobserved variations in mental health prior to the start of follow-up, prospective designs do not fix the problem of reverse causality. It seems probable (or even likely) that causality runs in both directions[143,144], but it would be helpful to know that a correlation between social cohesion and mental health is not entirely driven by reverse causation.

One approach to advance causal inference is to adopt "fixed effects models". In these models, individuals act as their own control by comparing measures at different time points, thereby removing confounding from all observed and unobserved time-invariant factors[145].

A panel study in Japan[146] compared the results obtained from alternative methods of analyzing the association between individual perceptions of social capital and psychological distress (measured by K6 scores). The association between psychological distress (K6 scores ≥5) and low social capital was progressively attenuated as more stringent methods were applied: OR=0.70 (95% CI: 0.68-0.71) in cross-sectional analysis, 0.82 (95% CI: 0.79-0.85) in prospective analysis, and 0.88 (95% CI: 0.84-0.92) in fixed effects analysis. These results suggest that many studies in the literature may have inadequately controlled for unobserved, time-invariant individual attributes, such as neuroticism, which may confound the association between social capital and mental health outcomes.

The principal limitations of fixed effects analyses are that: a) they cannot control for time-varying confounders (such as unobserved factors which prompt people to move neighborhoods), and b) lack of variation in either the exposure variable or the outcome variable (often attributable to short length of follow-up), which reduces the precision of estimates.

An alternative approach to strengthen causal inference is to take advantage of natural experiments. A fundamental problem in identifying the effects of neighborhood exposures (including social cohesion) is residential selection – that is, to some degree, people exercise choice in where they live[147]. To give an example from the literature on the built environment, people who like to exercise outdoors will tend to move into neighborhoods which are endowed with attractive amenities, and hence we should not be surprised if built environment features such as the presence of parks and walkways is correlated with higher physical activity levels among people who live in such places[148]. From the supply side perspective, fast food franchises carefully choose where to open their stores based on projected consumer demand for their products, so that we should not be surprised if living closer to a pizza shop is correlated with higher consumption of pizza.

The same problem arguably applies to neighborhood social cohesion: sociable people will tend to move out of unfriendly neighborhoods and gravitate to places where they feel more welcomed, or where they feel that they share the same values as their neighbors. Obviously, this is a gross generalization which overlooks significant structural barriers in residential choice, including housing supply, affordability, history of racial redlining, and so on. Nonetheless, many people do exercise some choice in where they settle.

Two groups of people who are constrained in their choice of neighborhoods are refugees who are resettled in destination countries, and people who are involuntarily displaced by natural disasters. An example of the former is the study by Hamad et al[149], which sought to take advantage of a Danish policy that distributed newly arrived refugees quasi-randomly across the country in 1986-1998. Refugees were dispersed to neighborhoods with varying degrees of socioeconomic disadvantage in a more or less random manner. This natural experiment allowed the researchers to examine the associations of neighborhood disadvantage with increased risks of cardiovascular disease[149], psychiatric disorders[150], and other health outcomes.

A different type of involuntary resettlement is often observed in the aftermath of natural disasters. After the 2011 Great Eastern Japan Earthquake and Tsunami, roughly a quarter million residents were displaced due to widespread tsunami destruction. In one affected locality, Iwanuma city in Miyagi Prefecture, Shiba et al[151] examined whether changes in social cohesion were correlated with new onset of depressive symptoms. An unusual aspect of this study was that pre-disaster information on neighborhood social cohesion was collected seven months prior to the day of the tsunami from over 5,000 older, community-dwelling adults who happened to be participating in a nationwide cohort study. One of the strongest predictors of deteriorated neighborhood social cohesion was the experience of home loss (OR=2.08; 95% CI: 1.42-3.04), which forced survivors to leave their neighborhoods and being relocated to temporary housing provided by the municipal authority. Among survivors who were relocated, post-disaster deterioration of social cohesion was associated with significant increases in depressive symptoms (assessed by the Geriatric Depression Scale)[151].

Another study in the aftermath of the 2016 Kumamoto earthquake, using a similar design but a smaller sample size (N=828), reached a similar conclusion[152]. Each standard-deviation drop in community level social cohesion (comparing pre-disaster to post-disaster assessments) increased the risk of incident depression (relative risk: 2.44, 95% CI: 1.33-4.47) assessed by the Screening Questionnaire for Disaster Mental Health[153].

An obvious limitation of the natural experiments described above is that the findings may not be generalizable to the general population. Refugees and people displaced by disasters differ in many ways from the general population, which may reduce the external validity of these natural experiments. The trade-off between internal validity (strengthening causal inference) and external validity (generalizability) is a common feature of experimental studies[154]. A potentially more significant issue is that the influx of displaced individuals/refugees into neighborhoods may, by itself, perturb social relations in the community and affect the level of social cohesion. That is, social cohesion is not a fixed or static property of the neighborhood, and may be influenced by

the populations we are trying to study. This was illustrated in the Iwanuma Study, based on the cohort of people impacted by the 2011 Great East Japan Earthquake and Tsunami mentioned above. In Iwanuma city, a significant proportion of residents (roughly 1 in 7 of the population) were internally displaced as a result of housing destruction caused by the tsunami. A study which tracked changes in the level of trust among Iwanuma residents[155] found that each standard-deviation increase in the influx of internally displaced persons within 250 m of a resident's home address was associated with higher odds of a decrease in their trust of neighbors (OR=1.17; 95% CI: 1.04-1.32).

The bottom line is that we need more randomized community trials to clarify the causal relationships between neighborhood (or workplace) social cohesion and mental health outcomes, a point we will return to below.

SOCIAL COHESION/SOCIAL CAPITAL INTERVENTIONS

Broadly speaking, two types of interventions that leverage social cohesion and/or social capital to promote mental health can be distinguished. In the first type, the manipulation consists of activities that seek to directly build or strengthen social cohesion and/or social capital. An example is community service programs such as the Experience Corps program in the US, in which retired seniors are encouraged to volunteer as teacher's aides in classrooms within resource-poor communities[156,157]. As well as fostering intergenerational social capital, the program has been shown to improve mobility among older adults as well as children's school performance. Participation in Experience Corps has been shown to improve older volunteers' physical and cognitive activity, although mental health has not been examined[156]. Similar programs have been described in Japan[158].

Interventions in this category have also targeted community capacity-building. Griffiths et al[159] conducted a study in a socioeconomically disadvantaged community in Sydney, Australia, where community health nurses were trained to expand their role beyond providing clinical care to include work to promote social cohesion by encouraging residents to participate in local community activities and services. Examples of the types of activities led by nurses included community celebrations, education and employment opportunities (e.g., free 10-week courses such as introduction to computers), community newsletters, and working with local media to promote a positive image of the community. A pre- and post-evaluation conducted two years apart, targeted to female residents, suggested modest improvements in perceptions of bridging social capital for the unemployed as well as women for whom English was not the first language. These were accompanied by small but significant improvements in mental health.

In the second category of interventions, social capital acts as a channel factor to affect mental health outcomes. That is, the strengthening of social capital is not the target of the intervention *per se*, but is a by-product or collateral benefit. For example, Pronyk et al[160] conducted a group-based microfinance intervention in rural South Africa that was combined with participatory gender and training on human immunodeficiency virus (HIV) infection. Although the primary objective of the intervention was to improve women's access to micro-credit, the accompanying activities also led to changes in solidarity, reciprocity and social group membership, eventually resulting in reduced risk of gender-based violence and HIV risk. After two years, adjusted effect estimates indicated higher levels of structural and cognitive social capital in the intervention than the comparison group.

Home visitation programs (e.g., nurse practitioner visits to homes of mothers with newborn infants) are another example of a channeling intervention. The objective of the nurse practitioner home visits is not to strengthen social capital *per se*, but to provide health check-ups for the newborn and the mother, as well as consultation on parenting in general. Nevertheless, these programs may help to reduce maternal social isolation and loneliness. A home visitation intervention conducted by public health nurses in Japan failed to demonstrate improvements in maternal stress or social trust, but the frequency of visits (at 1-2 months and 4 months after hospital discharge) may not have been sufficient to affect outcomes[161].

Interventions may further seek to target particular segments of the population who may selectively benefit from being connected to social capital. For example, a population subgroup that may particularly benefit from social capital interventions are refugees[162]. As with survivors of natural disasters described earlier, forced residential displacement can significantly disrupt access to social connections for refugees. A systematic review[163] identified seven studies that focused on social capital as a target or channel factor for improving mental health among refugees. Examples of interventions ranged from improving access to childcare for refugees and asylum seeking families[164], competency-based training of refugee leaders followed by peer-led community health workshops[165], group psychotherapy[166], social support groups for at-risk groups (e.g., lesbian, gay, bisexual, transgender, and queer refugees)[167], and community kitchens[168]. Gaps in the literature were noted, including that the majority of studies were cross-sectional, and none of them assessed social capital using recognized instruments. Nevertheless, the interventions were sufficiently encouraging in terms of their impact on refugees' mental health that the review called for further longitudinal and multi-level interventions to be conducted.

Community-based participatory approaches

The Power for Health Project is an example of a community-based participatory research intervention that sought to strengthen social cohesion to address health disparities in Black and Latino communities in Multnomah County, Oregon[169]. The intervention was co-designed by community health workers together with members of the community, to identify local needs and priorities. A basic principle of participatory research is that community members are engaged as equal partners and collaborators to develop the intervention[170]. This principle is reflected by the diverse range of activities developed and delivered through the inter-

vention. These included "an Aztec dance class; a soccer team for Latina women; a series of popular education classes about gang violence for Latino community members; a chronic pain support group at an African American faith community; a peace campaign with African American youth, in response to recent shootings of African Americans and Latinos; and a group designed to identify and address health issues in a predominantly Latino neighborhood"[169].

Evaluation of the intervention, based on pre- and post-surveys (8 months apart) indicated significant improvements in the number of people available in the community who could provide social support to others, as well as a decline in depressive symptoms. However, there were no changes in more specific indicators of social cohesion, such as civic engagement or perceived reciprocity. A limitation of this study is that it did not include a control group, although admittedly it is a challenge to recruit a control population in a community-based participatory research study.

Place-based interventions and neighborhood regeneration

The goal of most place-based interventions is not exclusively targeted to building social cohesion, but nonetheless increased cohesion can be a by-product. A recently published example comes from the quasi-experimental evaluation of a place-based intervention conducted in six neighborhoods of Hamilton, Canada[171]. The intervention consisted of a participatory approach to community development wherein residents came together to plan and prioritize activities with the goal of increasing health and safety, enhancing neighborhood beautification, and building communities and social connections. Examples of actions included expanding community gardens, developing recreation programs, graffiti cleanup, fostering apprenticeship programs, and organizing community events. Relative to baseline surveys (conducted from 2011 to 2014), the follow-up surveys (conducted from 2013 to 2016) indicated modest but statistically significant improvements in social cohesion in four of the six intervention neighborhoods[171]. Elsewhere, place-based interventions have reported success in strengthening social cohesion[172,173].

Neighborhood regeneration involves a combination of business development, infrastructure upgrades, community engagement and other initiatives with the goal of revitalizing deteriorated neighborhoods and improving their economic prospects, physical environment and social conditions. An example is the program called Communities First delivered by the Welsh government to the 10% most deprived neighborhoods in the country[174]. The program included activities addressing the areas of crime, education, housing and physical environment, vocational training and business support, and community development. Analysis of 7-year follow-up data demonstrated increased MHI-5 scores in the intervention group (1.3 points, 95% CI: 1.03-2.02) compared with a propensity-matched control group. In mediation analysis, improved perceptions of neighborhood quality and reduced neighborhood disorder accounted for 41% of the association between the regeneration intervention and improved mental health. However, regeneration was not associated with improvements in perceived social cohesion [174].

Social infrastructure investments

Social infrastructure refers to shared spaces in the community – such as libraries, parks, childcare centers, and bookstores – that potentially contribute to neighborhood cohesion by encouraging social encounters between residents[175]. We can further distinguish between two types of infrastructure: a) community spaces that are intentionally built for the purpose of facilitating social interactions, such as community centers, and b) features of the built environment – such as parks and playgrounds – that are provided on the basis of aesthetics or to promote physical activity, but produce an increase in informal interactions between residents as a by-product.

Community spaces

An example of an intervention which intentionally sought to generate social interactions among community residents is the Taketoyo Intervention Study which took place in Aichi Prefecture, Japan[176]. Municipal authorities launched a campaign to build ten new community centers in a town of 43,000 people. The community centers (called "salons" in Japan) were staffed by volunteers and offered diverse programs for local seniors, ranging from arts and crafts to cultural activities (singing, playing instruments, poetry composition), as well as informal socializing. A quasi-experimental evaluation of this intervention – utilizing the distance of residents' homes from the nearest salon as an instrumental variable – demonstrated significant increases in social participation and lower incidence of functional disability[176,177].

The Men's Shed movement, originating in Australia in the 1980s [178], provides community spaces for men – who are usually more reticent than women about visiting community centers – to engage in craftwork and social interaction. Men's sheds can now be found in the US, UK, Ireland, Canada, Finland, and New Zealand.

Built environment features

Other features of the built environment – such as dog parks[179], playgrounds and libraries – facilitate casual encounters among community residents. Such encounters do not typically build close ties, but over time they can build familiarity, neighborliness and trust[180]. Recently, researchers have begun to examine which specific types of built environment features are likely to activate bridging types of social connections between community residents.

Fraser et al[180] analyzed a large-scale, privacy-enhanced mobility dataset of >120,000 anonymized mobile phone users in Boston to map daily encounters between residents from different income and racial groups. They found that parks and cafes promote more

daily encounters between high- and low-income residents (bridging social capital), while community centers and libraries tend to promote more encounters between people from the same income group (bonding social capital). Findings such as these point to the need for developing a more granular understanding of specific types of social infrastructure to promote social cohesion. For example, growing evidence points to community gardens as an intervention to promote social cohesion and mental health[181].

Bridging social capital would also be enhanced by investing in public transit. Analysis of the travel behavior of 400,000 residents in America's 50 largest cities over a period of 18 months, based on over 650 million geocoded Twitter messages, revealed that residents of primarily Black and Hispanic neighborhoods are far less likely to visit middle-class neighborhoods, compared to residents of poor White neighborhoods[182]. This pattern reflects the underlying residential segregation of American neighborhoods, but also the need for cities to invest in affordable and convenient public transit to allow racial minority residents to visit localities (e.g., libraries, museums, parks) outside their own neighborhoods.

Interventions in schools

Schools usually offer a variety of programs with the goal of improving academic achievement or promoting student health (e.g., by seeking to increase physical activity), which may also have the collateral benefit of strengthening school social cohesion. Examples include after-school extra-curricular activities[183] (providing opportunities for students to participate in sports, clubs or other group activities to build relationships outside of the classroom); mentoring programs[184] (pairing older with younger students to provide guidance and support); and community service projects[185] (engaging students in collaborative projects that benefit the wider community).

Interventions that adopt a more intentional approach to strengthening school cohesion include family engagement initiatives, and positive school climate initiatives (implementing strategies to promote respect, inclusivity and positive interactions among students). With regard to engaging the families of schoolchildren, the role of parent-teacher organizations is often debated, because of their mixed effects on school social capital. Nonetheless, they may narrow inequalities in access to resources by generating social connections that bridge parents and children across disparate socioeconomic and racial backgrounds. Furthermore, some advantaged parents tend to use these networks to strengthen their bonding capital and to hoard opportunity.

In a qualitative case study of nine elementary schools in North Carolina[186], researchers identified the specific features of schools that succeeded in intentionally generating bridging social capital through their parent-teacher organizations. They found that successful schools were those that intentionally accommodated the diverse needs and interests of families within the school community. In these schools, leaders engaged in practices such as ensuring that school communications were available in multiple languages, and planning school events that reached across social boundaries[186].

An intervention specifically designed to foster family engagement was the Families and Schools Together (FAST)[187]. The program was premised on the theory that, for young children, social capital primarily functions through their parents, and therefore the goal was to establish connections between the parents of schoolchildren. Over 3,000 families participated in a cluster-randomized trial of 52 elementary schools. In the intervention schools, groups of families (called "hubs") took part in weekly meetings over 8 weeks. Each week, one family received a gift card to spend at a grocery store which they used to prepare a meal for all the other families. Parents supervised their children to serve the food and clean up after eating. Afterwards, the families played games with the children, sang together, and engaged in other activities that encouraged listening to each other, taking turns, and sharing feelings. According to the researchers, as families took turns providing meals for the entire FAST hub, they developed reciprocity in their relationships with each other, engendering trust across the social network.

Evaluation of the FAST program demonstrated that the intervention stimulated the development of social cohesion[187]. The score for social cohesion – a composite of reciprocity exchanges between parents, parents' perceptions of shared expectations with other parents, and inter-generational closure ("How many parents of your child's friends at the school do you know?") – increased by 0.52 standard deviations ($p<0.001$) in the intervention families. In the analysis of treatment compliers, the FAST intervention reduced internalizing behavior problems in children by 1.84 standard deviations ($p<0.001$). However, no significant changes were observed in children's externalizing behaviors.

Curriculum-based interventions represent a different avenue for building social cohesion. Alan et al[188] described an intervention involving the development of a curriculum targeted to build bridging social capital in ethnically diverse schools. A multidisciplinary team of educators, pedagogical consultants, and multimedia developers designed a set of curricular activities to develop children's ability to understand each others' perspectives and their capacity to make inferences about others' intentions, goals and motives. The cluster-randomized evaluation took place in a high stakes context (southeastern Turkey) where the ethnic composition of schools changed dramatically as a result of the influx of Syrian refugee children. The evaluation sample included over 6,500 school children, 16% of whom were refugees, from 80 elementary schools in Turkey. Teachers taught the curriculum for three hours per week over two years.

Results of the evaluation showed that treated children exhibited significantly more trust and reciprocity toward their classmates as well as toward anonymous peers outside of their schools. The program also succeeded in lowering the incidence of peer violence and victimization on school grounds. Over ten consecutive school days, about 1.9 violent events were perpetrated by children in the control group. This number was reduced by more than 60% in treatment schools ($p<0.01$). The program also reduced the probability of social exclusion, and increased the likelihood of forming inter-ethnic social ties. Overall, children in the treatment group

were about 6% more likely than untreated children to receive emotional support from their classmates. More specifically, the program increased the likelihood of refugee children in treated schools to receive emotional support from their classmates by 25%[188].

Lastly, interventions to increase inter-group contact have been advocated as a means of strengthening bridging social capital. An example is the National Citizen Service[189], a large scale government-funded program in England and Northern Ireland, focused on increasing inter-group contact between students from disparate ethnic backgrounds and building social cohesion among adolescents. Participants in the programme are drawn from the same region and organized into small, diverse teams who are set to work collaboratively in team- and skill-building activities over a period of 3-4 weeks. Based on a quasi-experimental pretest-posttest evaluation, it was found that the intervention reduced intergroup anxiety and increased outgroup perspective-taking, although it did not affect intergroup attitudes, intergroup trust, or perceptions of relative (dis-)advantage. Importantly, intervention effects were strongest for participants who had had fewer positive contact experiences before the intervention and who talked more about group differences during the intervention[189].

Interventions in workplaces

Intervention studies to date have yielded mixed results in increasing workplace social cohesion[190-193]. An important consideration is whether workplace interventions ought to target vertical social relations (i.e., respectful and trusting relationships between employees and supervisors at work) or horizontal social relations (i.e., trust and reciprocity between employees at the same hierarchical level)[194]. Evidence suggests that both vertical and horizontal social relations are independent predictors of mental health among workers, and therefore interventions should target both components[194]. A participatory approach to developing workplace interventions is recommended, because it increases the likelihood that proposed changes are appropriate and useful, based on employee knowledge of the organizational context, as well as enhancing the feeling of ownership and "buy in" from workers[192].

In a workplace social capital intervention implemented in six Danish dairy companies, Meng et al[192,193] adopted an intervention mapping approach. The five steps involved were: a) conducting workshops to identify problem areas in workplace social relations; b) conducting a needs assessment to identify targets for intervention; c) designing the intervention through brainstorming sessions involving workers and managers; d) implementing the intervention, including specifying a list of actions to be taken and assigning individuals responsible for taking action, and e) evaluating the intervention. Examples of actions taken in the dairy companies included steps to improve communications, developing a shared understanding of work tasks (e.g., by rotating job tasks between teams), and greater involvement of work teams in decision-making processes. After 20-month follow-up, moderately large increases in mean scores for workplace social cohesion and work engagement were found in the teams that had received the intervention compared to those that had not (Cohen's d = 0.5)[193].

Sometimes even participatory worksite interventions can fail because of low implementation fidelity. Framke et al[191] conducted a secondary data analysis of a cluster-randomized trial that was implemented among employees in 78 municipal Danish preschools. The original aim of the intervention was to improve employee well-being and reduce sickness absence. The intervention was not specifically designed to strengthen workplace social cohesion, but included several elements that may have affected it, including the establishment of steering groups consisting of a leader and two employee representatives who were tasked with enhancing workplace culture, improving communication and professional feedback; changes in allocation of overtime, work schedules and holiday schedules; and re-organization of staff meetings to advance professional reflection. Unexpectedly, at 24-month follow-up, workplace social cohesion declined in both the treatment and control groups, and the difference between the two groups was not statistically significant. However, roughly a third of the workplaces were found to have a low degree of implementation of the intervention. In post-hoc analysis, when workplaces with a low degree of implementation were excluded, there was a statistically significant difference between the intervention and the control group ($p = 0.049$), due to the fact that social cohesion decreased in the control group while it remained stable in the intervention group. Hence, the intervention failed to strengthen social cohesion, but instead seemed to put a brake on the decline in social cohesion over time (although caution is warranted in interpreting the results of post-hoc analysis)[191].

Other trials have indicated promise in strengthening workplace cohesion[195], but none of the foregoing studies focused on mental health outcomes. Hence, there is scope for mounting additional participatory workplace interventions to test whether they can be effective in improving workers' mental health.

Lastly, an example of a workplace intervention which did not directly target social cohesion but nonetheless produced carry-over effects on workplace social capital was reported by Andersen et al[196]. In their cluster-randomized trial, 200 female health care workers (nurses and nurses' aides) in Denmark were randomly allocated to 10 weeks of a) group-based physical exercise at work during working hours or b) physical exercise at home during leisure time. The results showed increased levels of social cohesion among individuals randomized to group-based physical exercise.

Critique of social cohesion/social capital interventions

An important limitation of social cohesion/social capital interventions summarized here is that they have all had relatively short follow-up durations. In a systematic review[197], the shortest follow-up period was 2 months and the longest was 42 months, with an average of 12.5 months. The short duration of observation means that we cannot establish whether any changes in mental health were sustained over the long term. More importantly, it takes time for social cohesion to be built. It is unrealistic to expect that trust or

norms of cooperation can be established within a group in a short period of time. The observational evidence on social cohesion and mental health presumably reflects years (possibly decades) of cumulative social interactions between members of a group. Therefore, we should not expect short-term interventions – especially interventions designed without a participatory approach – to move the needle on cohesion.

A second limitation of social cohesion/social capital interventions to date is that the majority of them have focused on individuals as the target of intervention, e.g., providing volunteering opportunities for individuals to become connected to the community, or home visitation programs to connect mothers with newborns to resources in the community[163]. Fewer interventions have sought to bring about collective change at the neighborhood, school or workplace level. An ideal intervention would target both individual and group level social connections, but such multi-level interventions are rarely seen[198].

A recurring theme in intervention studies is the importance of implementation fidelity, i.e., how well a program or intervention is carried out as intended. For example, Stjernqvist et al[199] conducted a participatory health education intervention which incorporated elements of strengthening school social capital. The intervention was designed to improve the dietary habits, physical activity, well-being and social capital among Danish school children aged 10-12 years. Pupils were provided opportunities to participate in the development of the program with their teachers, and the schools also established committees to oversee the intervention with representatives from school management, teachers and health staff. Unfortunately, after six months, multi-level analysis indicated no significant difference between the intervention and control groups for either horizontal or vertical social capital. Moreover, pupils from intervention schools were significantly *less* likely to report a higher sense of belonging in the school at follow-up compared with children at control schools (OR=0.54, 95% CI: 0.37-0.79). Reflecting back on the results, the researchers attributed the failure of the intervention to low implementation fidelity; specifically, insufficient commitment on the part of teachers and schools to take on board the voices of pupils[199].

A fourth significant limitation of studies is that they have paid insufficient heed to the social context of interventions. As Shiell et al [200] argued, "of all the different types of interventions one could employ to improve the health of the public, 'social capital' interventions are likely to be the most context specific". In other words, we cannot hope to intervene on social cohesion without an adequate understanding of the social context in which social relations are "created, maintained, distributed and mobilized"[200].

Finally, all studies of social cohesion report average treatment effects, but few studies have explicitly explored heterogeneous treatment effects. Social cohesion might be beneficial for those that are part of an in-group (e.g., White residents in a predominantly White neighborhood), but members of out-groups (e.g., racial minority residents) might be excluded from those benefits. Moreover, excessively powerful social cohesion itself can exert a negative influence on mental health for some individuals. There is a widely acknowledged "dark side" of social cohesion, including excessive demands for conformity and social exclusion of individuals who do not conform[201,202]. Standard regression approaches for estimating heterogeneous treatment effects are limited by testing a single effect modifier at a time and are subject to the problems of multiple comparisons. Advances in machine learning could assist in future studies to identify these effects[203]. The use of causal forests[204], an ensemble tree-based learning method, has been advocated as a way to detect as well as to estimate heterogeneous treatment effects using a data-driven approach. The goal is to identify particular subgroups – e.g., based on socioeconomic background, race/ethnicity, gender, age group, immigrant status, presence of disability – who may especially benefit from (or be harmed by) a given intervention.

In order for a social cohesion/social capital intervention to succeed, it needs to prospectively consider questions such as: Who will provide the resources and how will they be distributed in the community? Whose roles will be enhanced, or diminished, by the intervention, and what norms within the group will be reinforced by the intervention, or clash with it?[200] Taking these questions into consideration would assist intervention designers to anticipate and minimize the possible unintended consequences of strengthening social cohesion.

Carefully taking into account differences in local context also implies that there will be unavoidable heterogeneity in the types of interventions that result. Social cohesion/social capital interventions have been criticized because they are too scattered and lack uniformity; yet the line of argument introduced by Shiell et al[200] suggests that heterogeneity should be viewed as a feature of such interventions, not a bug.

CONCLUSIONS

The biomedical model of improving mental health is biased toward fixing deficits to restore people to health. After all, that is what health care providers are trained to do – fix people's complaints, such as feelings of loneliness or suffering from social isolation. At the policy level, decision makers are also apt to perceive greater urgency in addressing deficits, rather than expending resources on bolstering assets. In prevention efforts, there are more barriers to directing resources to communities (which is viewed as unfocused and inefficient) as opposed to targeting interventions that address the needs of individuals at greatest risk of mental disorder. Furthermore, investments to build community assets are likely to take a long time before rewards become evident, with the result that the payoff from interventions to strengthen social cohesion feels less palpable than expending resources to heal individuals with manifest disease. For all these reasons, attention to strengthening community assets – such as social cohesion – has lagged behind the expenditure of effort (in both the research and policy realms) directed toward addressing risk factors for mental disorder. Yet, as argued at the outset, addressing deficits without attending to assets is unlikely to suffice to attain a full state of mental well-being.

After nearly three decades of research, there is sufficient evi-

dence to justify a call for efforts to strengthen social cohesion – in communities, schools and workplaces – as a means to improve population mental health. Yet important gaps remain, as identified in this review. Improvements are needed in fundamental areas, starting with measurement – i.e., more consistency in the use of indicators to measure social cohesion, developing measures to capture bridging social capital, and enhancing the validity of multi-item instruments. Causal inference needs to be strengthened by moving beyond observational studies, or "business as usual", and taking advantage of natural experiments. We need more intervention studies that can demonstrate how to intentionally generate cohesion, and how they can be implemented at scale to improve population mental health. Last but not least, intervention trials are needed to better understand heterogeneous treatment effects, so that policies can be more effectively targeted to populations that benefit the most, whilst avoiding unintended consequences such as harming groups that are already burdened by providing support to others in their communities.

This review has identified several opportunities for future research. For example, even though workplace studies have examined whether interventions could lead to changes in social cohesion, few of them addressed the follow-up question of whether these changes led to improved mental health for employees. Similarly, the majority of school-based interventions to date have been conducted in the education field (outside public health) and, as a result, although all of them looked at social cohesion as an outcome, few of them examined impacts on children's mental health. Hence, there is scope for inter-disciplinary collaboration, given the evidence presented on the linkages between school cohesion and mental health among youth.

The US Surgeon General[205] recently called for increased attention to social connectedness as a public health issue. The bulk of attention is again focused on deficits (loneliness and social isolation), but this review reminds us that social cohesion is both an upstream driver of isolation and loneliness, as well as an independent determinant of mental health.

REFERENCES

1. Kirkbride JB, Anglin DM, Colman I et al. The social determinants of mental health and disorder: evidence, prevention and recommendations. World Psychiatry 2024;23:58-90.
2. Sampson L, Kubzansky LD, Koenen K. The missing piece: a population health perspective to address the U.S. mental health crisis. Daedalus 2023;152:24-44.
3. Holt-Lunstad J. Social connection as a critical factor for mental and physical health: evidence, trends, challenges, and future implications. World Psychiatry 2024;23:312-32.
4. Rose G. The strategy of preventive medicine. Oxford: Oxford University Press, 1992.
5. Harrison D, Ziglio E, Levin L et al. Assets for health and development: developing a conceptual framework. European Office for Investment for Health and Development. Venice: World Health Organization, 2004.
6. Kawachi I. The relationship between health assets, social capital and cohesive communities. In: Morgan A, Davies M, Ziglio E (eds). Health assets in a global context: theory, methods, action. New York: Springer, 2010:167-79.
7. Kawachi I, Berkman LF. Social ties and mental health. J Urban Health 2001; 78:458-67.
8. Moore S, Kawachi I. Twenty years of social capital and health research: a glossary. J Epidemiol Community Health 2017;71:513-7.
9. Kawachi I, Berkman LF. Social capital, social cohesion, and health. In: Berkman LF, Kawachi I, Glymour MM (eds). Social epidemiology, 2nd ed. New York: Oxford University Press, 2014:290-319.
10. Miller HN, Thornton CP, Rodney T et al. Social cohesion in health: a concept analysis. Adv Nurs Sci 2020;43:375-90.
11. Kawachi I. Social capital and health. In: Bird CE, Conrad P, Fremont AM et al (eds). Handbook of medical sociology, 6th ed. Nashville: Vanderbilt University Press, 2010:18-32.
12. Almedom AM. Social capital and mental health: an interdisciplinary review of primary evidence. Soc Sci Med 2005;61:943-64.
13. Kawachi I. Trust and population health. In: Uslaner EM (ed). The Oxford handbook of social and political trust. New York: Oxford University Press, 2018:447-70.
14. Hunter RF, Cleland C, Cleary A et al. Environmental, health, wellbeing, social and equity effects of urban green space interventions: a meta-narrative evidence synthesis. Environ Int 2019;130:104923.
15. Earls F, Carlson M. Voice, choice, and action. Cambridge: Belknap, 2020.
16. Magro-Montañés B, Pabón-Carrasco M, Romero-Castillo R et al. The relationship between neighborhood social capital and health from a biopsychosocial perspective: a systematic review. Public Health Nurs 2024;41:845-61.
17. Virtanen M, Ervasti J, Oksanen T et al. Social capital in schools. In: Kawachi I, Takao S, Subramanian SV (eds). Global perspectives on social capital and health. New York: Springer, 2013:65-86.
18. Oksanen T, Suzuki E, Takao S et al. Workplace social capital and health. In: Kawachi I, Takao S, Subramanian SV (eds). Global perspectives on social capital and health. New York: Springer, 2013:23-64.
19. Oberndorfer M, Dorner TE, Leyland AH et al. The challenges of measuring social cohesion in public health research: a systematic review and ecometric meta-analysis. SSM Popul Health 2022;17:101028.
20. Buckner J. The development of an instrument to measure neighborhood cohesion. Am J Commun Psychol 1988;16:771-91.
21. Sampson RJ, Raudenbush SW, Earls F. Neighborhoods and violent crime: a multilevel study of collective efficacy. Science 1997;277:918-24.
22. Harpham T. The measurement of community social capital through surveys. In: Kawachi I, Subramanian SV, Kim D (eds). Social capital and health. Springer: New York, 2008:51-62.
23. Rodgers J, Valuev AV, Hswen Y et al. Social capital and physical health: an updated review of the literature for 2007-2018. Soc Sci Med 2019;236:112360.
24. Baranyi G, Sieber S, Cullati S et al. The longitudinal associations of perceived neighborhood disorder and lack of social cohesion with depression among adults aged 50 years or older: an individual-participant-data meta-analysis from 16 high-income countries. Am J Epidemiol 2020;189:343-53.
25. Ehsan AM, De Silva MJ. Social capital and common mental disorder: a systematic review. J Epidemiol Community Health 2015;69:1021-8.
26. De Silva MJ, McKenzie K, Harpham T et al. Social capital and mental illness: a systematic review. J Epidemiol Community Health 2005;59:619-27.
27. Fone D, White J, Farewell D et al. Effect of neighbourhood deprivation and social cohesion on mental health inequality: a multilevel population-based longitudinal study. Psychol Med 2014;44:2449-60.
28. Fone DL, Farewell DM, Dunstan FD. An ecometric analysis of neighbourhood cohesion. Popul Health Metr 2006;4:1-17.
29. Raudenbush SW. The quantitative assessment of neighborhood social environments. In: Kawachi I, Berkman LF (eds). Neighborhoods and health. New York: Oxford University Press, 2003:112-31.
30. Hamano T, Fujisawa Y, Ishida Y et al. Social capital and mental health in Japan: a multilevel analysis. PLoS One 2010;5:e13214.
31. Mohnen SM, Völker B, Flap H et al. The influence of social capital on individual health: is it the neighbourhood or the network? Soc Indic Res 2014;121:195-214.
32. Morozumi R, Matsumura K, Hamazaki K et al. Impact of individual and neighborhood social capital on the physical and mental health of pregnant women: the Japan Environment and Children's Study (JECS). BMC Pregnancy Childbirth 2020;20:450.
33. Ehsan A, Klaas HS, Bastianen A et al. Social capital and health: a systematic review of systematic reviews. SSM Popul Health 2019;8:100425.
34. Carpiano RM, Hystad PW. "Sense of community belonging" in health surveys: what social capital is it measuring? Health Place 2011;17:606-17.
35. Tsai AC, Lucas M, Kawachi I. Association between social integration and suicide among women in the United States. JAMA Psychiatry 2015;72:987-93.
36. Tsai AC, Lucas M, Sania A et al. Social integration and suicide mortality among men: 24-year cohort study of U.S. health professionals. Ann Intern Med 2014; 161:85-95.
37. Fisher LB, Overholser JC, Ridley J et al. From the outside looking in: sense of belonging, depression, and suicide risk. Psychiatry 2015;78:29-41.

38. Durkheim E. Suicide. New York: Free Press, 1951.
39. Kushner HI, Sterk CE. The limits of social capital: Durkheim, suicide, and social cohesion. Am J Public Health 2005;95:1139-43.
40. Kim J, Park MJ. Multilevel effect of neighborhood social cohesion and characteristics on suicidal ideation among Korean older adults. Community Ment Health J 2021;57:522-8.
41. Noguchi M, Kobayashi T, Iwase T et al. Social capital and suicidal ideation in community-dwelling older residents: a multilevel analysis of 10,094 subjects in Japan. Am J Geriatr Psychiatry 2017;25:37-47.
42. Maimon D, Browning CR, Brooks-Gunn J. Collective efficacy, family attachment, and urban adolescent suicide attempts. J Health Soc Behav 2010;51:307-24.
43. Lee JH. Relationships between neighborhood collective efficacy and adolescent suicidal ideation. J Adolesc 2021;93:10-9.
44. Rotenberg M, Anderson KK, McKenzie K. Social capital and psychosis: a scoping review. Soc Psychiatry Psychiatr Epidemiol 2020;55:659-71.
45. Kirkbride JB, Morgan C, Fearon P et al. Neighbourhood-level effects on psychoses: re-examining the role of context. Psychol Med 2007;37:1413-25.
46. Lofors J, Sundquist K. Low-linking social capital as a predictor of mental disorders: a cohort study of 4.5 million Swedes. Soc Sci Med 2007;64:21-34.
47. Drukker M, Krabbendam L, Driessen G et al. Social disadvantage and schizophrenia. A combined neighbourhood and individual-level analysis. Soc Psychiatry Psychiatr Epidemiol 2006;41:595-604.
48. Kirkbride JB, Boydell J, Ploubidis GB et al. Testing the association between the incidence of schizophrenia and social capital in an urban area. Psychol Med 2008;38:1083-94.
49. Rotenberg M, Tuck A, Anderson KK et al. Neighbourhood-level social capital, marginalisation, and the incidence of schizophrenia and schizoaffective disorder in Toronto, Canada: a retrospective population-based cohort study. Psychol Med 2023;53:2643-51.
50. Binbay T, Drukker M, Alptekin K et al. Evidence that the wider social environment moderates the association between familial liability and psychosis spectrum outcome. Psychol Med 2012;42:2499-510.
51. Xue X, Reed WR, Menclova A. Social capital and health: a meta-analysis. J Health Econ 2020;72:102317.
52. Doll R. Weak associations in epidemiology: importance, detection and interpretation. J Epidemiol 1996;6:S11-20.
53. Stafoggia M, Michelozzi P, Schneider A et al. Joint effect of heat and air pollution on mortality in 620 cities of 36 countries. Environ Int 2023;181:108258.
54. Smith RW, Holt-Lunstad J, Kawachi I. Benchmarking social isolation, loneliness, and smoking: challenges and opportunities for public health. Am J Epidemiol 2023;192:1238-42.
55. Qin W, Nicklett EJ, Yu J et al. Neighborhood social cohesion and physical disorder in relation to social isolation in older adults: racial and ethnic differences. BMC Public Health 2024;24:2574.
56. Sampson RJJ, Wilson WJ. Great American City: Chicago and the enduring neighborhood effect. Chicago: University of Chicago Press, 2012.
57. Baranyi G, Di Marco MH, Russ TC et al. The impact of neighbourhood crime on mental health: a systematic review and meta-analysis. Soc Sci Med 2021;282:114106.
58. Cradock AL, Kawachi I, Colditz GA et al. Neighborhood social cohesion and youth participation in physical activity in Chicago. Soc Sci Med 2009;68:427-35.
59. Yip C, Sarma S, Wilk P. The association between social cohesion and physical activity in Canada: a multilevel analysis. SSM Popul Health 2016;2:718-23.
60. Gehris JS, Oyeyemi AL, Baishya ML et al. The role of physical activity in the relationship between exposure to community violence and mental health: a systematic review. Prev Med Rep 2023;36:102509.
61. Blanner Kristiansen C, Kjær JN, Hjorth P et al. Prevalence of common mental disorders in widowhood: a systematic review and meta-analysis. J Affect Disord 2019;245:1016-23.
62. Wu D, Liu F, Huang S. Assessment of the relationship between living alone and the risk of depression based on longitudinal studies: a systematic review and meta-analysis. Front Psychiatry 2022;13:954857.
63. Nakagomi A, Shiba K, Hanazato M et al. Does community-level social capital mitigate the impact of widowhood & living alone on depressive symptoms?: A prospective, multi-level study. Soc Sci Med 2020;259:113140.
64. Kingsbury M, Clayborne Z, Colman I et al. The protective effect of neighbourhood social cohesion on adolescent mental health following stressful life events. Psychol Med 2020;50:1292-9.
65. Jonsson KR, Busfield J, Södergren M et al. Social capital, deprivation and psychological well-being among young adolescents: a multilevel study from England and Wales. Int J Environ Res Public Health 2020;17:3420.
66. Kawachi I, Aida J, Hikichi H et al. Disaster resilience in aging populations: lessons from the 2011 Great East Japan Earthquake & Tsunami. J R Soc N Z 2020;50:263-78.
67. Aldrich DP. Building resilience: social capital in post-disaster recovery. Chicago: University of Chicago Press, 2012.
68. Tierney K. Disasters: a sociological approach. Medford: Polity, 2019.
69. Norris FH, Galea S, Friedman MJ et al (eds). Methods for disaster mental health research. New York: Guilford, 2006.
70. Van Griensven F, Chakkraband MS, Thienkrua W et al. Mental health problems among adults in tsunami-affected areas in southern Thailand. JAMA 2006;296:537-48.
71. Kumar MS, Murhekar MV, Hutin Y et al. Prevalence of posttraumatic stress disorder in a coastal fishing village in Tamil Nadu, India, after the December 2004 tsunami. Am J Public Health 2007;97:99-101.
72. Frankenberg E, Friedman J, Gillespie T et al. Mental health in Sumatra after the tsunami. Am J Public Health 2008;98:1671-7.
73. Hall CE, Wehling H, Stansfield J et al. Examining the role of community resilience and social capital on mental health in public health emergency and disaster response: a scoping review. BMC Public Health 2023;23:2482.
74. Hikichi H, Aida J, Tsuboya T et al. Can community social cohesion prevent posttraumatic stress disorder in the aftermath of a disaster? A natural experiment from the 2011 Tohoku earthquake and tsunami. Am J Epidemiol 2016;183:902-10.
75. Xiong J, Lipsitz O, Nasri F et al. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. J Affect Disord 2020;277:55-64.
76. Butterworth P, Schurer S, Trinh TA et al. Effect of lockdown on mental health in Australia: evidence from a natural experiment analysing a longitudinal probability sample survey. Lancet Public Health 2022;7:e427-36.
77. Borgonovi F, Andrieu E. Bowling together by bowling alone: social capital and COVID-19. Soc Sci Med 2020;265:113501.
78. Slater G. The effects of social capital deprivation for wellbeing: evidence from the Covid-19 pandemic. Econ Hum Biol 2024;54:101395.
79. Laurence J. Explaining the pathways through which social capital buffered mental health during the COVID-19 pandemic: a longitudinal analysis. J Affect Disord 2025;373:403-11.
80. Kawachi I, Ransome Y. Social capital, social cohesion, and COVID-19. In: Duncan DT, Kawachi I, Morse SS (eds). The social epidemiology of the COVID-19 pandemic. New York: Oxford University Press, 2024:363-94.
81. Naito Y, Ohta R, Sano C. Solving social problems in aging rural Japanese communities: the development and sustainability of the Osekkai Conference as a social prescribing during the COVID-19 pandemic. Int J Environ Res Public Health 2021;18:11849.
82. Ohta R, Yata A. The revitalization of "Osekkai": how the COVID-19 pandemic has emphasized the importance of Japanese voluntary social work. Qual Soc Work 2021;20:423-32.
83. Ohta R, Yata A, Arakawa Y et al. Rural social participation through Osekkai during the COVID-19 pandemic. Int J Environ Res Public Health 2021;18:5924.
84. Nakagawa Y, Shaw R. Social capital: a missing link to disaster recovery. Int J Mass Emerg Disasters 2004;22:5-34.
85. Breedvelt JJF, Tiemeier H, Sharples E et al. The effects of neighbourhood social cohesion on preventing depression and anxiety among adolescents and young adults: rapid review. BJPsych Open 2022;8:e97.
86. Kim ES, Wilkinson R, Case BW et al. Connected communities: perceived neighborhood social cohesion during adolescence and subsequent health and well-being in young adulthood – An outcome-wide longitudinal approach. J Community Psychol 2024;52:774-91.
87. VanderWeele TJ, Mathur MB, Chen Y. Outcome-wide longitudinal designs for causal inference: a new template for empirical studies. Stat Sci 2020;25:437-66.
88. Newbury J, Arseneault L, Caspi A et al. Why are children in urban neighborhoods at increased risk for psychotic symptoms? Findings from a UK longitudinal cohort study. Schizophr Bull 2016;42:1372-83.
89. Solmi F, Colman I, Weeks M et al. Trajectories of neighborhood cohesion in childhood, and psychotic and depressive symptoms at age 13 and 18 years. J Am Acad Child Adolesc Psychiatry 2017;56:570-7.
90. Morrow V. Conceptualising social capital in relation to the well-being of children and young people: a critical review. Sociol Rev 1999;47:744-65.
91. Veerman GJ, Denessen E. Social cohesion in schools: a non-systematic review of its conceptualization and instruments. Cogent Educ 2021;8:1940633.
92. Hirota T, Adachi M, Takahashi M et al. Cross-cultural adaptation and psychometric properties of the Social Capital Questionnaire for Adolescent Students among preadolescents and adolescents in Japan. Psychiatry Clin Neurosci 2019;73:601-2.

93. Mori H, Takahashi M, Adachi M et al. The association of social capital with depression and quality of life in school-aged children. PLoS One 2022;17: e0262103.
94. Carrillo-Álvarez E, Villalonga-Olives E, Riera-Romaní J et al. Development and validation of a questionnaire to measure family social capital. SSM Popul Health 2019;8:100453.
95. Nielsen L, Koushede V, Vinther-Larsen M et al. Does school social capital modify socioeconomic inequality in mental health? A multi-level analysis in Danish schools. Soc Sci Med 2015;140:35-43.
96. Sakai-Bizmark R, Richmond TK, Kawachi I et al. School social capital and tobacco experimentation among adolescents: evidence from a cross-classified multilevel, longitudinal analysis. J Adolesc Health 2020;66:431-8.
97. Subramanian SV, Jones K, Duncan C. Multilevel models for public health research. In: Kawachi I, Berkman LF (eds). Neighborhoods and health. New York: Oxford University Press, 2003:65-111.
98. Takakura M, Miyagi M, Ueji M et al. The relative association of collective efficacy in school and neighborhood contexts with adolescent alcohol use. J Epidemiol 2019;29:384-90.
99. Nikunlaakso R, Reuna K, Oksanen T et al. Associations between accumulating job stressors, workplace social capital, and psychological distress on work-unit level: a cross-sectional study. BMC Public Health 2023;23:1559.
100. Oshio T, Inoue A, Tsutsumi A. The mediating and moderating effects of workplace social capital on the associations between adverse work characteristics and psychological distress among Japanese workers. Ind Health 2014;52:313-23.
101. Inoue A, Kawakami N, Eguchi H et al. Buffering effect of workplace social capital on the association of job insecurity with psychological distress in Japanese employees: a cross-sectional study. J Occup Health 2016;58:460-9.
102. Nakahori N, Sekine M, Tatsuse T et al. Effect modification by workplace social capital on the association between depression and workplace and family stress: the Japanese civil servant study. BMC Public Health 2021;21:726.
103. Berthelsen H, Owen M, Westerlund H. Does workplace social capital predict care quality through job satisfaction and stress at the clinic? A prospective study. BMC Public Health 2021;21:1320.
104. Clausen T, Meng A, Borg V. Does social capital in the workplace predict job performance, work engagement, and psychological well-being? A prospective analysis. J Occup Environ Med 2019;61:800-5.
105. Fujita S, Kawakami N, Ando E et al. The association of workplace social capital with work engagement of employees in health care settings: a multilevel cross-sectional analysis. J Occup Environ Med 2016;58:265-71.
106. Zhang H, Sun L, Zhang Q. How workplace social capital affects turnover intention: the mediating role of job satisfaction and burnout. Int J Environ Res Public Health 2022;19:9587.
107. Iida M, Watanabe K, Ando E et al. The association between unit-level workplace social capital and intention to leave among employees in health care settings: a cross-sectional multilevel study. J Occup Environ Med 2020;62:e186-91.
108. Pihl P, Albertsen K, Hogh A et al. Social capital and workplace bullying. Work 2017;57:535-45.
109. Murayama H, Nonaka K, Hasebe M et al. Workplace and community social capital and burnout among professionals of health and welfare services for the seniors: a multilevel analysis in Japan. J Occup Health 2020;62:e12177.
110. Kouvonen A, Kivimaki M, Vahtera J et al. Psychometric evaluation of a short measure of social capital at work. BMC Public Health 2006;6:251.
111. Eguchi H, Tsutsumi A, Inoue A et al. Psychometric assessment of a scale to measure bonding workplace social capital. PLoS One 2017;12:e0179461.
112. Berthelsen H, Westerlund H, Pejtersen JH et al. Construct validity of a global scale for workplace social capital based on COPSOQ III. PLoS One 2019; 14:e0221893.
113. Idrovo AJ, Camacho-Avila A, García-Rivas J et al. Social capital at work: psychometric analysis of a short scale in Spanish among Mexican health workers. Rev Bras Epidemiol 2012;15:536-47.
114. Kouvonen A, Oksanen T, Vahtera J et al. Low workplace social capital as a predictor of depression: the Finnish Public Sector Study. Am J Epidemiol 2008;167:1143-51.
115. Gao J, Weaver SR, Dai J et al. Workplace social capital and mental health among Chinese employees: a multi-level, cross-sectional study. PLoS One 2014;9:e85005.
116. Eguchi H, Tsutsumi A, Inoue A et al. Association of workplace social capital with psychological distress: results from a longitudinal multilevel analysis of the J-HOPE Study. BMJ Open 2018;8:e022569.
117. Jensen JH, Flachs EM, Török E et al. Work-unit social capital and incident purchase of psychotropic medications: a longitudinal cohort-study of healthcare workers. J Affect Disord 2020;276:53-61.
118. Jung J, Ernstmann N, Nitzsche A et al. Exploring the association between social capital and depressive symptoms: results of a survey in German information and communication technology companies. J Occup Environ Med 2012;54:23-30.
119. Pattussi MP, Olinto MT, Canuto R et al. Workplace social capital, mental health and health behaviors among Brazilian female workers. Soc Psychiatry Psychiatr Epidemiol 2016;51:1321-30.
120. Tsuboya T, Tsutsumi A, Kawachi I. Change in psychological distress following change in workplace social capital: results from the panel surveys of the J-HOPE study. Occup Environ Med 2015;72:188-94.
121. Cagney KA, Wen M. Social capital and aging-related outcomes. In: Kawachi I, Subramanian SV, Kim D (eds). Social capital and health. New York: Springer, 2008:239-58.
122. Cannuscio C, Block J, Kawachi I. Social capital and successful aging: the role of senior housing. Ann Intern Med 2003;139:395-9.
123. Forsman AK, Herberts C, Nyqvist F et al. Understanding the role of social capital for mental wellbeing among older adults. Ageing Soc 2013;33:804-25.
124. Jenkinson CE, Dickens AP, Jones K et al. Is volunteering a public health intervention? A systematic review and meta-analysis of the health and survival of volunteers. BMC Public Health 2013;13:773.
125. Davies B, Abrams D, Horsham Z et al. The causal relationship between volunteering and social cohesion: a large scale analysis of secondary longitudinal data. Soc Indic Res 2024;171:809-25.
126. Nyqvist F, Forsman AK, Giuntoli G et al. Social capital as a resource for mental well-being in older people: a systematic review. Aging Ment Health 2013; 17:394-410.
127. Cao W, Li L, Zhou X et al. Social capital and depression: evidence from urban elderly in China. Aging Ment Health 2015;19:418-29.
128. Lu N, Peng C. Community-based structural social capital and depressive symptoms of older urban Chinese adults: the mediating role of cognitive social capital. Arch Gerontol Geriatr 2019;82:74-80.
129. Norstrand JA, Xu Q. Social capital and health outcomes among older adults in China: the urban-rural dimension. Gerontologist 2011;52:325-34.
130. Ziersch AM, Baum F, Darmawan IG et al. Social capital and health in rural and urban communities in South Australia. Aust N Z J Public Health 2009;33:7-16.
131. Lu S, Guo Y, Chui C et al. Neighborhood environment and mental well-being among Chinese older adults: the mediating role of social capital. Innov Aging 2022;6:igac070.
132. Mao S, Lu N, Xiao C. Perceived neighborhood environment and depressive symptoms among older adults living in urban China: the mediator role of social capital. Health Soc Care Community 2022;30:e1977-90.
133. Kim ES, Chen Y, Kawachi I et al. Perceived neighborhood social cohesion and subsequent health and well-being in older adults: an outcome-wide longitudinal approach. Health Place 2020;66:102420.
134. Berrío AI, Gómez-Benito J, Arias-Patiño EM. Developments and trends in research on methods of detecting differential item functioning. Educ Res Rev 2023;31:100340.
135. Villalonga-Olives E, Majercak KR, Wang W et al. Different responses to social capital among Black people and White people: what racial differential item functioning reveals for racial health equity. Am J Epidemiol 2023;192:1264-73.
136. Gilbert KL, Ransome Y, Dean LT et al. Social capital, Black social mobility, and health disparities. Annu Rev Public Health 2022;43:173-91.
137. Osterling KL. Social capital and neighborhood poverty: toward an ecologically-grounded model of neighborhood effects. J Hum Behav Soc Environ 2007;16:123-47.
138. Caughy MO, O'Campo PJ, Muntaner C. When being alone might be better: neighborhood poverty, social capital, and child mental health. Soc Sci Med 2003;57:227-37.
139. Narayan D. Bonds and bridges: social capital and poverty. In: Isham J, Kelly T, Ramaswamy S (eds). Social capital and economic development. Cheltenham: Elgar, 1999:58-82.
140. Villalonga-Olives E, Kawachi I. The measurement of bridging social capital in population health research. Health Place 2015;36:47-56.
141. Derr AS. Mental health service use among immigrants in the United States: a systematic review. Psychiatr Serv 2016;67:265-74.
142. Gong S, Xu P, Wang S. Social capital and psychological well-being of Chinese immigrants in Japan. Int J Environ Res Public Health 2021;18:547.
143. Salvatore MA, Grundy E. Area deprivation, perceived neighbourhood cohesion and mental health at older ages: a cross lagged analysis of UK longitudinal data. Health Place 2021;67:102470.
144. Prati G. Within-person, longitudinal associations between neighborhood cohesion and adult mental health: a test of bidirectional relations. Int J Soc Psy-

chiatry 2025;71:575-84.
145. Gunasekara FI, Richardson K, Carter K et al. Fixed effects analysis of repeated measures data. Int J Epidemiol 2014;43:264-9.
146. Oshio T. The association between individual-level social capital and health: cross-sectional, prospective cohort and fixed-effects models. J Epidemiol Community Health 2016;70:25-30.
147. Oakes JM. The (mis)estimation of neighborhood effects: causal inference for a practicable social epidemiology. Soc Sci Med 2004;58:1929-52.
148. Duncan DT, Kawachi I (eds). Neighborhoods and health, 2nd ed. New York: Oxford University Press, 2018.
149. Hamad R, Öztürk B, Foverskov E et al. Association of neighborhood disadvantage with cardiovascular risk factors and events among refugees in Denmark. JAMA Netw Open 2020;3:e2014196.
150. Foverskov E, White JS, Norredam M et al. Neighbourhood socioeconomic disadvantage and psychiatric disorders among refugees: a population-based, quasi-experimental study in Denmark. Soc Psychiatry Psychiatr Epidemiol 2023;58:711-21.
151. Shiba K, Yazawa A, Kino S et al. Depressive symptoms in the aftermath of major disaster: empirical test of the social support deterioration model using natural experiment. Wellb Space Soc 2020;1:100006.
152. Sato K, Amemiya A, Haseda M et al. Postdisaster changes in social capital and mental health: a natural experiment from the 2016 Kumamoto earthquake. Am J Epidemiol 2020;189:910-21.
153. Fujii S, Kato H, Maeda K. A simple interview-format screening measure for disaster mental health: an instrument newly developed after the 1995 Great Hanshin Earthquake in Japan – the Screening Questionnaire for Disaster Mental Health (SQD). Kobe J Med Sci 2008;53:375-85.
154. Shadish WR, Cook TD, Campbell DT. Experimental and quasi-experimental designs for generalized causal inference. Boston: Houghton Mifflin, 2002.
155. Gero K, Aida J, Kondo K et al. Evaluation of trust within a community after survivor relocation following the Great East Japan Earthquake and Tsunami. JAMA Netw Open 2020;3:e2021166.
156. Fried LP, Carlson MC, Freedman M et al. A social model for health promotion for an aging population: initial evidence on the Experience Corps model. J Urban Health 2004;81:64-78.
157. Gruenewald TL, Tanner EK, Fried LP et al. The Baltimore Experience Corps Trial: enhancing generativity via intergenerational activity engagement in later life. J Gerontol Ser B Psychol Sci Soc Sci 2015;71:1-10.
158. Yasunaga M, Murayama Y, Takahashi T et al. Multiple impacts of an intergenerational program in Japan: evidence from the Research on Productivity through Intergenerational Sympathy Project. Geriatr Gerontol Int 2016;1(Suppl. 1):98-109.
159. Griffiths R, Horsfall J, Moore M et al. Building social capital with women in a socially disadvantaged community. Int J Nurs Pract 2009;15:172-84.
160. Pronyk PM, Harpham T, Busza J et al. Can social capital be intentionally generated? A randomized trial from rural South Africa. Soc Sci Med 2008;67:1559-70.
161. Fujiwara T, Natsume K, Okuyama M et al. Do home-visit programs for mothers with infants reduce parenting stress and increase social capital in Japan? J Epidemiol Community Health 2012;66:1167-76.
162. Villalonga-Olives E, Wind TR, Armand AO et al. Social-capital-based mental health interventions for refugees: a systematic review. Soc Sci Med 2022;301:114787.
163. Villalonga-Olives E, Wind TR, Kawachi I. Social capital interventions in public health: a systematic review. Soc Sci Med 2018;212:203-18.
164. Dolan N, Sherlock C. Family support through childcare services: meeting the needs of asylum-seeking and refugee families. Child Care Pract 2010;16:147-65.
165. Im H, Rosenberg R. Building social capital through a peer-led community health workshop: a pilot with the Bhutanese refugee community. J Community Health 2016;41:509-17.
166. Garland C, Hume F, Majid S. Remaking connections: refugees and the development of "emotional capital" in therapy groups. Psychoanal Psychother 2002;16:197-214.
167. Logie CH, Lacombe-Duncan A, Lee-Foon N et al. "It's for us - newcomers, LGBTQ persons, and HIV-positive persons. You feel free to be": a qualitative study exploring social support group participation among African and Caribbean lesbian, gay, bisexual and transgender newcomers and refugees in Toronto, Canada. BMC Int Health Hum Right 2016;16:18.
168. Ibrahim N, Honein-AbouHaidar G, Jomaa L. Perceived impact of community kitchens on the food security of Syrian refugees and kitchen workers in Lebanon: qualitative evidence in a displacement context. PLoS One 2019;14:e0210814.
169. Michael YL, Farquhar SA, Wiggins N et al. Findings from a community-based participatory prevention research intervention designed to increase social capital in Latino and African American communities. J Immigr Minor Health 2008;10:281-9.
170. Minkler M, Chang C. Engaging communities in participatory research and action. In: Kawachi I, Lang I, Ricciardi W (eds). Oxford handbook of public health practice, 4th ed. Oxford: Oxford University Press, 2020:218-30.
171. Marisa Y, Halapy E, Dunn JR. Effect of a neighbourhood intervention on social cohesion in Hamilton, Ontario, Canada. Wellb Space Soc 2024;7:100217.
172. Semenza JC, March TL, Bontempo BD. Community-initiated urban development: an ecological intervention. J Urban Health 2007;84:8-20.
173. Shen C, Wan A, Kwok LT et al. A community based intervention program to enhance neighborhood cohesion: the Learning Families Project in Hong Kong. PLoS One 2017;12:e0182722.
174. Greene G, Fone D, Farewell D et al. Improving mental health through neighbourhood regeneration: the role of cohesion, belonging, quality and disorder. Eur J Public Health 2020;30:964-66.
175. Klinenberg E. Palaces for the people: how social infrastructure can help fight inequality, polarization, and the decline of civic life. New York: Crown, 2018.
176. Ichida Y, Hirai H, Kondo K et al. Does social participation improve self-rated health in the older population? A quasi-experimental intervention study. Soc Sci Med 2013;94:83-90.
177. Hikichi H, Kondo N, Kondo K et al. Effect of a community intervention programme promoting social interactions on functional disability prevention for older adults: propensity score matching and instrumental variable analyses, JAGES Taketoyo study. J Epidemiol Community Health 2015;69:905-10.
178. Clarke JJ, Haslam SA, Sharman LS et al. Leading by example: identity leadership and mental health in Men's Sheds members. J Appl Gerontol 2024;44:815-24.
179. Wood L, Martin K, Christian H et al. Social capital and pet ownership – A tale of four cities. SSM Popul Health 2017;3:442-7.
180. Fraser T, Yabe T, Aldrich DP et al. The great equalizer? Mixed effects of social infrastructure on diverse encounters in cities. Comput Environ Urban Syst 2024;113:102173.
181. Briggs R, Morris PG, Rees K. The effectiveness of group-based gardening interventions for improving wellbeing and reducing symptoms of mental ill-health in adults: a systematic review and meta-analysis. J Ment Health 2023;32:787-804.
182. Wang Q, Phillips NE, Small ML et al. Urban mobility and neighborhood isolation in America's 50 largest cities. Proc Natl Acad Sci USA 2018;115:7735-40.
183. Acar E, Yigit MF. Beyond the classroom: exploring the relationship between extracurriculars, social capital, and academic achievement. J Educ Practice 2023;14:101-7.
184. Shier ML, Gouthro S, de Goias R. The pursuit of social capital among adolescent high school aged girls: the role of formal mentor-mentee relationships. Child Youth Serv Rev 2018;93:276-82.
185. Koliba CJ. Generating social capital in schools through service-learning. Acad Exch Q 2003;7:336-46.
186. Murray B, Domina T, Petts A et al. "We're in this together": bridging and bonding social capital in elementary school PTOs. Am Educ Res J 2020;57:2210-44.
187. Turley RNL, Gamoran A, McCarty AT et al. Reducing children's behavior problems through social capital: a causal assessment. Soc Sci Res 2017;61:206-17.
188. Alan S, Baysan C, Gumren M et al. Building social cohesion in ethnically mixed schools: an intervention on perspective taking. CESifo Working Papers 2020:8754.
189. Reimer NK, Love A, Wölfer R et al. Building social cohesion through intergroup contact: evaluation of a large-scale intervention to improve intergroup relations among adolescents. J Youth Adolesc 2021;50:1049-67.
190. Sun X, Zhang N, Liu K et al. Effects of a randomized intervention to improve workplace social capital in community health centers in China. PLoS One 2014;9:e114924.
191. Framke E, Sørensen OH, Pedersen J et al. Effect of a participatory organizational workplace intervention on workplace social capital: post-hoc results from a cluster randomized controlled trial. BMC Public Health 2019;19:693.
192. Meng A, Borg V, Clausen T. Enhancing the social capital in industrial workplaces: developing workplace interventions using intervention mapping. Eval Program Plann 2019;72:227-36.
193. Meng A, Borg V, Clausen T. Enhancing the social capital in industrial work teams: results from a participatory intervention. Ind Health 2020;58:433-42.
194. Oksanen T, Kouvonen A, Vahtera J et al. Prospective study of workplace social capital and depression: are vertical and horizontal components equally important? J Epidemiol Community Health 2010;64:684-9.
195. Jakobsen MD, Clausen T, Andersen LL. Can a participatory organizational

intervention improve social capital and organizational readiness to change? Cluster randomized controlled trial at five Danish hospitals. J Adv Nurs 2020; 76:2685-95.
196. Andersen LL, Poulsen OM, Sundstrup E et al. Effect of physical exercise on workplace social capital: cluster randomized controlled trial. Scand J Public Health 2015;43:810-8.
197. Flores EC, Fuhr DC, Bayer AM et al. Mental health impact of social capital interventions: a systematic review. Soc Psychiatry Psychiatr Epidemiol 2018; 53:107-19.
198. Schölmerich VL, Kawachi I. Translating the socio-ecological perspective into multilevel interventions: gaps between theory and practice. Health Educ Behav 2016;43:17-20.
199. Stjernqvist NW, Sabinsky M, Morgan A et al. Building school-based social capital through 'We Act - Together for Health' – a quasi-experimental study. BMC Public Health 2018;18:1141.
200. Shiell A, Hawe P, Kavanagh S. Evidence suggests a need to rethink social capital and social capital interventions. Soc Sci Med 2020;257:111930.
201. Portes A. Downsides of social capital. Proc Natl Acad Sci USA 2014;111:18407-8.
202. Villalonga-Olives E, Kawachi I. The dark side of social capital: a systematic review of the negative health effects of social capital. Soc Sci Med 2017;194:105-27.
203. Kino S, Hsu YT, Shiba K et al. A scoping review on the use of machine learning in research on social determinants of health: trends and research prospects. SSM Popul Health 2021;15:100836.
204. Jawadekar N, Kezios K, Odden MC et al. Practical guide to honest causal forests for identifying heterogeneous treatment effects. Am J Epidemiol 2023; 192:1155-65.
205. Office of the US Surgeon General. Our epidemic of loneliness and isolation: the US Surgeon General's Advisory on the healing effects of social connection and community. Washington: Office of the US Surgeon General, 2023.

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Child and adolescent psychiatry: challenges, solutions, opportunities, and future directions

Samuele Cortese[1-5], Celso Arango[6], Claudia Aymerich[7-9], Ana Catalan[8-12], Mohamed Chetouani[13], David Cohen[14], David Coghill[15], Alessandra Gabellone[16], Raquel Iniesta[17,18], Anoop Kadan[1], Hala Kerbage[19,20], Lars Vedel Kessing[21,22], Lucia Margari[5], Emilia Matera[5], Lucia Marzulli[23], Signe Mezinska[24], Melissa Mulraney[15], Peter Nagy[25], Dominic Oliver[12,26-28], Anne Katrine Pagsberg[21,29], Maria Giuseppina Petruzzelli[30], Veit Roessner[31,32], Gonzalo Salazar de Pablo[7,33,34], Paramala Santosh[7,35,36], Dejan Stevanovic[37], Gisela Sugranyes[38-40], Eduard Vieta[38-41], Christoph U. Correll[42-46], Gil Zalsman[47,48], Diane Purper-Ouakil[19,20], Carmen Moreno[34], Paolo Fusar-Poli[12,49-51]

[1]Developmental EPI (Evidence synthesis, Prediction, Implementation) Lab, Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK; [2]Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK; [3]Hampshire and Isle of Wight Healthcare Foundation NHS Trust, Southampton, UK; [4]Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, NY, USA; [5]Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro", Bari, Italy; [6]Hospital Universitario La Paz, School of Medicine, Universidad Autónoma de Madrid, CiBERSAM, Madrid, Spain; [7]Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [8]Biobizkaia Health Research Institute, University of the Basque Country, Bilbao, Spain; [9]Instituto de Salud Carlos III, CIBERSAM, Barakaldo, Bizkaia, Spain; [10]Department of Neuroscience, University of the Basque Country, Leioa, Bizkaia, Spain; [11]Department of Psychiatry, Basurto University Hospital, Bilbao, Spain; [12]Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, King's College London, London, UK; [13]Institute for Intelligent Systems and Robotics, Sorbonne University, UMR 7222, Inserm U1150, Paris, France; [14]Department of Child and Adolescent Psychiatry, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; [15]Department of Paediatrics, University of Melbourne, and Murdoch Children's Research Institute, Melbourne, VIC, Australia; [16]Childhood and Adolescence Neuropsychiatry Complex Operative Unit, Department of Neuroscience, Policlinico "Riuniti", Foggia, Italy; [17]Department of Biostatistics & Health Informatics, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [18]King's Institute for Artificial Intelligence, King's College London, London, UK; [19]Department of Child and Adolescent Psychiatry, Saint Eloi Hospital, CHU Montpellier, Montpellier, France; [20]Center for Epidemiology and Population Health, Inserm, Paris-Saclay University, Paris, France; [21]Copenhagen Affective Disorder Research Centre, Psychiatric Centre Copenhagen, Copenhagen, Denmark; [22]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [23]Childhood and Adolescence Neuropsychiatry Complex Operative Unit, Department of Mental Health, Taranto, Italy; [24]Institute of Clinical and Preventive Medicine, University of Latvia, Riga, Latvia; [25]Bethesda Children's Hospital, Budapest, Hungary; [26]Department of Psychiatry, University of Oxford, Oxford, UK; [27]NIHR Oxford Health Biomedical Research Centre, Oxford, UK; [28]OPEN Early Detection Service, Oxford Health NHS Foundation Trust, Oxford, UK; [29]Child and Adolescent Mental Health Center, Mental Health Services in the Capital Region of Denmark, Bispebjerg Bakke, Copenhagen, Denmark; [30]Department of Translational Biomedicine and Neurosciences, University of Bari "A. Moro", Bari, Italy; [31]Department of Child and Adolescent Psychiatry and Psychotherapy, Faculty of Medicine, Dresden University of Technology, Dresden, Germany; [32]German Center for Child and Adolescent Health, partner site Leipzig/Dresden, Dresden, Germany; [33]Child and Adolescent Mental Health Services, South London and Maudsley NHS Foundation Trust, London, UK; [34]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario "G. Marañón", IiSGM, CIBERSAM, ISCIII, School of Medicine, Universidad Complutense, Madrid, Spain; [35]Centre for Interventional Paediatric Psychopharmacology and Rare Diseases, South London and Maudsley NHS Foundation Trust, London, UK; [36]HealthTracker Ltd., Gillingham, UK; [37]Clinic for Neurology and Psychiatry for Children and Youth, Belgrade, Serbia; [38]Fundació Clínic de Recerca Biomèdica, Institut d'Investigacions Biomèdiques August Pi i Sunyer (FRCB-IDIBAPS), Barcelona, Spain; [39]Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clínic Barcelona, Barcelona, Spain; [40]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain; [41]Institute of Neuroscience, SGR21-01319, Department of Medicine, University of Barcelona, Barcelona, Spain; [42]Department of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; [43]Department of Child and Adolescent Psychiatry, Charité - Universitätsmedizin Berlin, Berlin, Germany; [44]German Center for Mental Health, partner site Berlin, Berlin, Germany; [45]German Center for Child and Adolescent Health, partner site Berlin, Berlin, Germany; [46]Einstein Center for Population Diversity, Berlin, Germany; [47]Geha Mental Health Center, Petah Tikva, Israel; [48]Department of Psychiatry, Tel Aviv University, Tel Aviv, Israel; [49]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy; [50]Outreach and Support in South-London (OASIS) service, South London and Maudlsey NHS Foundation Trust, London, UK; [51]Department of Psychiatry and Psychotherapy, University Hospital, Ludwig-Maximilian-University, Munich, Germany

It is estimated that, globally, the mean point prevalence of diagnosable mental disorders in children and adolescents is higher than 11%, and around half of cases of major mental disorders have their onset before the age of 18. Mental disorders with onset in childhood or adolescence have an enormous impact on the developing brain, body and personal identity, as well as on the short- and long-term social, educational and functional capacity of individuals. Child and adolescent psychiatry – as a discipline, profession, academic field, and network of clinical services – is still relatively young, with its formal evolution beginning in the 20th century. Therefore, it is not surprising that there are currently many challenges, but also opportunities and expected future developments, in this area. In this paper, we identify and address the core challenges, possible solutions, opportunities, and future directions of child and adolescent psychiatry. In the first part of the paper, challenges and possible solutions are discussed regarding diagnostic issues, stigma, access to care, shortage of mental health professionals, evidence-based treatments, treatment adherence, parental participation/engagement, integration with schools, digital influences and cyberbullying, and war/forced displacement. In the second part, opportunities and developments are addressed that relate to early identification and intervention, resilience, interdisciplinary collaborations, integration with primary care, community-based approaches, use of digital technologies, precision child and adolescent psychiatry, artificial intelligence and related ethical issues, and cultural diversity and competences. Despite the significance and impact of mental disorders in children and adolescents, clinical delivery and research on these conditions remain underfunded and underprioritized, even in high-income countries, with clinical services and prevention/early intervention research receiving minimal investment. Addressing mental health in children and young people requires multi-level strategies beyond individual treatment, including tackling structural and socioeconomic barriers and creating opportunities for strengthening resilience and well-being. A well-trained workforce, adequate policies, and increased public awareness are crucial. Overall, the current gaps demand urgent action and global funding rebalancing to more adequately meet the critical needs of children and young people challenged by mental illness.

Key words: Children, adolescents, mental health, child and adolescent psychiatry, diagnostic issues, evidence-based treatments, early intervention, digital technologies, resilience, interdisciplinary collaborations

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According to the Global Burden of Disease study[1], in 2019, 293 million out of 2.516 billion individuals aged 5 to 24 years had at least one mental disorder globally, translating into a mean point prevalence of diagnosable mental disorders in children and young

people of 11.63%. When considering specific age ranges, the mean point prevalence of mental disorders was 6.80% among children aged 5-9 years, 12.40% among those aged 10-14 years, and 13.96% in young people aged 15-19 years[1]. Around one-fifth of all disease-related disability was attributable to mental disorders in children and adolescents, with 24.85% of all years lived with disability (YLDs) attributable to mental disorders recorded before age 25 years[1].

Furthermore, meta-analytic evidence summarizing almost two hundred epidemiological studies[2] showed that the peak age at onset across all mental disorders is 14.5 years, with one third (35%) emerging before age 14, around half (48%) before age 18, and the majority (63%) before age 25. Specifically, about 83% of neurodevelopmental disorders have their clinically evident onset during childhood or adolescence[2]. Onset before age 18 is seen in over half (52%) of anxiety and fear-related disorders, nearly half (48%) of feeding and eating disorders, and about 45% of obsessive-compulsive and related disorders[2]. Stress-related disorders are found to begin before age 18 in roughly 28% of cases[2]. Substance use and addictive behaviors show earlier signs in about 15% of individuals, while schizophrenia-spectrum and primary psychotic disorders start before age 18 in around 12% of cases[2]. Mood disorders and personality disorders are less likely to emerge early, but still have their onset before age 18 in about 12% and 10% of individuals, respectively[2].

Based on these figures, the crucial relevance of child and adolescent psychiatry within the mental health arena is self-evident. However, despite its importance, child and adolescent psychiatry – as a clinical discipline, profession, academic field, and network of clinical services – is still relatively young.

Until the 19th century, it was commonly assumed that children's minds were too undeveloped and unstable to exhibit significant signs of psychopathology[3]. Although emotional and behavioral problems have been acknowledged among children and adolescents throughout history, they were not traditionally viewed as medical issues. Instead, such behaviors were largely considered as moral failings, warranting punishment rather than treatment[3]. In the US, for instance, B. Rush, widely regarded as the first American psychiatrist, made no reference to children in his influential textbook *Medical Inquiries and Observations upon the Diseases of the Mind*, published in 1812[4].

However, "juvenile insanity" gradually gained widespread acceptance in the 19th century. This development mirrored the progressive interest in the child as a matter of clinical attention, reflected for instance in the foundation of the Hôpital des Enfants-Malades (Hospital for Sick Children), founded in Paris in 1802[5]. This was followed by the Great Ormond Street Hospital in London 50 years later[3]. By the late 19th century, most psychiatric textbooks included sections on children, and juvenile insanity began to be distinguished from conditions such as mental retardation and epilepsy[6]. For example, in the UK, Maudsley's 1895 publication *The Pathology of Mind*[7] included a chapter entitled *The Insanity of Early Life*, and the German psychiatrist Griesinger in 1867 recognized that conditions such as mania and melancholia could also affect children[8]. In 1887, another German psychiatrist, H. Emminghaus, published one of the earliest textbooks on child psychiatry, *Psychic Disturbances in Childhood*[9]. In contrast, Kraepelin's influential psychiatric classification system, introduced in 1883, entirely overlooked childhood-onset disorders[3].

Significant progress in the early 1900s laid the foundation for child psychiatry to evolve into the established discipline it is today. Key developments included: a) advancements in measurement techniques (e.g., the publication of the first standardized scale of intelligence, the Binet-Simon test, in 1905[10]); b) the rise of developmental psychology, following the publication of *The Mind of the Child*[11], in which the German psychologist W. Preyer presented his observations on the development of his own son from birth to the age of three; c) the rise of psychoanalysis, including the pivotal contributions of A. Freud and M. Klein, both of whom played a central role in founding child psychoanalysis; d) the influence of the mental hygiene movement, aimed at promoting mental health, preventing mental illness, and improving care for people with mental disorders by shifting focus from custodial care to proactive support; and e) the child guidance movement, started by the neurologist W. Healy in Chicago in 1906, that aimed to move the focus from the juvenile justice system to the family, school and neighborhood to support children with maladjustment, thus representing a "form of preventive medicine promoting children's mental well-being"[12]. Furthermore, the *encephalitis lethargica* epidemic, that spread worldwide after World War I, led to a substantial number of children developing behavioral issues such as hyperactivity, thus creating a greater demand for services. In response, specialized units were established, such as the children's unit at Bellevue Hospital in New York City in 1920[13].

From the academic standpoint, the first chair of child psychiatry was established in 1923 in Rosario, Argentina, and was held by the Italian neuropsychiatrist and psychoanalyst L. Ciampi. This development occurred before the founding of the first academic child psychiatry department in the US, which was set up by L. Kanner in 1930 at Johns Hopkins Hospital in Baltimore[3].

The second half of the 20th century, particularly following World War II, saw a surge in research that greatly expanded our understanding of childhood mental disorders – their nature, diagnosis, classification and treatment. This era was marked by major contributions from both psychological therapies (e.g., the development of family therapy, beginning in the late 1940s, with the emergence of several approaches in the 1960s, such as the Milan systemic model[14]) and psychopharmacology (e.g., the synthesis of methylphenidate in 1944, following the serendipitous discovery[15] in 1937 of the beneficial effects of amphetamines for what would later be termed attention-deficit/hyperactivity disorder, ADHD). Together, these advances helped solidify child and adolescent psychiatry as a recognized medical specialty.

In relation to classification systems, the ICD-6[16], released in 1948, for the first time included a section dedicated to mental disorders, but did not refer to child disorders. The DSM-I[17], published in 1952, did not specifically address childhood mental health disorders, although it did include a reference to "mental deficiency". However, the DSM-II[18], released in 1968, did feature a section on behavioral disorders in childhood and adolescence, categorizing

various types of "reactions", including withdrawal, excessive anxiety, running away, unsocialized aggression, group delinquency, and hyperactivity.

Regarding training, in some countries – such as Germany and the US – child psychiatry has developed as an independent medical discipline[3]. In others – including Australia, New Zealand, the UK, and Canada – it functions as a subspecialty within general psychiatry. In some other countries, child psychiatry has been formally established as a full specialty and recognized as a distinct field only recently – for example, in Spain in 2021[3]. However, in many low- and middle-income countries (LMICs) – where a relatively high proportion of the population are children and adolescents – child psychiatry has yet to be formally recognized as a distinct specialty[19].

Child and adolescent psychiatry also had to clarify its relationship to pediatrics. Historically, two separate perspectives have emerged. On the one side, child psychiatry has been supported as a field separate from pediatrics. For example, in the UK, A. Lewis, appointed in 1946 as the first chair of psychiatry at the newly established Institute of Psychiatry in London, strongly advocated for the independence of the field, emphasizing the need for specialized training[19]. This view significantly influenced M. Rutter, broadly considered the founder of modern child psychiatry, to pursue a career in that discipline. In contrast, D. Winnicott, a pediatrician trained in psychoanalysis, believed that pediatricians should also be trained as child psychiatrists, primarily through the practice of child psychoanalysis[19]. Building on these debates, in the 1980s, several institutions in the US established a five-year training program combining pediatrics, general psychiatry, and child and adolescent psychiatry, known as the "triple board certification"[20]. We also note that in a few countries (e.g., Austria and Italy[21]), child psychiatry training is combined with pediatric neurology, offering opportunities for a more comprehensive management of many conditions including both neurological and psychiatric presentations.

In terms of clinical services, in the 1960s-1980s, the bulk of care was delivered in specialist clinics or as part of adult psychiatric institutions, with limited coordination and often stigma attached to young people's mental health access[22]. By the 1990s and into the 21st century, specialized child and adolescent mental health services have emerged, with the development of dedicated policies and workforce initiatives[23].

Given this relatively recent and diversified history, it is not surprising that there are currently many challenges, but also opportunities and expected future developments, in child and adolescent psychiatry. In this paper, members of the European College of Neuropsychopharmacology (ECNP) Child and Adolescent Psychiatry Network[24] and the ECNP Prevention of Mental Disorders and Mental Health Promotion Network[25], alongside authors co-opted based on their expertise, discuss these challenges, possible solutions, and opportunities, grouped by specific thematic areas. The paper was conceived as a critical, rather than systematic, review. However, for the selection of the relevant literature, we prioritized meta-analyses or umbrella reviews over primary studies, whenever relevant.

CHALLENGES AND POSSIBLE SOLUTIONS IN CHILD AND ADOLESCENT PSYCHIATRY

The diagnostic process

The late 20th-century introduction of diagnostic categories based on operationalized criteria enabled standardized descriptions of mental disorders, including those in children and adolescents, supporting efficient communication among professionals and evidence-based practices[26,27]. Overall, DSM-5 field trials showed good inter-rater reliability for some categorical diagnoses in children and adolescents (e.g., autism, kappa: 0.69; ADHD, 0.61; bipolar I disorder, 0.52), but low kappa values for others (e.g., major depressive disorder, 0.28; disruptive mood dysregulation disorder, 0.25), even though the pragmatic design of these trials, with less standardization than in research settings, may have led to reduced reliability[28].

Categorical classifications provided the basis for (semi-)structured interviews that contributed to shifting child and adolescent psychiatry away from purely art-form assessments[29] (see Table 1 for a summary of the psychometric properties of three key semi-structured interviews[30-32] in child and adolescent psychiatry).

While the categorical diagnostic approach has contributed to increasing reliability in child and adolescent diagnoses, and despite the continuing evolution of diagnostic criteria, some scholars argue that this approach has reached the limits of its clinical utility[35], and this may particularly be the case in child and adolescent mental health[36], due to several reasons.

First, the validity of current categorical diagnoses is questionable and variable according to the type of disorder and validator. Regarding genetic validators, while some syndromes involving intellectual disability and severe problems in neurodevelopment, such as Rett syndrome, can be defined entirely based on the presence of genetic anomalies, this is not the case for the majority of the other disorders[36]. Of note, no genetic diagnostic biomarker

Table 1 Key psychometric properties of three semi-structured interviews used in child and adolescent psychiatry

Development and Well-Being Assessment (DAWBA)[30]	Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)[31]	Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)[32]
Fair agreement between DAWBA-based and routine clinical diagnoses (overall percentage diagnostic agreement for any disorder: 74%)[33]	Fair agreement between MINI-KID-assigned and expert consensus diagnoses (overall percentage diagnostic agreement for any disorder: 76.2%)[34]	High inter-rater agreement for both screening scores and diagnoses, ranging from 93% to 100%. Excellent or good test-retest reliability for present and/or lifetime diagnoses[32]

is supported by adequate levels of specificity and sensitivity to be used in clinical practice in child and adolescent psychiatry (e.g., for neurodevelopmental disorders[37]), even though genetic protocols including single nucleotide polymorphism or comparative genomic hybridization arrays, followed by whole exome sequencing, can identify alterations in 52-53% of cases in individuals with autism spectrum disorder and intellectual disability[38].

Biological indices beyond genetics provide accurate validation for some sleep disorders (e.g., narcolepsy and sleep disorder breathing), but weak grounds to validate many other diagnostic categories[36]. Regarding cognitive validators, while these represent a defining feature of learning disorders, they are only partially related to other diagnostic categories[36]. For instance, in ADHD, no neuropsychological test is considered diagnostic[39], and the only test cleared by the US Food and Drug Administration (FDA) and the UK National Institute for Health and Care Excellence (NICE) – the Quantified behavior (Qb) test, a combination of a performance task and motion tracking – is meant to support, rather than replace, a clinical categorical diagnosis, although it is not clear how exactly this test should support the clinical assessment[40].

Second, children and adolescents frequently exhibit concurrent symptoms – such as sleep disturbances, motivational shifts, and behavioral or mood fluctuations – that do not align clearly with categorical diagnoses. These symptoms often evolve across diagnostic boundaries and can lead to diverse clinical outcomes[41]. This is reflected in high levels of psychiatric comorbidity: by age 7, 6.4% of children fulfill two or more psychiatric diagnoses[42]; by age 11-15, 32% of children with a mental disorder have comorbid diagnoses[43]. Comorbidity cannot be fully attributed to shared symptomatology, as many comorbid diagnoses share no common criteria[44].

Third, existing classification systems such as the ICD and DSM are not designed to adequately reflect developmental symptom trajectories. Their categorical structure, based on stable cross-sectional diagnostic entities with clearly defined symptom clusters[45], fails to accommodate the dynamic syndromic shifts typical in child and adolescent psychiatric presentations[46].

Alternative approaches have been proposed to overcome these challenges.

Dimensional approaches have gained some traction, albeit also facing criticism[47]. They are based on latent theory models, including one prominent model that divides mental disorders into internalizing (e.g., anxiety, depression) and externalizing (e.g., ADHD, conduct disorder) spectrums[48,49]. Other models have added domains for thought disorders/psychosis[50,51], neurodevelopmental issues such as inattention and hyperactivity[52,53], and detachment[54]. The Hierarchical Taxonomy of Psychopathology (HiTOP) framework[54-58] is a prominent example of the dimensional approach, viewing mental health problems as nested dimensions related to extremes of psychological functions.

Of note, approaches resembling the HiTOP have been used for many years in child and adolescent psychiatry. Examples include approaches based on the Strengths and Difficulties Questionnaire (SDQ)[59], the Child Behavior Checklist (CBCL)[60], the Pediatric Symptom Checklist (PCS)[61], and the Ontario Child Health Study Emotional Behavioural Scales (OCHS-EBS)[62]. These dimensional approaches provide broadband assessments of symptoms that can be clustered into internalizing, externalizing, and attention problem domains, alongside sleep, thought, somatic, and peer problems[63].

Another approach, the network model, regards symptoms and their correlated features, such as risk factors, as components of a mutually reinforcing network. The network model has been influential in research within child and adolescent psychiatry, as it analyzes the ways in which symptoms change over development by modelling temporal networks[64]. Longitudinally, depressed mood, inattention and worry might be symptoms that increase the likelihood of presenting other symptoms in the future[65]. There have been studies reporting that some symptoms – including irritability, crying, and feelings of loneliness – could bridge internalizing and externalizing spectrums[63,66].

A tension between dimensional and categorical models may arise because clinical decisions often require categorical choices, such as whether to treat or not[36]. However, categories can be derived from dimensions using cut-off scores, when these are properly validated, and dimensions can be formed by scaling categories[36,67]. Diagnoses can typically be assigned when symptom severity crosses a threshold, similar to how conditions such as hypertension or diabetes mellitus are defined. For example, the CBCL uses T-scores, which standardize total scores around a mean of 50, with each 10-point increment representing one standard deviation. Scores above 70 suggest the need for clinical attention[63].

The development of further dimensional tools for children and adolescents with mental health challenges is ongoing. For instance, the Stavros Niarchos Foundation (SNF) Global Center for Child and Adolescent Mental Health, in partnership with the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP), is developing a culturally sensitive measurement tool to assess over 30 mental health domains among children and adolescents[68].

Approaches that heavily rely on neuroscientific constructs have also been proposed. The US National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC)[69,70] is the prototypical example of this approach, focusing on six domains of functioning (arousal/regulatory systems, positive and negative valence, sensorimotor, cognitive, and social processes) measured across multiple levels, from molecular to behavioral. Since its introduction in 2010, the RDoC framework has been applied in many studies in child and adolescent psychiatry, including those on ADHD, autism and irritability[71]. However, despite rapid scientific progress, the clinical application of neuroscience research findings has not yet materialized, leaving RDoC-like models disconnected from everyday clinical practice.

The clinical staging framework highlights the developmental course and progression of mental disorder, not just the individual's current clinical state[72]. The goal is to identify the probability of progression from low-level risk (stage 0) to mild/subthreshold or nonspecific symptoms (stage 1), to a recognized clinical syndrome with some functional impairment (stage 2), moving to incomplete remission or a recurrent syndrome with functional impairment

and cognitive decline (stage 3), and then to a severe unremitting syndrome with functional impairment and cognitive decline resistant to treatment (stage 4)[63]. A specific clinical staging has been proposed as an adjunctive tool for classifying internalizing and externalizing syndromes that emerge in children aged 5-11 years[73].

When considering altogether the above alternative models to categorical diagnosis, it should be emphasized that, in order for them to stand as a viable substitute for ICD/DSM-based diagnostic systems, they would need to demonstrate two key qualities: a) sufficient feasibility for use in everyday clinical contexts, across different settings and by various types of professionals, and b) greater clinical value than current diagnostic models, particularly in terms of guiding treatment decisions and predicting patient outcomes[35]. At present, such supporting evidence has yet to be established[35]. It has been thoughtfully noted that, ideally, the field would require trials comparing the benefits of categorical diagnoses versus alternative approaches[47].

Crucially, it has been pointed out that models alternative to categorical diagnoses should not necessarily replace categorical frameworks, but could complement them by providing additional information that helps characterizing individual cases with respect to a variety of domains. These include relevant psychopathological dimensions, the current developmental stage of the disorder; antecedent factors such as family history of mental illness, perinatal and early environmental influences, psychomotor development, premorbid adjustment, and potentially polygenic risk scores; and concomitant factors such as personality traits, cognitive and social functioning, neurological soft signs, substance use, recent environmental exposures, and, in the future, possible biological markers[35]. Therefore, alternative approaches could be helpful for case formulation, which should be regarded as a central process in child and adolescent psychiatry.

Stigma around mental health

Stigma – defined as "an attribute that is deeply discrediting, turning a whole and usual person to a tainted and discounted one"[74] – can be related to non-concealable attributes, e.g., a physical disability, or predominantly concealable attributes, e.g., mental disorder. Stigma is commonly categorized into public stigma, which refers to the prejudice and discrimination faced by individuals with mental illness when societal stereotypes are accepted and reinforced by the general population, and self-stigma, which describes the feelings of shame and diminished self-worth that arise when individuals internalize these negative stereotypes[75].

While the impact of stigmatization of mental disorder has been thoroughly investigated in adults[76], less research has been conducted on stigma in child and adolescent mental health[77]. According to the *Perceptions of Youth Mental Health Report 2025* by the United Nations Children's Fund (UNICEF) across seven countries, 4 out of 10 people aged 14-25 perceived mental health stigma in school and working places[78]. There is also evidence that stigma is prevalent in younger children, particularly in some sociocultural contexts. For instance, in a survey of parents of children accessing child and adolescent mental health services in Sri Lanka, 44% of them reported that their children had been discriminated in education[79].

Compared to adults, the experience of stigmatization may be more challenging in youth, as they are in a phase of life marked by an intense need to fit in socially with their peers[77]. Children and adolescents with mental disorders can face stigma from various sources, including peers, their families, teachers, and even health care professionals[80,81]. Unlike non-psychiatric conditions, the pursuit of help and treatment for mental disorders may be a key contributor to stigma. In terms of specific issues, adolescents with autism, for instance, may be concerned about losing social relationships, "messing things up with people", experiencing rejection, and feeling "humiliated or embarrassed" in social situations"[82].

A meta-analysis[83] of 74 randomized controlled trials (RCTs) tested interventions aimed at reducing mental health stigma and improving help-seeking among children and young people (aged 10-24 years). The primary outcomes were stigma-related knowledge, attitudes and behaviors, overall stigma, and help-seeking attitudes, intentions and behaviors – further categorized into formal sources (e.g., health professionals) and informal sources (e.g., friends). Secondary outcomes comprised self-efficacy and empowerment. Overall, interventions involving social contact appeared more effective in changing stigma-related behaviors than educational approaches.

While the meta-analysis did not include separate analyses for school-aged children and older adolescents, previous evidence indicates that educational approaches tend to be more effective in school-aged populations[84], whereas social contact interventions are more effective among higher education students[85]. An observed decline in effect sizes over longer follow-up highlights the difficulty of sustaining the benefits of stigma-reduction interventions. This suggests that short-term programs alone may be insufficient for producing lasting change, and that ongoing efforts, booster sessions, or follow-up activities may be needed to maintain and strengthen initial improvements.

Given that interventions involving social contact tend to produce greater changes in stigma-related behaviors than educational approaches, future studies should include direct, personal interactions with children and young people experiencing mental disorder. Future RCTs could also benefit from mixed-methods designs to better capture the complexity of stigma and help-seeking behaviors, shedding light on the factors that influence them. Furthermore, few antistigma interventions for children and young people have been implemented so far in LMICs[86], pointing to a global priority need in the field. Expanding digital approaches – which are still rare in this field – may provide scalable and accessible solutions for young people around the world.

When assessing stigma in children and adolescents, it is crucial to consider that their parents/caregivers can also be stigmatized due to perceived responsibility for their children's symptoms. They often worry about their children's ability to adapt to and integrate into society while grappling with fears of stigmatization and discrimination in schools, health care, and broader social contexts [87,88]. These concerns can lead to a deep sense of isolation, with

caregivers frequently feeling ostracized and excluded from societal activities[89]. Therefore, regular mental health screenings integrated into children's medical appointments should be considered to identify caregiver burden and ensure timely interventions, even for those who do not actively seek support[90].

Overall, while significant strides have been made in understanding both public and self-stigma related to mental health problems in children and adolescents, there remains a critical need for evidence-based interventions that are developmentally appropriate, culturally sensitive, and applicable across diverse settings.

Access to care

Data from the Global Burden of Disease study indicate that the rates of disability-adjusted life years (DALYs) for mental disorders in children and adolescents increased from 803.8 to 833.2 per 100,000 between 1990 and 2019[91]. Furthermore, a meta-analysis showed a more than two-fold increase in the prevalence rates of anxiety and depression during the first year of the COVID-19 pandemic compared to pre-pandemic rates, with pooled prevalence estimates of clinically elevated depression and anxiety symptoms at 25.2% and 20.5%, respectively, and an even higher prevalence in older adolescents and girls[92].

Despite this increase in need, only a limited proportion of children and adolescents with mental health problems are accessing care, and even less receive evidence-based treatment, also in high-income countries. For instance, in the US, only 53% of individuals with a mental disorder aged 3-17 received treatment or counselling from a mental health professional in the previous year[93]. Even in nations with universal health care, such as the UK and Canada, delays are common. For instance, in England, during the 2022-2023 period, the average wait time for children accessing mental health services was 108 days, with some waiting for treatment over two years[94]. The situation is even more dire in LMICs, where it is estimated that 94% of children and adolescents with mental disorders receive no treatment at all[95].

A systematic review[96] of quantitative (22 studies) and qualitative (30 studies) research identified four primary types of barriers to access to care in child and adolescent mental health. Nearly all studies (96%) reported barriers related to individual factors in young people, such as limited mental health knowledge and general attitudes toward help-seeking. The second most frequently reported theme (92%) involved social factors, including perceived stigma and feelings of embarrassment. The third theme (68%) concerned young people's perceptions of the therapeutic relationship with professionals, encompassing issues such as confidentiality and the ability to trust unfamiliar providers. The fourth theme (58%) pertained to systemic and structural barriers and facilitators, such as the financial costs of mental health services, logistical challenges, and the availability of professional support. Further health system-related barriers include insufficient insurance coverage, long distances, long waiting times, unpractical consultation schedules, and restrictive intake procedures[97]. Paucity of policies, a shortage of child and adolescent mental health specialists, insufficient financial resources dedicated to child and adolescent mental health care, and a scarcity of culturally appropriate assessment tools have been identified as key barriers to care access particularly in LMICs[98].

Improving access to and utilization of appropriate mental health care for children and adolescents requires initiatives at multiple levels. As shown by an umbrella review[99], crucial elements to target should include: a) enhancing the sense of trust in professionals (intrapersonal level); b) support from close others for treatment (interpersonal level): c) cost (institutional level); d) availability (community level); and e) insurance (public policy level). Users' perceptions of adequate services pertain to their availability, including the possibility of self-referral, practitioners' qualities and expertise with relational continuity, personalized support tailored to actual needs, and the development of self-care skills and mental health literacy in parents and children[100].

A meta-analysis[101] of 34 RCTs evaluating interventions aimed at improving either supply-side elements of service accessibility (e.g., approachability, availability or affordability) or demand-side abilities of individuals (e.g., the ability to perceive the need for care, pay for services, or engage with treatment) found that universal school-based interventions for the general population significantly improved early steps in accessing care, with 80% showing effects on knowledge and 67% on attitudes, but had minimal impact on help-seeking (22%) or taking action (20%). Interventions targeting at-risk children already identified by health care systems showed stronger effects: 71% improved care access, and 80% increased satisfaction with care. Therefore, to produce broad, population-level improvements in access to care, a stepped or two-stage approach may be necessary – first identifying young people who require support, and then ensuring that they are effectively linked with appropriate services. However, the current evidence base for such models remains very limited[101]. Given that existing research does not yet justify large-scale mental health screening of children[102], rigorous RCTs are needed to evaluate screening strategies and weigh their potential benefits against possible harms[103].

Importantly, there is increasing recognition that structural and environmental changes – such as reforming policies, service infrastructure, and financing systems – may exert a stronger influence on help-seeking behavior than educational initiatives alone[104]. This highlights the need for more studies targeting contextual barriers to care. Crucially, attempts to remove a single barrier, for example by reducing financial costs, are unlikely to be sufficient if issues relating to availability, accessibility or acceptability remain unaddressed[104]. Emerging models that provide rapid assessment, including crisis or consultation services delivered by phone, show potential to support a shift toward more proactive and needs-based care. Longer follow-up periods are also required to determine whether improvements in access are sustained over time [105].

The additional challenges in LMICs – such as limited service infrastructure, more pervasive stigma, and low detection rates[106] – suggest that strategies effective in high-income settings cannot

simply be transferred without adaptation[107]. Further research is therefore essential to identify context-appropriate approaches for improving access to mental health services especially in these environments.

Funding and insurance limitations

Funding and insurance limitations represent significant barriers to the accessibility and quality of child and adolescent mental health care worldwide. These challenges affect both high-income countries and LMICs, although they differ in scale and nature across regions[106].

For instance, in the UK, while 30% of the mental health needs in the national health system (NHS) are related to children, children's mental health services receive only around 8% of the total budget[108]. As to LMICs, an analysis focusing on 15 countries in the Western Pacific Region[109] found that spending for child and adolescent mental health ranged from 0.01% of the total health expenditure in Cambodia to 1.06% in Mongolia, with seven countries spending less than 1%. Notably, in LMICs, from 2007 to 2015, only a negligible share of global development assistance for health – about 0.1% – was directed toward child and adolescent mental health[110]. In the years 2016 to 2021, funding for adolescent mental health rose only slightly to 0.32%[111].

However, the economic case for investing in mental health of children and adolescents is becoming increasingly compelling. In fact, there is strong and growing evidence that supporting the mental well-being of children and young people not only enhances their quality of life, but also generates long-term economic benefits. These include lower health care and public service costs, as well as greater future productivity and earnings[112]. For example, an economic analysis conducted across 36 countries found that implementing a package of mental health care interventions for adolescents produced a return on investment of 23.6, at a cost of $102.9 per DALY averted over 80 years[112].

Addressing the current systemic barriers requires different strategies in high-income countries and LMICs. In the former, despite more advanced health care systems, insurance policies often place mental health services, in particular those for children and adolescents, as secondary to other medical needs. Moreover, insurance policies may limit the number of covered sessions or require high out-of-pocket costs, making it difficult for families to access consistent, long-term care. This issue is particularly pressing for families from lower socioeconomic backgrounds, who face financial barriers even in the context of public health insurance. Therefore, high-income countries must expand insurance coverage to fully include child and adolescent mental health services and promote their integration into primary health care.

Encouraging successful initiatives, albeit with some caveats, are available. For instance, in the US, access to mental health care has been increased in recent years through expansions in public health insurance (i.e., the State Children's Health Insurance Program). There is evidence that these programs have led to an increased mental health coverage for children in older age groups, including those with a family income under 300% of the federal poverty line[113].

LMICs should prioritize the development of mental health service infrastructure, workforce training, and policy integration. Engaging with governments, non-governmental organizations, and research institutions at the global level can offer crucial support. For instance, in Bosnia and Herzegovina, ongoing financial and technical partnerships contributed to the strengthening and expansion of existing mental health care systems. Between 2010 and 2022, the Swiss Agency for Development and Cooperation played a key role in this process through a program designed to enhance and scale up services without establishing parallel structures[114]. Nevertheless, collaborating with global partners requires careful attention to potential challenges: short-term, project-based funding can hinder long-term planning; narrowly targeted initiatives may divert scarce national resources from building comprehensive services; and approaches that restrict the involvement of local professionals and policy makers can limit their ability to shape and oversee their own systems.

In sum, overcoming funding and insurance limitations is essential for advancing equitable, sustainable and effective child and adolescent mental health care worldwide, requiring coordinated policy reform, long-term investment, and international collaboration.

Shortage of mental health professionals

The number of child and adolescent psychiatrists varies significantly across countries, with figures ranging worldwide between 0.1 and 3.4 per 100,000 inhabitants aged 0-19 years, although data are not readily available for many countries[115]. A UK workforce survey indicated that, in 2023, the rate of vacant positions in child and adolescent psychiatry was the highest among all psychiatric subspecialties (34.8%)[116]. In the US, from 2007 to 2016, the ratio of child and adolescent psychiatrists per 100,000 children has increased by over 20%[117], but regional maldistribution is significant, with more than 70% of US counties, especially those with lower levels of income and education, having no child psychiatrists at all. Additionally, in 2018, in the US, there were only sufficient child psychiatrists to treat 17% of children with severe mental health problems[118]. This number is projected to increase only to 27% by 2030[119].

The situation in the UK and US is emblematic of a global trend. Notably, the median number of child psychiatrists per 100,000 population is 0.1-2 in LMICs[95]. Importantly, even when staff is available, a sizable portion of them may experience burnout and low levels of well-being, which are exacerbated by being overburdened and constantly facing urgency, the increasing complexity of presenting cases, insufficient collaboration with schools, and the advancing digitalization with all its associated challenges[120].

The shortage of child and adolescent mental health professionals has been associated with many adverse outcomes, with one of the most important being completed suicide of children and adolescents[121]. The lack of funding for training programs and low

salaries for mental health professionals further exacerbate this issue, discouraging new generations of physicians from entering the field.

Various strategies have been proposed to address this workforce crisis. Examples of specific successful initiatives include the following.

Summer Immersion Programs provide medical students with early exposure to child and adolescent psychiatry, fostering interest and encouraging pursuit of this subspecialty. Evaluations of such programs show that they led to successful recruitment of students into child and adolescent psychiatry, with up to 80% of participants expressing increased interest in the field and over 60% pursuing psychiatry residencies afterward[122].

Mentorship Networks are structured mentorship programs for medical students, that have been shown to increase recruitment into child and adolescent psychiatry by offering guidance, professional support, and exposure to subspecialty practice. A study[123] based on qualitative interviews of nine program directors and 29 medical students or graduates across 14 medical schools in the US indicated that mentorship participation has the potential to increase the likelihood of entering child and adolescent psychiatry by approximately 40%, demonstrating the value of sustained professional relationships.

Loan Forgiveness and Training Expansion offer financial incentives and additional training positions to attract and retain child and adolescent mental health professionals. Programs providing loan repayment[124] and stipends may lead to an increase in residency retention in child psychiatry, reducing barriers to entry and promoting long-term workforce sustainability.

Peer Workforce Expansion aims to integrate youth peer workers (i.e., young persons, typically adolescents or young adults, who have lived experience with mental health challenges, emotional difficulties, or other related struggles, and who are trained to provide support to their peers facing similar issues) into mental health services, enhancing outreach and service delivery. Qualitative research using data collected through semi-structured interviews highlighted that programs incorporating peer support can successfully improve engagement and mental health outcomes[125].

Child Psychiatry Access Programs are programs offering rapid remote pediatric mental health consultation to primary care providers. These have emerged as a promising option to address the shortage of child and adolescent mental health workforce. A systematic review[126] assessing the impact of these programs found 33 studies, none of which was randomized. The programs showed year-over-year growth in adoption and were generally well-received by providers and caregivers. Health care provision costs varied widely. No study reported changes in patient mental health outcomes using validated measures. As such, these programs require further investigation[126].

Collectively, these initiatives demonstrate that a multifaceted approach – combining early exposure, mentorship, peer integration, financial incentives, and collaborative care – can significantly expand and strengthen the child and adolescent psychiatry workforce.

Evidence-based treatments

Pharmacological treatment

Global pharmacoepidemiological data indicate a rising trend in the use of psychotropic medications among children and adolescents over the past two decades. A study across 65 countries reported that total sales of psychotropic drugs for both children and adults increased between 2008 and 2019, with an average annual growth rate of 4.08% (95% CI: 2.96-5.21)[127].

A substantial number of RCTs, synthesized in large-scale umbrella reviews, indicate that medications used to treat various mental health conditions in children and adolescents show moderate to high effect sizes[128] (see Table 2) and overall good tolerability[129].

Despite the availability of various psychotropic medications, many challenges – as well as potential opportunities – related to child and adolescent psychopharmacology were recently highlighted in a Position Paper by the ECNP Child and Adolescent Neuropharmacology Network, in collaboration with representatives from the European Medicines Agency (EMA) and associations of people with lived experience[24].

A first challenge is that there are several disorders for which no evidence-based pharmacological treatments exist, or existing interventions have not been thoroughly studied. Notably, in many instances, medications are used off-label, with studies suggesting that up to 55% – and, when excluding medications for ADHD, as much as 95% – of psychotropic prescriptions for children are off-label[130]. This exposes children and adolescents, especially those more vulnerable – such as those with intellectual disabilities – to possible harm[130].

A survey among members of the above-mentioned ECNP Network[24] identified multiple conditions requiring further pharmacological development. Ranked by the number of votes (priority), these conditions were: autism spectrum disorder (core symptoms); emotional dysregulation/irritability; anorexia nervosa; depression; suicidal behaviors; conduct disorder/aggressiveness; addiction to drugs or alcohol; negative symptoms of schizophrenia; insomnia/sleep disorders; anxiety; rare diseases such as Prader-Willi syndrome; borderline personality disorder; eating disorders other than anorexia nervosa; obsessive-compulsive disorder; body dysmorphic disorder; cognitive dysfunction in intellectual disability; somatoform symptoms; and ADHD comorbid with cocaine or methamphetamine addiction.

Additional challenges include the following: a) most compounds have been tested only in single placebo-controlled trials, underscoring the need for further studies that directly compare two or more active medications, focus on children and young people who do not respond to initial treatments, or address those who cannot tolerate first-line options; b) the predominant research focus is on core symptoms, while the impact of medications on other important outcomes, such as functional abilities, remains underexplored; and c) there is limited understanding of long-term effects, both beneficial and harmful, of psychotropic medications on the developing brain and body.

Table 2 Efficacy of medications approved by the US Food and Drug Administration for indications in child and adolescent psychiatry (vs. inactive controls)[128]

	Age (years)	Effect size (95% CI)
Attention-deficit/hyperactivity disorder		
Amphetamine/dextroamphetamine mixed salts	3-17	
Amphetamine/dextroamphetamine mixed salts, extended release	6-17	
Dextroamphetamine	3-17	–1.02 (–1.19 to –0.85)
Dextroamphetamine, sustained release	6-16	
Lisdexamfetamine	6-17	
Methamphetamine	6-17	
Atomoxetine	6-17	–0.56 (–0.66 to –0.45)
Clonidine, extended release	6-17	–0.71 (–1.17 to –0.24)
Guanfacine, extended release	6-17	–0.67 (–0.85 to –0.50)
Methylphenidate	6-17	–0.78 (–0.93 to –0.62)
Dexmethylphenidate	6-17	
Viloxazine	6-17	NA
Generalized anxiety disorder		
Duloxetine	7-17	–0.09 (–0.27 to 0.09)
Escitalopram	≥7	NA
Autism spectrum disorder		
Aripiprazole	6-17	–0.24 (–0.40 to –0.08) (aggressive behavior)
Risperidone	5-17	–0.29 (–0.48 to –0.11) (aggressive behavior)
Bipolar disorder (depressive episodes)		
Lurasidone	10-17	NA
Olanzapine/fluoxetine combination	10-17	NA
Bipolar disorder (manic or mixed episodes)		
Aripiprazole	10-17	–1.08 (–1.32 to –0.85)
Asenapine	10-17	NA
Olanzapine	13-17	NA
Quetiapine XR	10-17	NA
Risperidone	10-17	NA
Lithium	12-17	NA
Conduct disorder		
Risperidone		–0.48 (–0.71 to –0.24)
Depressive disorder		
Fluoxetine (major depressive episode unresponsive to psychotherapy)	8-18	–0.51 (–0.84 to –0.18)
Escitalopram	12-17	–0.17 (–0.88 to 0.54)
Obsessive-compulsive disorder		
Clomipramine	10-17	–0.31 (–0.64 to 0.02)
Fluoxetine	7-17	–0.24 (–0.47 to –0.01)
Fluvoxamine	8-17	–0.21 (–0.49 to 0.06)
Sertraline	6-17	–0.24 (–0.46 to –0.03)
Schizophrenia		
Aripiprazole	13-17	–0.43 (–0.63 to –0.24)
Brexpiprazole	13-17	NA
Lurasidone	13-17	–0.48 (–0.71 to –0.25)
Olanzapine	13-17	–0.74 (–1.05 to –0.44)
Paliperidone	12-17	–0.42 (–0.66 to –0.18)
Quetiapine	13-17	–0.42 (–0.65 to –0.19)
Risperidone	13-17	–0.62 (–0.89 to –0.34)
Tourette syndrome		
Aripiprazole	6-17	NA

NA – not available

Furthermore, a survey of experts with lived experience (644 participants from 13 countries)[24] identified knowledge gaps related to safety and tolerability, including concerns about medication addictiveness, as major unmet needs. The survey also highlighted the need for a better understanding of the respective roles of pharmacological and non-pharmacological interventions.

Possible solutions and opportunities in child and adolescent psychopharmacology to address these challenges include: a) the development of novel medications; b) applying lessons learned from failed RCTs; c) improving understanding of placebo effects and minimizing them; d) assessing outcomes beyond core symptoms; e) considering developmental windows; f) conducting trials that compare pharmacological and non-pharmacological treatments; g) moving beyond standard placebo-controlled RCTs; h) advancing precision medicine and stratification approaches (including biomarker research and therapeutic drug monitoring); i) investigating, researching and implementing digital technologies such as ecological momentary assessment; j) focusing research on individuals who have not responded to initial treatments; k) innovating regulatory and legislative frameworks; and l) transforming how research is conducted, reported and disseminated. These possible solutions and opportunities are further detailed in Table 3.

While the field eagerly anticipates the development and testing of novel compounds, a prudent strategy remains to implement evidence-based practices and critically evaluate the use of medications lacking supportive evidence in child and adolescent psychopharmacology. In this context, the Umbrella-Review, Evaluation, Assessment, and Communication-Hub (U-REACH) approach [153-156] – which implements evidence from umbrella reviews with the creation of open-access online platforms that make these findings accessible to diverse stakeholders in a user friendly way – represents an innovative and promising opportunity.

Table 3 Key challenges and possible solutions/opportunities in the field of child and adolescent psychopharmacology

Developing novel psychotropic medications

- No ground-breaking medications in child and adolescent psychiatry have been introduced in the past decades, and no major developments are ongoing[131].
- While pre-clinical animal studies are a major bottleneck in drug development, cell-based *in vitro* models for efficacy and safety testing could help address these challenges (e.g., induced pluripotent stem cells)[132].

Randomized controlled trials (RCTs)

- RCTs remain the gold standard for assessing medication efficacy and tolerability, but challenges such as poor recruitment and drug supply issues can threaten their success.
- Involving people with lived experience in the study design is essential and aligns with European Clinical Trials Regulation. Sharing study results with participants is a regulatory requirement once the trial is completed[133].
- Regional research networks can enhance recruitment, especially from non-university hospitals and community services.

Understanding and minimizing the placebo effects

- Placebo effects can confound the interpretation of trial findings and lead to reduced effect size of active compounds[134-136].
- Placebo effects and drug-placebo differences depend on trial design, conduct and participant factors[134-136].
- Effective strategies to minimize placebo effects include recruiting from fewer sites, avoiding open-label lead-in, conducting longer trials, using validated assessments, and including more severely affected participants, and those with a first episode or shorter illness duration[137]. However, these recommendations are based on evidence mostly from adult studies; youth-specific research is still needed.

Assessing outcomes beyond core symptoms

- The bulk of available RCTs focus on outcome measures related to core symptoms.
- Trials should be incentivized to include outcomes beyond core symptoms, such as functional measures[138]. Notably, the European Medicines Agency (EMA) supports adding quality of life and functional outcomes alongside symptom ratings[24].
- Valid, age-appropriate functional and cognitive measures in child and adolescent psychiatry are urgently needed.
- Cognitive outcomes should be used more broadly, with developmentally sensitive norms similar to those we have for growth and blood pressure.

Consideration of developmental windows

- Extrapolating results from trials in adults may be misleading.
- Research should consider age-related differences in medication response and adapt study design accordingly.
- Timing interventions to developmental stages and assessing effects on normative development are crucial.

Trials comparing pharmacological and non-pharmacological interventions

- Inferring the comparative efficacy and tolerability of pharmacological and non-pharmacological treatments from trials focusing only on pharmacological or non-pharmacological treatments may be misleading, due to differences in control conditions[139].
- Methodological advances, such as including both placebo and sham arms, should be encouraged to compare interventions rigorously.

Moving beyond standard placebo-controlled randomized trials

- RCTs have limitations for studying real-world patients, rare events, and long-term outcomes.
- Pharmacoepidemiologic studies leveraging large datasets to detect rare adverse effects should be encouraged.
- Self-controlled methods[140] and emulation of target trials[141,142] should be encouraged.
- Stepped wedge cluster randomized trials[143], platform trials[144], and *in silico* trials may provide unprecedented opportunities[145].

Moving towards precision medicine / stratification approaches

- One-size-fits-all approaches limit personalized treatments.
- Biomarker research is limited by lack of incorporation in pharmacological trials and scarce academic funding.
- Future success likely depends on multi-level biomarker approaches validated in independent samples and tested for cost-effectiveness[146].

Therapeutic drug monitoring (TDM)

- TDM helps guide compliance, dosing and interactions, and combined with pharmacogenetics supports personalized medicine.
- Wearable sensors offer promising on-body monitoring.

Implementation of digital technologies

- Digital tools, including artificial intelligence and real-world data, can enhance diagnostics, recruitment, and drug safety monitoring.
- Remote and decentralized clinical trials using secure digital platforms can increase flexibility and inclusivity[147].

Ecological momentary assessment

- Traditional self-reports are prone to recall bias, while ecological momentary assessment captures real-time data in natural settings.
- Ecological momentary assessment can track dynamic patterns across various disorders and support transdiagnostic, dimensional assessment approaches[148].
- Problems with feasibility in ordinary clinical practice and patient engagement need to be addressed.

Focusing on individuals who have not responded to initial treatment

- Treatment-resistant individuals are often excluded from trials[149], limiting evidence-based options after initial non-response.
- More trials are needed in this group, exploring augmentation strategies and the possible role of non-pharmacological adjuncts.

Table 3 Key challenges and possible solutions/opportunities in the field of child and adolescent psychopharmacology *(continued)*

Need for innovations in regulatory and legislative framework

- Small market size and ethical challenges limit robust evidence for pediatric psychopharmacology.
- Psychiatry accounts for only 2.4% of pediatric trials[24], despite regulatory frameworks (i.e., pediatric investigation plans in Europe[150]) which outline how a medicine should be tested in children to ensure that it is safe, effective and appropriately dosed for pediatric use.
- Including adolescents in adult trials or running parallel trials in adults and adolescents/children with conditions that have significant unmet needs at young ages may accelerate access to treatments for youth.

Innovation in the way research is conducted, reported and promoted

- Brain research in youth remains underfunded despite its strategic importance.
- Stronger academia-industry collaboration is needed for drug development.
- Research should involve people with lived experience to improve relevance, access and impact.
- Individual participant data meta-analyses, especially when coupled with real-world data[151], can inform on efficacy or tolerability in subgroups of individuals with more heterogeneous characteristics.
- Current nomenclature in child and adolescent psychopharmacology can be confusing (e.g., "antipsychotic" for tics), and may be replaced by classifications based on mechanisms of action[152].

Reducing stigma related to child and adolescent psychopharmacology

- Stigma related to psychopharmacologic treatment is common.
- Education for families, school staff, and the public - ideally involving people with lived experience - is vital to reduce stigma around mental illness and psychotropic medications.

Psychological treatments

Psychological treatments in children and adolescents have been studied for over 50 years. A meta-analysis[157], including 447 trials spanning four decades of research on a range of psychotherapies across disorders, found an overall effect size (g) of 0.46. The pooled effect size was highest for the treatment of anxiety (g=0.61), followed by conduct problems (g=0.46), ADHD (g=0.34) and depression (g=0.29), with age generally not being a significant moderator of effect.

These results should be interpreted in the light of possible caveats. Notably, pooled studies were highly variable in relation to the type of control and rater of symptoms. It should be considered that, while "usual care" provides a notably strong comparison, other passive conditions, such as clinical monitoring or waitlist, represent easy-to-beat controls[139]. Type of rater of outcome may also influence the effect size, possibly due, at least in part, to expectancy effects, but also to setting-dependent behaviors.

For instance, a seminal meta-analysis of non-pharmacological interventions for ADHD showed that the effects of behavioral parent training were significant and large when considering symptom scores from raters proximal to the delivery of the intervention (typically, parents) (effect size of 0.40). In contrast, the effect became non-significant when relying on scores from distal raters (likely blinded, such as teachers) (effect size of 0.02)[158].

In relation to the specific type of intervention, the following were found superior to control conditions in an umbrella review of meta-analyses[128]: social skills training and behavioral therapy in ADHD; social skills training, parent-child interaction therapy, intensive behavioral therapy, and cognitive behavioral therapy (CBT) in autism; combined parental and child behavioral interventions for conduct disorders; interpersonal therapy, problem-solving therapy, family therapy, CBT, and interpersonal therapy for depression; CBT for anxiety disorders; group CBT, behavioral therapy, and behavioral therapy with exposure and response prevention for obsessive-compulsive disorder; group CBT for post-traumatic stress disorder (PTSD); and family therapy for anorexia nervosa.

Despite advances in treatment development, a significant research-practice gap persists. A low proportion of trials have examined candidate mechanisms of change, with small study samples resulting in low power to detect mediation effects[159]. In addition, many evidence-based treatments still leave a portion of youth clinically impaired post-treatment, and some conditions (e.g., early-onset eating disorders[160]) are often treated with therapies not supported by research.

Notably, treatment effects for anxiety disorders and ADHD have not improved over time, while effects for depression and conduct problems have declined[161]. This may be partly due to evolving study designs, with early trials often using waitlist or no-treatment controls, potentially inflating efficacy estimates[159]. Moreover, although 90% of the world's youths live in LMICs, fewer than 10% of youth RCTs have been conducted in these settings[162], pointing to the need of scalable interventions. Finally, possible side effects of therapies are rarely assessed[163].

These challenges underscore key opportunities. Dismantling studies can compare specific treatment components or sequences to identify active ingredients. These studies are currently limited in youth, but show promise (e.g., parent involvement in CBT improves anxiety outcomes)[164]. Furthermore, experimental therapeutics targeting and manipulating specific risk factors/processes (e.g., cognitive biases in anxiety[165]) can provide useful information.

Treatment personalization will be key to move beyond the one-size-fits-all approach that is associated to suboptimal effect sizes. The synthesis of participant data from multiple RCTs using advanced meta-analytic methods is a promising avenue to inform decisions about treatments for individual patients[166]. Moreover, sin-

Table 4 Additional key challenges and solutions related to psychological treatments for children and adolescents

Better representation of and treatment development for all youth

- Most participants in randomized controlled trials (RCTs) are White, middle/upper class[169], limiting generalizability.
- Intervention adaptations for diverse cultural and socioeconomic groups are mixed in effectiveness[170].
- New efforts should aim to develop/adapt interventions for marginalized groups via co-creation of contextually grounded, affirming and accessible models[171].

Sustained implementation of evidence-based interventions in delivery settings

- Effective psychotherapies for children and adolescents are often not implemented in real world[172].
- Implementation science frameworks help tailor treatments for frontline providers and community settings[173].
- Integration of social determinants of health may improve fit of interventions[174].
- Training and organizational support are key to uptake and sustainment of evidence-based treatments[175].
- Feedback loops from real-world practice to research can close gaps in accessible, effective intervention delivery[176].
- Incorporating core RCT elements (targets, measures, mechanisms) into practice can advance implementation science[177].

Balancing between rigorous clinical science and service delivery access

- There is tension between rigorous testing and the realities of service delivery[178].
- Engaging stakeholders (youth, families, providers, systems) in intervention design can promote better dissemination[179].
- Systems and policy changes, alongside collaborative development, can reduce the research-practice gap[178].
- Long-term innovation must integrate precision medicine with real-world application, addressing both established and novel treatments in diverse populations[180].

gle session therapies have been found effective in a meta-analysis of 50 RCTs[167] (effect size of 0.32), with effects stronger for anxiety (effect size of 0.56) and conduct problems (effect size of 0.54), suggesting that brief scalable interventions, which could be implemented in LMICs, might complement traditional multisession treatments, which are often started but not completed.

Other meta-analytic evidence[168] shows similar effects for in-person and online-delivered therapies in youth for some conditions (e.g., anxiety and conduct problems), although not all (e.g., ADHD and prison populations), suggesting that at least some individuals with specific conditions may benefit from online scalable interventions.

Table 4 details other challenges and solutions in relation to psychological treatments for children and adolescents.

Neuromodulation

A comprehensive umbrella review, covering the effects of neurostimulation across mental health conditions in children and adolescents, found only evidence of small effects of neurofeedback for ADHD, with low reliability, and not confirmed when analyses were restricted to probably blinded raters[128].

However, two neurostimulation therapies have been cleared by the FDA for children and adolescents: a) external trigeminal nerve stimulation for individuals with ADHD (aged 7-12), based on a pilot RCT[181], but not confirmed by a later definitive RCT[182]; b) transcranial magnetic stimulation as add-on treatment for depression in youth aged 15-21, based mainly on analyses of observational data, compounded by meta-analytic evidence from six RCTs[183].

Overall, neuromodulation represents an area that deserves more dedicated funding to establish efficacy, safety and age-appropriate protocols, understand underlying neural mechanisms, identify biomarkers to predict treatment response, improve accessibility, and address ethical and regulatory considerations.

Physical exercise

Physical exercise has been associated with moderate to high effect sizes across several disorders in umbrella reviews, but the level of evidence is often unclear or low, for example, in anxiety/depression[184] and ADHD[155] in youth. As such, recommending it as a specific intervention in guidelines awaits further evidence.

Treatment adherence

Treatment adherence refers to the extent to which patients and their families follow prescribed pharmacological treatments, therapy sessions, behavioral interventions, or lifestyle modifications[185]. In child and adolescent mental health, adherence presents unique challenges due to developmental, social and familial factors[186]. Non-adherence remains a critical obstacle to the effective implementation of evidence-based mental health treatments.

Barriers to adherence in children and adolescents with mental health issues often arise from developmental immaturity, limited resources, and pervasive stigma surrounding mental health[187]. Family dynamics and attitudes, in particular, play an essential role in fostering adherence, particularly through managing medications, attending or facilitating therapy sessions, ensuring consistency with treatment plans, and implementing changes in the home, including parenting practices, that are necessary to support recovery[188].

Recognizing the broader family context is essential to addressing adherence challenges effectively. Adherence can be affected by erroneous beliefs of parents and young people, such as the belief that mental disorder does not warrant the use of medication, or that use of psychotropics is dangerous, or that medications should not be used for maintenance care.

According to a meta-analysis of 28 studies, only about 65.9% of youth with severe mental illness adhere, on average, to prescribed medications[186]. Risk of non-adherence was significantly higher among youth with comorbid ADHD (odds ratio, OR=0.61), substance use disorders (OR=0.66), or more severe illness (OR=0.44), whereas adherence to pharmacological treatment was strongly associated with engagement in psychotherapy (OR=5.70), positive patient attitudes (OR=3.41), and supportive family beliefs about

treatment (OR=2.82)[186].

Age, sex/gender and socioeconomic status did not significantly moderate the rates of medication adherence, but studies with a higher percentage of female participants found that older children were more likely to be adherent, compared with studies with fewer female participants. Medication type was not a significant predictor of adherence overall; however, in studies of youth with psychotic disorders, antipsychotic medications were linked to a higher risk of non-adherence than other medications[186].

The complexity of the medication regimen was not a significant predictor of non-adherence overall. However, when analyses were stratified by diagnosis, regimen complexity was linked to a higher risk of non-adherence specifically among patients with bipolar disorder[186]. Finally, family attitudes toward psychiatric treatment were significantly associated with rates of adherence, wherein youth from families with more positive attitudes experienced higher levels of medication adherence[186].

Regarding factors specifically associated with dropout from psychotherapy, data collected on 1,177 intakes from a large sample of children and adolescents (aged 5-18)[189] suggested that ethnicity (specifically being African American) was a significant factor increasing dropout. Residing in a single-caregiver household, living with a non-biological family, receiving state-funded low-income insurance support, having lower parent-reported youth functioning, undergoing a routine (rather than urgent) intake, and experiencing longer wait times were additional factors associated with dropout, with varying levels of significance depending on the dropout definition used[189].

Strategies have been tested to improve adherence to treatment in child and adolescent mental health services, building on the evidence provided by the aforementioned studies. Adherence to pharmacotherapy has been found to benefit from recognizing the larger context of the family, allowing time for parents and children to change their attitudes toward treatment, ensuring easy access to medications and support systems, and enhancing motivation through targeted education and encouragement. Respecting the preferences of patients and families, while guiding them towards evidence-based interventions, has been shown to foster cooperation and build trust within the therapeutic process[190].

Examples of evidence on strategies to improve adherence include: a) meta-analytic evidence[191] (six RCTs) showing the effectiveness of strategies to improve ADHD medication adherence (pooled OR=2.39), including behavioral approaches (e.g., rewards, reminders or counseling), educational programs (e.g., psychoeducation or skills training), and technology-based interventions (e.g., mobile apps or electronic reminders); b) a systematic review[192] of 17 studies showing that brief, intensive interventions that directly addressed families' practical and psychological barriers were effective in improving early session engagement in parent and child mental health programs. Additionally, long-term improvements in engagement and retention were achieved by interventions that combined motivational interviewing, family systems approaches, and enhanced support for family stress and coping throughout treatment[192].

Digital tools and technologies present substantial opportunities to address adherence challenges. Mobile apps, wearable devices, and telehealth platforms offer real-time monitoring, reminders, and motivational tools to support adherence. Moreover, these innovations can extend access to care for underserved populations, addressing geographical and logistical barriers while collecting valuable data for treatment optimization[193,194].

In conclusion, improving adherence among children and adolescents with mental disorders will require multi-level innovation. Future efforts should integrate family-centred and developmental-sensitive strategies alongside patient education. Embedding digital tools (such as reminders, apps and telehealth) and behavioral supports (motivational interviewing, contingency management) shows promise. Enhancing collaboration between caregivers and youth, tailoring interventions by age and diagnosis, and embedding adherence promotion into routine care pathways are vital. Robust prospective trials targeting high-risk groups, implemented in real-world settings and evaluating long-term outcomes are critical to translate evidence into sustained practice.

Parental participation/engagement

Parental participation/engagement (PPE) refers to parents' active involvement in various processes, including help-seeking for their child, gathering information about their child's condition, participating in therapeutic decisions, facilitating attendance to visits, and implementing treatment components in the clinic or at home [81,195].

Additionally, certain clinical situations in children and adolescents necessitate parent-mediated therapy, which seeks to implement behavioral strategies such as contingency management or adequate eating behaviors, as in family-based treatment for eating disorders. In intensive family-centered programs, such as family systems therapy and multisystemic therapy, therapeutic alliance and PPE are core elements of the intervention.

PPE has consistently been linked to improved outcomes in child functioning across various mental health conditions, although results are more variable at the symptom level[195]. Meta-analytic evidence from twenty RCTs showed that interventions involving parents had a significantly greater impact on adolescent psychopathology compared to interventions focused solely on adolescents (g=–0.18)[196].

PPE is often assessed through homework completion by parents. In a review of the literature[195], the average completion rate was 49%, with a broad range from 19% to 89%. Generally, mothers are at the forefront of seeking health care and implementing treatment. In interventions for child mental health disorders, studies show that mother-led is significantly higher than father-led involvement, with mother participation exceeding 90%[195]. When examining health care seeking attitudes of self-referred families, on average 12.6% of referrals were from fathers, and 87.4% from mothers[197].

Parents often face psychological barriers (such as their own mental health problems or low motivation) which reduce their capacity to engage meaningfully. One study found that poorer par-

ent mental health predicted lower session attendance and lower therapist-rated engagement[198]. Moreover, situational and structural factors – such as competing demands (work, other children), inconvenient scheduling, transportation issues, or service location – create barriers to access that disproportionately affect low-income or marginalized families[199]. In addition, relational and attitudinal factors impact engagement: parents may feel judged, blamed or not listened to in therapeutic settings, reducing their willingness to participate actively[195].

To improve PPE in interventions for children and adolescents with mental disorders, services need to adopt a multi-pronged, flexible strategy that addresses both practical and relational barriers. One effective approach is tailoring intervention delivery to parents' lives by offering flexible scheduling, varied formats (e.g., digital/web components, brief modules), and integration with existing family routines, thus reducing the burden of competing demands and enhancing accessibility[200].

Strengthening knowledge and awareness is also crucial: parents may not engage simply because they lack clear information about the intervention's purpose, their role, or expected outcomes. Notably, a systematic review found that PPE strategies based on established theories – such as the health belief model (which suggests that people's participation depends on how strongly they believe that they are at risk of a problem) and the theory of planned behavior (which proposes that behavior is driven by intention, shaped by attitudes, social norms, and perceived control) – may help increase parents' engagement[201].

Services should therefore invest in clear orientation, transparent communication and building parents' self-efficacy (helping them feel confident and competent in their role), consistent with motivational frameworks of parent/child engagement that emphasize hope, readiness and self-efficacy[202]. Further, employing community-based outreach (for example, via community health workers in underserved settings) can enhance engagement by building trust and aligning interventions with families' lived contexts[202]. Lastly, interventions should deliberately involve all relevant caregivers (including fathers) and be culturally sensitive and inclusive.

Together, these strategies can make parental participation not merely a required "add-on", but a central and supported component of youth mental health intervention efforts.

Integration between clinical care and support provided in schools

As primary environments in which children and adolescents spend much of their time, schools represent a critical setting for collaboration between mental health professionals and educational personnel to more effectively identify psychological difficulties that hinder learning and to implement strategies that promote both mental well-being and academic achievement[203].

The World Health Organization (WHO) underlines the inseparable nature of learning and mental health and the fact that mental health issues can disrupt learning[204]. As an example, a study from the UK[205] showed that educational attainment for youth with depression declined significantly compared to unaffected peers (estimated z-score change = –0.52). According to another study conducted in Chile[206], mental health issues significantly decreased students' end-of-year grade point averages (d=0.25) and the percent of school days attended.

There are multiple ways in which schools can support youth mental health and, vice versa, mental health professionals can support learning. Schools can be a vehicle to deliver preventive strategies, including for bullying, inadequate use of substances, and youth suicide, and identify emerging issues that warrant early intervention. Further, as young people with diagnosable mental disorders are entitled to high-quality/intensified education programs, this may require input from mental health professionals to appropriately adapt the curriculum and provide accommodations.

Despite these opportunities, child and adolescent psychiatry has historically often been poorly integrated with schools and education systems. For instance, the National Evaluation of Targeted Mental Health in Schools 2008 to 2011, commissioned by the UK Department for Children, Schools and Families, highlighted that the relations of schools with child and adolescent mental health services were poor and limited at the start of the evaluation, even though they improved over the three years of the study[207].

Several challenges can explain this lack of integration. These include a shortage of child and adolescent psychiatrists, as previously discussed. Consequently, there may be concerns of being overwhelmed by demands if these psychiatrists work within schools[208,209]. Additionally, training for mental health professionals on how to effectively work within complex systems, particularly the education system, is often inadequate[210,211].

A frequent barrier to integrating child and adolescent psychiatry in schools is the perspective of schools and education systems. Child and adolescent psychiatrists are seen as a costly resource in what is often a resource-poor environment[212]. Furthermore, a systematic review[209] found that, when child and adolescent psychiatry is integrated, there are often issues of poor engagement at all levels of schools. When mental health practitioners are present in schools, their role is often limited to conducting assessments or providing one-on-one counselling for students[209].

Although any model needs to be adaptive to meet local needs and resources[210], it would be advisable that child and adolescent psychiatrists – and other highly skilled mental health practitioners such as psychologists, social workers, nurses and case managers – interact directly with stakeholders at every level of the school[208]. This approach would allow the development of skills and knowledge in evidence-based practice, so that teachers and school well-being staff can effectively implement universal mental health promotion and mental health literacy programs.

A common problem encountered with mental health programs in schools is the lack of fidelity in implementation (i.e., the intervention is not implemented as it was originally designed)[213,214]. Therefore, the role of mental health professionals could also include providing training, support and feedback to teachers to accurately identify students who need assessment and support for their

mental health, and to manage and accommodate various mental health and neurodevelopmental needs within the classroom.

Both school staff[215] and health practitioners[216] have argued that integration of mental health into schools would require some level of on-site support. However, given the flexibility afforded by technology, this on-site presence could be minimized to ensure that the psychiatry support is used as effectively and efficiently as possible[209]. This would be particularly valuable in rural locations and LMICs where mental health professionals are scarce[209,217,218].

Notably, another critical barrier identified by child and adolescent psychiatrists regarding their willingness and capacity to work within schools is a lack of training on how to navigate the ethical issues involved[210,211]. For example, there are challenges related to balancing confidentiality and meeting young people's needs. It has been reported[211] that more than 75% of adolescents and parents wanted minimal information to be shared with school, whereas 95% of school staff wanted as much information as possible to understand a student's challenges and how to accommodate those needs most appropriately.

While some psychiatric training programs include school consultations, the depth of coverage varies, and not all programs do so[210]. For child and adolescent psychiatric programs, it would be highly beneficial to include specific training about the school environment and how to work and consult effectively and ethically within educational systems. Indeed, in a study based on interviews to child and adolescent mental health practitioners in UK[219], it was found that, after receiving such training, psychiatrists were able to effectively work with schools and develop partnerships between schools and families to support the mental health needs of students.

A successful example of an initiative aimed at enhancing the mental health of students and teachers is the European Union-funded Promoting Mental Health at School (PROMEHS) project[220]. This is a school-based, universal mental health promotion program, aimed to: a) develop an evidence-based, universal curriculum for mental health in schools, targeting students aged 3-18; b) provide training for teachers and school staff, involving parents and school leadership, and integrate it into educational policy and practice; c) promote social-emotional learning and resilience, while preventing behavioral, emotional and social problems among students.

This project demonstrated effectiveness in improving the mental health of both students and teachers across all six European countries where it was implemented[220]. Most parameters reflecting social emotional learning improved significantly ($p<0.001$ for most domains). The project was also able to reduce mean internalizing and externalizing difficulties scores, and improve prosocial behavior scores from pre- to post-test ($p=0.006$)[220].

In sum, strengthening communication channels, developing shared care plans, and providing joint training for clinicians and school personnel can ensure that interventions are consistent, timely, and tailored to each student's needs. This integrated approach has the potential to improve early identification, continuity of care, and overall mental health outcomes for students.

Digital influences and cyberbullying

Digital technologies have profoundly transformed childhood and adolescent development, bringing with them unprecedented opportunities for learning, connection and creativity[221]. Despite the undisputed benefits, the pervasive integration of digital technologies into daily life has introduced significant mental health risks, associated with the way children and adolescents use digital media[212]. Excessive screen time has been linked to sleep disturbances, reduced physical activity, and poor academic performance[222,223].

Importantly, it has also been associated with social isolation. For instance, a recent study by the National Society for the Prevention of Cruelty to Children in the UK found a significant decline in daily in-person play among children: only 25% of children engaged in face-to-face play daily, with this figure dropping to 21% among teenagers aged 12 to 16[224]. In young people aged 15 to 24, the time spent in-person with friends has decreased by 70% from 150 min per day in 2003 to 40 min per day in 2020[225,226].

Furthermore, the phenomenon of "social comparison", in which users compare their lives to curated and idealized representations of others, can erode self-esteem and fuel feelings of inadequacy[227]. This is particularly evident in adolescents, whose self-image is still developing and is highly sensitive to peer evaluation[228]. This drive for social validation is further reinforced by immediate gratification through the rewarding effect of browsing, e.g., likes and comments, and continuous streams of novel content on social media, which stimulates the dopaminergic system, reinforcing prolonged engagement and addictive behaviors[229].

Overall, longitudinal research suggests a bidirectional relationship between use of digital technologies and mental health in children and adolescents: while poor mental health may lead to increased engagement with digital media as a form of escape, excessive and problematic use of digital platforms may, in turn, precipitate or exacerbate mental health difficulties[230]. Crucially, it is important to appreciate that the amount of time spent on screens is not the main factor influencing mental health outcomes. Instead, the "quality" of how individuals use their devices – their online experiences, interactions, and how these relate to other lifestyle factors such as physical activity and sleep – has the greatest impact[231].

A particularly pressing issue related to digital influence is cyberbullying, a form of peer aggression that uses digital platforms to harass, intimidate, or socially exclude others. Without time or place constraints, it can occur at any time, violate the perceived safety of one's home, and reach a large audience[232]. For instance, in a large survey of more than 10,020 UK participants aged 12-20, 42% of them were found to have experienced cyberbullying on Instagram, 37% on Facebook, and 31% on Snapchat[233].

The architecture of social media platforms – with algorithms that amplify sensational or emotionally charged content – can escalate the scope and impact of harmful consequences, including increased rates of anxiety, depression, self-harm, and suicidal ideation, particularly among adolescents, who already face the complex developmental challenges of forming personal and social

Table 5 Directly actionable advice to promote healthy digital device usage[237]

For adolescents

- Use built-in smartphone features (e.g., "Do Not Disturb", notification controls) to reduce distractions rather than relying on timers alone.
- Focus on *replacing* screen time with alternative engaging activities (especially ones involving friends/family) so that social, physical and mental health behaviors are supported, rather than simply restricting usage.
- Shift from passive consumption (e.g., endlessly scrolling feeds) to more intentional online engagement (e.g., content creation, supportive interactions, goal-oriented digital activity).

For parents and families

- Familiarize yourselves with device and app settings (notifications, screen-tracking, privacy controls) so that you can guide usage habits and model healthy behavior.
- Create structured "screen-free" times or zones (especially around bedtime) to protect sleep and promote real-world social interaction and physical activity.
- Encourage and facilitate device use that aligns with your child's interests, goals and positive behaviors (e.g., online communities around hobbies, or creating content) rather than only emphasizing limitation.

identity[234].

A number of factors predispose to a greater risk of cyberbullying. Compared with controls, children and adolescents with neurodevelopmental disorders are over two times more likely to be victims of cyberbullying (OR=2.85), due to difficulties in oral and/or social communication that could lead to a misinterpretation of the behaviors of online communication partners, while difficulties in controlling frustration and impulsivity could increase the likelihood of being involved in negative online interactions[235,236].

Regarding ways to tackle these issues posed by digital technologies, a multidisciplinary team of experts in child and adolescent mental health, social media research, behavior change interventions, and public health recently reviewed the available guidelines, recommendation articles, online resources, and reports from independent think tanks. Based on this review, they provided directly actionable recommendations in this journal[237], summarized in Table 5.

Clinicians can play a critical role in guiding families toward healthy digital habits, promoting balance rather than abstinence, and advocating for systemic changes that prioritize children's online safety. Collaboration with educators, policy makers, and technology developers is essential to create environments that support positive digital engagement and protect against digital harm[238].

Regarding more specifically cyberbullying, current interventions fall into two main types[239]: a) programs that have evolved from traditional bullying interventions or other mental health initiatives, providing multifaceted prevention and intervention strategies; b) programs specifically designed for cyberbullying, including both preventive measures and post-incident harm reduction, such as school education programs, peer support initiatives, group counseling, and online interventions.

A meta-analysis of 33 longitudinal programs[239] found that interventions targeting adolescents aged 10-19 produced a significant but small effect (g=–0.169). Programs were most effective in modifying behavioral outcomes, with no significant impact on cognition or psychological states. Moreover, intervention effectiveness was influenced by factors including proportion of female participants, cultural context, program type, intervention strategy, delivery method, and duration.

Despite availability of interventions and strategies, challenges persist. The rapid evolution of digital technologies often outpaces the development of evidence-based guidelines and public health policies. The role of clinicians, particularly those working in child and adolescent psychiatry, is essential in this context. Routine assessment of digital media use, including exposure to cyberbullying, should be integrated into mental health assessments[240]. Future research should prioritize longitudinal studies that clarify causal pathways, explore moderating factors, such as personality traits and family dynamics, and evaluate the effectiveness of targeted interventions.

In conclusion, although digital technologies have become an integral part of modern childhood and adolescent life, their influence on mental health is complex and multifaceted. Addressing this challenge requires a comprehensive, multidisciplinary approach that keeps pace with novel digital developments and balances the opportunities afforded by digital interaction with proactive strategies to prevent and mitigate its risks.

The impact of war and forced displacement

The number of children and adolescents exposed to war globally has been estimated to be approximately 400 million between 1989 and 2015[241]. In recent years, the international community has witnessed an escalation of violence affecting multiple regions, including Ukraine, Sudan, Israel, Gaza and Lebanon. In Gaza alone, as of October 2025, at least 20,000 children have reportedly died since the onset of the conflict[242].

The risks posed by war, displacement, and forced migration to children and adolescents are multifaceted, with traumatic experiences, loss of family members, loss of cultural identity, gaps in education, and poor physical and mental health care, leading to potential lifelong consequences for their physical, mental and social well-being. The adverse effects on children's health stem not only from direct violence but also from insufficient health care, malnutrition, infectious diseases, and the distress experienced by their families[243].

Children exposed to war or displacement exhibit a wide range of stress-related reactions in the short-term, including specific fears, clingy behavior, prolonged crying, disinterest in their surroundings, psychosomatic symptoms, and aggressive behaviors[244]. Children's responses to violent experiences vary based on their developmental stage, making it crucial to interpret these reactions within the context of their social, emotional and cognitive development[244]. In the longer-term, a meta-analysis of eight studies on child and adolescent refugees and asylum seekers reported a prevalence of 22.7% for PTSD, 13.8% for depression, and 15.8% for anxiety disorders[245].

A meta-analysis of risk factors for PTSD in youth highlighted

that pre-trauma factors and the objective nature of the event itself had small to moderate effects. However, medium to large effect sizes were associated with subjective experiences of the event and modifiable post-trauma variables, such as low social support, perceived life threat, social withdrawal, poor family functioning, and thought suppression[246]. These findings emphasize the critical role of adequately addressing peri-traumatic and post-traumatic factors to mitigate the development, severity and chronicity of PTSD in youth.

Another major consequence of war and displacement is the loss of safety. Prolonged exposure to danger disrupts children's cognitive schemas of social safety, which are crucial for their development. These schemas, shaped by a child's experiences and the narratives constructed by their caregivers, influence their long-lasting self-perception, view of the world, and outlook on the future[247].

The significant psychological burden outlined above underscores the need for sustained mental health care beyond the initial period of resettlement. Interventions aimed at supporting war-affected youth must be comprehensive, sustainable, and free from harm[247]. Such interventions should adopt multisystemic and multilevel strategies that integrate individual, family and community support, while advocating for the cessation of armed conflicts and the promotion of political justice.

However, to date there is a limited evidence base for treating large numbers of war-affected children and adolescents, especially those who remain inside the conflict zones. A recent scoping review[248] identified six relevant studies: one study examined digital mental health interventions for children and adolescents impacted by war, while five studies focused on those affected by disasters. The majority of interventions were aimed directly at young people and their parents or caregivers, and were designed to be self-guided. About a quarter of these interventions had been evaluated through RCTs. However, since most interventions had not been adapted for specific cultural or linguistic contexts, their feasibility for implementation remains uncertain.

Expert recommendations[248] highlighted that future research should focus on building up interventions that are culturally and developmentally appropriate, engaging affected communities – especially young people – and delivered in locally spoken languages. Interventions should be rigorously tested, including via RCTs in war-affected settings, particularly for those targeting severe conditions. Content should address war-related issues such as parental separation, concern for family on the battlefield, and ongoing grief. Studies should anticipate implementation barriers, including cost, data protection, and digital access, and explore how digital interventions can be integrated with existing scalable psychosocial support in humanitarian contexts.

OPPORTUNITIES AND FUTURE DIRECTIONS

Focus on early identification and intervention

Decades of research have demonstrated that early identification and intervention in people aged 14-25 (thus crossing the transitional cutoff at around age 18) are the most cost-effective approach to reducing the economic burden and poor long-term outcomes of mental disorders, while at the same time fostering educational, social and functional development[249].

Indeed, in response to the growing crisis of youth mental health and the associated societal burden, the WHO advocates for evidence-based, rights-focused strategies to early identification and intervention in children and adolescents, as well as for their families[250]. These goals can be met by leveraging recent conceptual and methodological innovations that are detailed below.

First, over recent years, child and adolescent mental health has increasingly moved toward a transdiagnostic approach, emphasizing shared mechanisms and risk factors across different psychiatric conditions[251-253], rather than focusing strictly on categorical diagnoses with unclear boundaries and questionable clinical significance. The transdiagnostic approach to early detection and intervention offers several advantages: it aligns more closely with the heterogeneous and overlapping symptom profiles often seen in youth; facilitates earlier intervention by targeting broad vulnerabilities, and can inform the development of more flexible, scalable prevention and treatment strategies[72].

At the same time, a transdiagnostic approach also presents challenges. Transdiagnostic literature often carries the same biases that it claims to correct, such as poor reporting and tautological reasoning[254], and is frequently based on loose psychopathological knowledge and definitions[255,256]. As such, it may risk overlooking disorder-specific features that are critical for accurate diagnosis and tailored treatment, such as the differentiation of non-affective vs. affective psychoses in young people. Moreover, by de-emphasizing categorical distinctions, this approach may inadvertently contribute to further delays in the early detection and treatment of certain conditions, such as bipolar disorder in young people, which is already associated with a mean diagnostic delay of almost a decade[257].

With these limitations in mind, early detection and intervention need to place greater emphasis on transdiagnostic targets that cut across multiple psychiatric conditions in young people. Among the most pressing is suicidality, which is a major driver of mortality in young people regardless of diagnosis[258]. Early detection and intervention for suicidality in children and adolescents requires systematic screening for depression, anxiety, trauma, bullying, and self-harm across schools, primary care, and community settings[259-261].

Strengthening protective factors, including supportive relationships and community engagement, is essential. Expanding access to mental health services, by training gatekeepers such as teachers[262,263] and primary care providers, ensures timely intervention, particularly in the global South. School-based programs focused on resilience, crisis intervention, and technological tools for monitoring further enhance early detection and intervention efforts[264].

Substance abuse is another transdiagnostic factor that should be targeted by early detection and intervention in young people. An early onset of this abuse in children and adolescents is associated with poorer clinical outcomes and an increased risk of suicidality. Substance use can mask or mimic core psychiatric symp-

toms, thereby delaying appropriate diagnosis and care[265]. Yet, it frequently remains under-detected in routine child and adolescent mental health assessments[266]. The frequent lack of integration between substance misuse and child and adolescent mental health services contributes to this poor detection. Addressing this issue requires integrating systematic screening and early detection for substance use and related risk behaviors, and implementing early intervention frameworks in health care settings.

An early use of cannabis, in particular high-potency cannabis such as synthetic cannabinoids, has been shown to trigger the onset of psychotic disorders, accelerating trajectories that might otherwise have developed later or remained subthreshold[267]. Specialized clinical services are now being implemented, taking care of young people with comorbid psychosis and cannabis use[268].

There is a pressing need for expanding preventive approaches to children and adolescents, encompassing both targeted (i.e., clinical high risk, CHR, or family risk) and universal (i.e., population-level) interventions[269]. A central challenge lies in the currently limited capacity for early detection of CHR individuals, especially during the vulnerable transition from adolescence to early adulthood. This period is often marked by service discontinuity, as young people face abrupt transfers from child to adult mental health services, which can interrupt care and increase the risk of poor outcomes[270]. Preventive frameworks must be "transitional", age-flexible, to provide continuity of care across the age-18 threshold. Such models can ensure that vulnerable youth are not overlooked or underserved within existing services and that early interventions are sustained at the very moment when they are most needed[270]. On the other side, there are no established universal approaches that can substantially reduce the incidence of the most severe mental disorders, such as psychosis[271,272]. This is an area that needs to be addressed by future research.

It is important to recognize that early detection and intervention cannot be achieved by mental health services alone. Effective early identification depends on a multi-layered approach spanning community, primary and specialist care. This requires coordinated efforts across sectors to reduce fragmentation, extend the reach of detection strategies, and ensure that risk indicators are systematically recognized. There is also a pressing need to adapt early detection and interventions for settings with less resources[106].

In sum, early identification and intervention in child and adolescent mental health are crucial for improving long-term outcomes. Integrating transdiagnostic approaches together with more targeted strategies and interagency collaboration can create more effective, equitable and sustainable systems to support youth and their families. In the next section, we focus more specifically on prevention programs focusing on resilience as an essential building block of sustained mental health.

Focus on resilience

Resilience is defined as a "multisystemic dynamic process of successful adaptation or recovery in the context of risk or threat"[273]. According to the WHO, the promotion of resilience represents a central pillar in the prevention of mental disorders, including those in children and adolescents[274]. Notably, the conceptualization and study of resilience initially emerged from research on children at high risk for severe psychopathology[275].

A meta-analysis of 19 studies in individuals aged 10-25 (17,746 participants)[276] found a moderately negative correlation between resilience and levels of perceived stress, anxiety, burnout and depression (r=–0.391). The same analysis found a moderately strong positive correlation between resilience and mental well-being, quality of life, life satisfaction and self-efficacy (r=0.499). Therefore, promoting resilience within clinical practice has the potential to support mental health across childhood and adolescence, functioning not only as a protective factor against the onset of mental disorders, but also as a means of attenuating the severity of such conditions when they do occur.

Interventions designed to foster resilience typically target specific factors, such as active coping, cognitive flexibility, self-esteem, and social support[277]. The most recent meta-analytic evidence[278], based on 68 RCTs, found a moderate effect of mindfulness-based interventions (standardized mean difference, SMD=0.32), a moderate effect of sport-based interventions (SMD=0.49), and no significant effect of CBT (SMD=0.12) on resilience.

School-based programs designed to build resilience have also been increasingly implemented. Resilience interventions can take many forms, including structured lessons within the curriculum or broader initiatives that enhance a school's ability to leverage internal and external resources to strengthen protective factors. They vary in duration, frequency, facilitator involvement, and delivery method, such as in-person or online sessions. Most of these initiatives are universal in scope, targeting entire student populations rather than focusing solely on individuals at risk of mental health problems. Research in children aged 5-10 has shown small benefits for reducing anxiety (SMD=0.25) and general psychological distress (SMD=0.13). In adolescents, similar programs have demonstrated small positive effects on internalizing problems (SMD= 0.19)[279].

Despite progress, important research needs remain to be addressed in this field. The bulk of available studies is cross-sectional. However, since resilience is a dynamic process, additional prospective studies in children and adolescents are needed[280]. Another research need is around understanding which resilience factors to target, as children and adolescents differ in exposure to adversity, making one-size-fits-all approaches inappropriate[281]. Additionally, multilevel interventions may yield better outcomes than single-level ones, but are more complex and costly, requiring assessment of cost-effectiveness[282]. Determining the optimal intervention length is also challenging, since childhood adversity is often chronic, yet resources in affected communities may limit sustainability. These factors complicate designing effective, practical resilience-based programs[283].

While future research should address these outstanding issues, current evidence can already inform clinical practice and public health initiatives. From a clinical point of view, because higher levels of resilience are clearly linked to a child's well-being and the surrounding context plays a significant role, incorporating resilience assessment into standard clinical care should be rec-

ommended[273]. Children and families with lower resilience may require additional therapeutic support and closer monitoring compared with those who have higher resilience and a stable, supportive environment[273].

From a public health standpoint, child and adolescent mental health professionals can play an important role in guiding policies and health care systems toward evidence-based resilience strengthening strategies. This process should include coordinated efforts among educators, health care professionals, social workers, and community organizations to create supportive environments that foster mental well-being[284]. Future work should prioritize the refinement of theoretical models, the rigorous evaluation of evidence-based interventions, and the implementation of longitudinal studies to ensure the effectiveness of resilience-based approaches across diverse developmental stages.

Finally, cross-cultural factors should be taken into account. Western contexts favor individual-focused strategies, emphasizing self-efficacy and self-esteem, while Eastern contexts benefit more from family and social support[285]. Tailoring interventions to these cultural differences can enhance effectiveness in helping individuals manage stress and build resilience[278].

Integrated multidisciplinary care

As mental health conditions in children and adolescents impact multiple aspects of life – academic, social, emotional and occupational – an integrated interdisciplinary approach is crucial[286]. Interdisciplinary collaboration can bring together a broad group of health care professionals – including child and adolescent psychiatrists, psychologists, pediatricians, general practitioners, nurses and occupational therapists – as well as educators and social workers. An interdisciplinary team-based approach can offer a wide range of benefits both to the patient and the health care system. These include improved communication and information sharing among professionals, patients, families, and support networks; the integration of diverse perspectives; a broader range of ideas and approaches; more comprehensive problem solving, and enhanced decision-making[287].

Benefits of integrated models can be expected at every stage across the clinical journey. General practitioners, nurses, psychologists, and allied health professionals, if properly trained and supported, can all contribute significantly to comprehensive mental health assessments. Medication initiation and optimization obviously require a prescriber, yet non-prescribing nurses can provide valuable support. Similarly, well-trained non-medical staff can ensure high-quality monitoring of medication effects and adverse outcomes. While psychological therapies have traditionally been delivered by psychologists and psychiatrists, there is now strong clinical support for including trained nurses and other allied health clinicians in these roles[288].

To date, true interdisciplinary care remains uncommon in routine child and adolescent mental health practice globally, due to barriers related to organizational, cultural and structural factors (i.e., health care organizations often lack the necessary infrastructure and culture to support interdisciplinary collaboration), resource constraints, and the lack of supportive policies and governance models.

However, evidence suggests that integrated interdisciplinary mental health care can be both safe and highly effective. A systematic review[289] covering 15 studies, six of which were included in a meta-analysis, evaluated the effects of integrated care on clinical outcomes and health care utilization for individuals aged 12-25 with any mental health condition in community-based settings. Compared with standard care, integrated care was associated with a significantly greater reduction in depressive symptoms at 4-6 months (SMD=–0.26). Among the seven studies that assessed access or engagement, all found higher rates in the groups receiving the integrated care intervention. The most commonly reported elements of integration were multidisciplinary team involvement (13 of 15 studies), collaborative treatment planning (11 of 15 studies), and workforce training within the integrated care model (14 of 15 studies).

However, despite compelling arguments for interdisciplinary child and adolescent mental health care, the evidence base remains limited regarding optimal implementation, particularly in rural and remote settings or in LMICs. Further research is necessary to refine these approaches and extend their reach.

Integration between mental health and primary care

Integration between child and adolescent mental health and primary care encompasses a variety of models, including approaches in which behavioral health professionals provide consultation via in-person, digital or telephone-based means; the physical co-location of mental health providers within primary care practices; and structured, team-based collaborative care frameworks[290].

A meta-analysis of 31 RCTs evaluating integrated mental health and primary care in children and adolescents[291] demonstrated a significant improvement in behavioral health outcomes compared with usual primary care (d=0.32). Further analyses revealed that the effects were stronger in treatment-focused trials addressing specific diagnoses or elevated symptoms (d=0.42) than in prevention-focused trials (d=0.07).

The extent of integration between child and adolescent mental health and primary care is influenced by health care infrastructure, cultural attitudes toward mental health, and financial constraints. In the US, studies show that up to 75% of children with mental disorders are seen in primary care settings, yet only about 22% receive mental health care in those settings[292]. A 2023 American Academy of Child and Adolescent Psychiatry report noted that less than one-third of pediatricians in the US feel adequately trained to manage common childhood mental health problems[293].

Insurance and reimbursement limitations are another barrier. For example, a US national survey found that only 43% of pediatricians reported being reimbursed for mental health consultations, limiting the feasibility of sustained integration[293]. However, the US, but also countries such as the UK and Canada, are making

significant progress by embedding mental health professionals, including psychologists and psychiatrists, into pediatric teams. This approach not only ensures comprehensive care but also reduces the stigma associated with seeking mental health treatment[292,294]. For instance, in the US, the Centers for Medicare & Medicaid Services launched in 2024 the Innovation in Behavioral Health Model to promote coordinated care through value-based payments and infrastructure support for providers[295].

In LMICs, the integration of mental health with primary care is even more critical, but faces more substantial barriers. Many countries have fewer than 0.1 psychiatrists per 100,000 population, with most lacking any child and adolescent psychiatrists[95]. Mental health stigma is a major deterrent: in some regions, over 60% of parents report reluctance to seek help for their children due to cultural taboos[296]. A WHO review found that more than 80% of LMICs lack formal systems for integrating mental health into pediatric or primary care[294]. To address this issue, the WHO Mental Health Gap Action Programme (mhGAP) has trained over 100,000 primary health workers in more than 90 countries to identify and manage priority mental health conditions, including in pediatric populations[294].

Overall, integrating child and adolescent psychiatry with primary care is essential for improving global mental health outcomes. While high-income countries have made advances, gaps in training, reimbursement and service coordination persist. In LMICs, the need is urgent, and innovative, scalable models are trying to bridge critical workforce and access gaps.

Novel community-based rehabilitation programs

Over the past few decades, adolescent-oriented community-based rehabilitation programs have been launched in several countries, including Australia, Canada, Ireland, and the UK[297]. A 2023 scoping review[298] found 27 types of community-based rehabilitation programs for adolescents with mental health conditions, grouped into leisure recovery programs, integrated recovery programs, and advocacy recovery programs.

Leisure recovery programs provide adolescents with opportunities to engage in social and recreational activities within the community, addressing their age-appropriate need for self-definition and socialization with peers. Evidence shows that adolescents' unwillingness to receive professional help may be related to their fear of being stigmatized by their peers. Therefore, adolescent-friendly facilities can increase their engagement in programs and are perceived as less stigmatizing when they are located in the community rather than in a mental health institution[299]. Additionally, research indicates that participation in leisure activities can foster empowerment, a sense of purpose, and stronger social connections with peers and the broader community[300]. Also, allowing adolescents to choose their own activities is crucial, as it can boost both engagement and subjective well-being[301]. In recent years, an increasing number of programs have incorporated peer support into their services[302,303].

An example of a leisure recovery program is the Young People's Outreach Program (YPOP) in Australia[304], which provides peer support, mentoring users aged 17-25 in life skills such as housing, employment, and maintaining healthy routines and relationships. Building on YPOP's success, the Youth Community Living Support Service (YCLSS) was launched in 2016 in New South Wales, funded by the state government[305]. YCLSS promotes community engagement, education and employment while providing psychosocial support, case management, and early interventions at users' locations for adolescents and young adults aged 16-24.

Another example of a leisure recovery program is the Transitional Age Youth (TAY) program in Canada[306], which serves youth aged 14-26 with mental health challenges and/or complex conditions such as substance use or physical health issues. Staff promote personal recovery through peer support, life skills and social groups, education and employment support, three youth wellness "drop-in" hubs in Toronto, and outreach case management. TAY is part of LOFT (Leap of Faith Together), a mental health charity established in 1953 and funded by the Province of Ontario and several donations[306].

Integrated recovery programs offer a holistic approach, combining leisure and social activities with physical and mental health services for users. One example in youth is the Headspace National Youth Mental Health Foundation[307], established in 2006 by the Australian government, which operates over 100 centers across Australia, providing a "one-stop-shop" for youth aged 12-25. The centers collaborate with schools and social services, and host community events such as concerts, skating and gaming. Headspace also cultivates young opinion leaders, including volunteers and program graduates, who provide feedback, support peers, and engage in advocacy to reduce stigma. Evaluations show high satisfaction among adolescents and families, with nearly half of users reporting reduced mental distress after treatment[308].

Another example is offered in France by the Association Nationale des Maisons des Adolescents[309], established in 2004, which runs 104 centers offering psychosocial and medical care for youth aged 11-25. The centers host various leisure activities (e.g., arts, music, sports, cooking, gardening and literature), and provide youth-friendly spaces with seating areas, gardens, cafés and libraries.

Advocacy recovery programs seek to raise awareness of mental health issues by involving youth with mental health challenges in campaigns that reduce stigma and empower participants. In the UK, the YoungMinds movement[310], founded in 1993, offers four main programs for users aged 14-25: Youth Panel, YoungMinds Activist, YoungMinds Blogger, and YoungMinds App Tester. Youth Panel allows users to advise and co-influence the organization's operations, campaigns and fundraising. YoungMinds Activist trains users with mental health experience in campaigning, facilitation and presentation skills while connecting with peers. YoungMinds Blogger enables users to share personal stories and advice online, and App Testers contribute to app development, content, campaigns, and policy influence.

Another example of an advocacy recovery program is provided by the Youth MOVE National program[311], established in 2007, which stands for "Motivating Others through Voices of Experience" and aims to promote participants' rights through commu-

nity engagement across 60 branches in 35 states in the US.

Overall, while these novel community-based rehabilitation programs have received positive feedback from users, they have not been formally assessed in terms of effectiveness in studies reported in academic publications[298]. This is a major need in the field.

Innovative community-based strategies

Innovative strategies, such as outreach and mobile mental health units, have been developed to reach underserved populations in the child and adolescent mental health field. Mobile services provide flexible, on-the-ground support, ensuring that mental health care is accessible to young people who might not otherwise seek help in traditional clinical settings[312]. By offering services in familiar, non-clinical environments, mobile units can reduce stigma, and improve engagement and outcomes.

Evidence shows that children and young people feel more comfortable accessing mental health support in these settings, leading to better participation and reduced dropout rates[313]. Such initiatives can be particularly valuable in rural or deprived areas, where access to conventional mental health care is limited.

Home visiting programs are interventions delivered in the home environment to support families with young children, high vulnerability and complex needs, as part of a continuum of care[314]. Delivering interventions at home reduces attrition, fosters rapport, and involves the whole family. Providers range from health professionals and para-professionals to trained volunteers[314].

A meta-analysis[315] of 22 home visiting programs aimed at improving caregivers' mental health and psychosocial outcomes, as well as developmental outcomes for children aged 0-4 years in high-risk families, found mean standardized effect sizes ranging from –0.31 to 0.20. Only one of the four outcomes – socioemotional and/or behavioral development – showed a statistically significant effect (SMD=–0.31). Future research should expand rigorous evaluations, reduce bias, assess diverse child and parent outcomes, and clarify which program elements are most effective for different family needs.

A potentially relevant development for community-based programs is their combination with digital interventions (see next section). Digital platforms such as *LINA*[316], an augmented reality game, have shown promise in enhancing peer connection and mental health awareness among early adolescents. These innovative approaches highlight the importance of integrating community engagement and technology to address the mental health needs of youth. Future research should focus on evaluating the scalability, cultural adaptability, and long-term impact of such interventions to inform evidence-based practices in diverse settings.

Telepsychiatry

Telepsychiatry is typically described as the delivery or support of psychiatric care through electronic communication and information technologies, allowing services to be provided remotely[317]. Typically, telepsychiatry includes the use of remotely-delivered consultations through platforms such as MSTeams or Zoom to conduct assessment or to provide online psychotherapy or medication advice[318,319].

These approaches may be particularly helpful for children and adolescents, as this population is generally comfortable with digital technologies and may engage more effectively with support delivered through familiar platforms such as smartphones and online tools[320]. Indeed, telepsychiatry has been used, particularly in the last decade, to deliver care to children and adolescents in various countries[321], with significant increase triggered by the COVID-19 pandemic. In the US, for instance, the use of telepsychiatry among children enrolled in Medicaid increased by 829.6% from 2019 to 2020, with ADHD, trauma-related disorders, anxiety disorders, depression, and behavior/conduct disorders being the most prevalent psychiatric diagnoses among children using telehealth services[322].

The most obvious benefit that telepsychiatry offers is improving access to mental health care, especially in rural and remote areas where patients are often forced to travel long distances to reach the referral center[323,324]. Children and adolescents suffering from conditions such as autism that make it challenging for them to leave their homes could also benefit from better accessibility through virtual health care services[318]. Another benefit is greater privacy for patients, who are less exposed to stigmatizing attitudes and beliefs of others[318,325].

However, telepsychiatry has limitations and difficulties that have not yet been fully overcome[326]. Lack of digital devices, lack of knowledge of digital technology, and poor Internet connectivity represent significant barriers to the use of telepsychiatry in part of the population[326,327]. It should also be considered that a child or adolescent accessing a telepsychiatry service, particularly if he/she has cognitive, sensory or behavioral problems, may have greater difficulty than an adult in communicating his/her symptoms to the person on the other side of the screen. Moreover, for children and adolescents with hyperactivity, it may be difficult to sit in front of a screen for long periods of time. In these cases, the use of a remote pan-tilt-zoom camera may be preferable to the fixed integrated cameras used with adults[328,329]. It is also important to avoid assessment in settings that are not considered neutral for children and adolescents, such as a hostile home environment[321].

Organizational barriers include the cost of acquiring and maintaining technology and security systems[324], and adequate training for the implementation of telemedicine and virtual software platforms[326]. Furthermore, financial and reimbursement barriers represent a major challenge. The confusing patchwork of government regulations and insurance policies have led to significant limitations in the reimbursement of telemedicine services[326,330]. In some countries, these services are reimbursed by the public health system, while in others they are partially covered by health insurance[331].

Regarding the use of telepsychiatry for treatment purposes in children and adolescents, when considering specifically depression and anxiety, a systematic review and meta-analysis of 26

studies[332] found that telepsychiatry interventions produced large pre-post improvements (Hedges' g=0.83 for depression, 1.15 for anxiety) and moderate effects versus waitlist controls (g=0.54 for depression), pointing to strong potential, but also variable methodological quality.

In ADHD, a systematic review[333] reported low-quality but consistent evidence that digital interventions – such as game-based training, cognitive exercises, and neurofeedback – reduced inattention (SMD≈–0.25) and improved executive function, though heterogeneity was high and adverse effects were occasionally noted. For social anxiety disorder, a systematic review and meta-analysis[334] pooled 21 RCTs involving youth aged 10-25 years, finding a medium effect (Hedges' g=0.51) favouring digital CBT and exposure-based programs over any control condition.

Overall, future research and implementation efforts of telepsychiatry in children and adolescents should explore developmentally appropriate frameworks tailored to the cognitive, emotional and social maturity of these users[335,336]. Safeguarding mechanisms, such as pre-session safety planning, clear protocols for managing risk remotely, and involvement of caregivers or trusted adults where appropriate, should be embedded in telepsychiatry practice[337]. Finally, policies should promote training for clinicians in child-specific telepsychiatry competences, including engagement strategies, digital rapport-building, and cultural sensitivity, to ensure effective and ethical virtual care for children and young people[335,336].

Use of other digital technologies for assessment and treatment purposes

Beyond telepsychiatry, other digital technologies can be used to support assessment and treatment in child and adolescent psychiatry.

Technologies that can be used to aid and improve assessment include wearable devices that passively collect continuous data (digital phenotyping); and active methods, such as ecological momentary assessments, which involve users completing brief in-the-moment questionnaires, reducing recall bias and improving ecological validity. These latter active methods can be used to investigate, for instance, daily emotional dynamics of child and adolescent depression, such as negative affect variability[338]; sociability, including patterns of interactions with peers and parents[339]; and how the use of substances or social media influence young people's mood[340].

An umbrella review[341] encompassing 30 reviews (19% in children and adolescents, 29% in adolescents and young adults, and 52% in young adults) summarized studies on passive data tracing (33%), ecological momentary assessments (29%), or both (38%), finding that only 43% of the reviews reported the presence of control groups. In addition, only 52% of the reviews reported that data were validated using traditional assessments with standardized tools. Therefore, overall, the use of these digital technologies requires additional testing and stronger evidence.

Despite such limitations, advances in machine learning and artificial intelligence (AI) methods have led to the development of softwares and devices that are currently implemented in some clinical contexts. For instance, the FDA-approved *Canvas Dx* implements algorithms on data received from parents/caregivers, video-analysts, and health care professionals, informing about a possible diagnosis of autism. This tool demonstrated excellent sensitivity (98.4%) and good specificity (78.9%) among participants for which the tool was able to make a decision (<50% of the sample)[342]. This makes *Canvas Dx* a good example of promising applications of digital technologies to support the diagnostic assessment of autism spectrum disorder.

With regard to technologies used for treatment purposes, examples include mobile applications, virtual reality, serious games, and social robotics. The objectives of employing digital therapeutics in children and adolescents are multifold: a) enhancing social communication: many digital tools are tailored to improve social interaction, emotional recognition, and non-verbal communication[343]; b) improving behavioral functioning: through structured interventions, digital platforms help reduce maladaptive behaviors and promote adaptive skills, often by providing real-time feedback[344]; c) increasing accessibility and personalization of mental health care: digital platforms facilitate remote delivery of care, thereby reaching underserved populations, and are designed to adapt to the specific needs of the user, offering personalized experiences based on real-time data[345]; d) complementing traditional therapies: by serving as an adjunct to conventional interventions, digital therapeutics can reinforce treatment effects and provide additional layers of support[346]; and e) increasing learning: many digital tools are tailored to improve performance on specific cognitive domains (e.g., reading, attention, working memory, writing)[347].

Strong cognitive effects of virtual reality-based attention training (SMD from –1.07 to –1.50) have been documented in ADHD (ages 8-18)[348]. In depression, a moderate pooled effect (Hedges' g=0.49) has been reported for immersive virtual reality programs integrating relaxation and cognitive exercises (ages 13-24)[349]. For autism spectrum disorder, a 2024 meta-analysis[350] found large improvements in social skills (SMD=1.43) following virtual reality-based social training (ages 6-18).

Regarding serious games, it is worth highlighting that in 2020 the FDA approved *EndeavorRx*, the first prescription video game for children with ADHD, to specifically improve attention through engaging, adaptive gameplay. The pivotal RCT[351] supporting FDA clearance showed significant improvements in attention measures compared to controls, with a medium effect size (Cohen's d ≈ 0.36) for overall attention, but not in behavioral symptoms of ADHD.

Regarding robotics, a meta-analysis of 12 RCTs in children and adolescents (<18 years) with autism showed that robot-mediated interventions significantly improved social functioning (g=0.35), but not emotional or motor outcomes[352]. Far from replacing humans, therapists used robots to engage children and youth in case they found human interaction challenging, leading to an increased number of interactions with humans[352-354].

Overall, the collective evidence from meta-analyses and systematic reviews supports the transformative potential of digital

therapeutics in child and adolescent psychiatry. However, despite moderate/high effect sizes across various modalities, critical gaps remain in study quality, personalization, and long-term monitoring of outcomes. Clinicians need more education on integration of digital treatments into their practice. Research should prioritize evidence-based digital interventions that complement rather than replace traditional face-to-face care. Further, research involving both youth and clinicians in the co-design and testing of these tools is essential to ensure that they address specific needs and preferences[355].

Studies should evaluate adherence with privacy and ethical standards when designing digital interventions. Transdisciplinary collaboration among mental health professionals, researchers, digital therapeutics developers, and policy makers should be encouraged[356-358]. Lastly, promoting policies that facilitate the incorporation of digital therapeutics into health care frameworks will assist their usage and support sustainability[359].

Precision child and adolescent psychiatry

Current clinical practice in psychiatry – including child and adolescent psychiatry – often relies on trial-and-error approaches to intervention and has limited ability to predict outcomes, underscoring the need for more targeted, or at least stratified, approaches[360]. The emergence of precision psychiatry represents a possible paradigm shift, with the vision to tailor diagnosis, prognosis and treatment to the unique genetic, biological, environmental, psychosocial and ecological profiles of each patient[361].

Moving away from the traditional "one-size-fits-all" model, this aspirational approach aims to enhance diagnostic accuracy, optimize treatment efficacy, and minimize adverse effects[193]. Drawing inspiration from successful applications in oncology[362], precision child and adolescent psychiatry aims to integrate genetic, epigenetic and neurobiological insights as well as emotional, cognitive and behavioral data into the clinical care of children and adolescents with mental disorders.

However, the multifactorial and heterogeneous nature of mental disorders presents unique challenges, especially in children and adolescents, in whom developmental factors significantly influence neurobiological processes[363] and affect illness expression, diagnosis, prognosis, and treatment response[193]. This situation is further complicated by a limited understanding of normative brain development, less stable diagnoses over time, and increasing psychosocial complexity, which suggests that models trained on adult populations may translate poorly to childhood and adolescence[364].

The successful implementation of precision psychiatry depends heavily on the development, validation and implementation of multivariable clinical prediction models designed to support diagnosis and predict prognosis or treatment outcomes[365]. Although numerous models have been developed in psychiatry, their application in real-world settings remains very limited, as shown by a systematic review of 308 prediction models, with the potential utility in clinical practice being tested in one model only[365].

Child and adolescent psychiatry reflects this gap even more. A systematic review of prediction models published between 2018 and 2021[360] retrieved 100 eligible studies in children and adolescents. Of these studies, 41 focused on developing a new prediction model, 48 on validation of an existing model, and 11 included both development and validation. Among the 52 newly developed prediction models, 6 (11%) targeted suicidal outcomes, 18 (35%) focused on future diagnoses, and 5 (10%) addressed child maltreatment. Other outcomes included violence, crime, and functional impairments. Eleven models (21%) were specifically developed for high-risk populations. However, only one-third of the development studies were adequately powered, and this proportion was even lower among validation studies. Model performance, assessed via the C-statistic, ranged from 0.57 (low) – reported for a tool predicting ADHD diagnosis in an external validation sample – to 0.99 (high) for a machine learning model predicting foster care permanency. None of the models was tested in terms of practical implementation.

To provide an example restricted to a specific disorder, in a systematic review of 100 prediction models in ADHD[366] (88% diagnostic, 5% prognostic, and 7% on treatment response), internal validation was performed for 96% of the models, whereas only 7% underwent external validation. None of the models had been implemented in clinical practice. Only 8% of the models were rated as having a low risk of bias, while 67% were considered at high risk of bias. Clinical, neuroimaging and cognitive predictors were incorporated in 35%, 31%, and 27% of the studies, respectively. Models that included clinical predictors demonstrated higher predictive performance compared with those that did not.

Overall, none of the available multivariable models can currently be recommended for clinical practice, due to a series of barriers including limited model accuracy, very few implementation studies, high costs, clinician biases, and ethical concerns. Datasets used for algorithm generation are often not representative of clinical populations; data from minority groups are systematically excluded; and there are concerns about data privacy and potential risks derived from providing diagnostic and prognostic information. These challenges are especially important in the pediatric population, where ethical considerations must prioritize safeguarding vulnerable individuals. Addressing these barriers requires clinicians with a broad set of skills, covering scientific, ethical and legal domains, and who are able to communicate effectively with patients and their caregivers, taking into account the developmental stage of the youth.

Looking ahead, some possible avenues are worth exploring in child and adolescent psychiatry. Pharmacogenomics and biomarker-driven interventions show initial potential to guide pharmacological treatment. For instance, pharmacogenetic data on genes such as *CYP2D6* and *CYP2C19* could guide dose selection, reducing side effects and improving efficacy in treating ADHD when using atomoxetine[367], and in depression[368]. Additionally, biomarkers such as neuroimaging findings and inflammation markers could help identify early risk for conditions such as autism spectrum disorder and depression, enabling timely interventions[369]. However, replicated pharmacogenomic and neuroimag-

ing data supporting treatment decision-making in children and youth are still very limited.

Beyond pharmacology, precision psychiatry could support tailored psychosocial and behavioral interventions. CBT, for example, can be adapted to a child's developmental stage and cultural context to improve engagement and adherence. Early identification of at-risk individuals through genetic screening and comprehensive assessments may further support preventive measures, including psychoeducation and lifestyle interventions tailored to individual needs[370].

Ethical considerations are central to the development and implementation of precision child and adolescent psychiatry. Transparency in clinical prediction models, data privacy, equitable health care delivery, and effective communication of risk estimates are essential for building trust with patients and families [371]. Collaboration between patients, families and clinicians must occur throughout the development and deployment of these tools [372]. The lived experiences of youth with mental health conditions, as well as input from their families and caregivers, are invaluable for addressing potential ethical challenges and ensuring responsible use of predictive tools[372].

Future efforts must prioritize bridging the gap between research and practice. Investments in multi-omic approaches, digital health tools, and cost-effectiveness studies are crucial for scaling precision psychiatry across diverse health care systems. Real-time data from electronic health records[373], wearable devices[374], and smartphone applications[375] offer new avenues for dynamic treatment adjustments. However, these innovations also raise privacy concerns, necessitating robust safeguards and ethical oversight[376].

While precision psychiatry often focuses on genes and neurobiological underpinnings, one should not underestimate, particularly in children and adolescents, the crucial role of the environment. This role is reflected in the concept of *exposome*, which encompasses not only exposure to environmental stressors, but also factors such as the physical and built environments, socioeconomic conditions, access to health care, and individual life habits and behaviors[377]. Longitudinal cohort data, showing that genome-by-exposome models – based on 133 variables at the family, peer, school, neighborhood, life event, and broader environmental levels – explained up to 63% of variance in internalizing and externalizing symptoms in children aged 9-10, seem promising[378].

Fully personalizing diagnosis, prognosis and treatment based on the complex interplay of genes and exposome may not be achievable in the near future. However, stratifying treatment based on clinical characteristics (such as comorbidities) and, importantly, personal preferences (for example, attitudes toward medication side effects) seems more attainable. For instance, efforts are underway to apply approaches currently being tested in adult psychiatry – such as the PETRUSHKA[151] project – to child and adolescent psychiatry, notably in the context of ADHD[379].

PETRUSHKA aims to develop and test an online decision-support tool that uses machine learning and large-scale data (electronic health records and clinical trials) to help personalize antidepressant treatment for adults with depression. It does so by combining patient characteristics (age, gender, symptom severity, treatment history) and patient preferences (e.g., concerns about side effects) to generate a ranked list of recommended antidepressants, thereby facilitating shared decision-making between clinician and patient.

To potentially realize the benefits of precision psychiatry, collaborative research initiatives modeled on successful programs in other fields of medicine, such as the Children's Oncology Group, which promote multisite collaborative clinical studies, could be highly valuable. These initiatives may help foster shared expertise and infrastructure, supporting more equitable access to advancements in precision psychiatry for all children and adolescents[369].

Development and application of artificial intelligence

AI is a collection of technologies that combine large scale data, algorithms and computing power, in which machines conduct operations comparable to those of humans, including learning and logical reasoning[380].

In child and adolescent mental health, there is hope that the development and application of AI will lead to algorithms which will improve diagnosis and treatment. Machine learning techniques[381], a subfield of AI, are helping progress from identifying group-level statistical associations to predictions at the individual level. These techniques are able to test many potential predictors simultaneously and assess non-linear relationships, which is especially relevant when evaluating complex bio-psycho-socio-ecological interactions in the context of neurodevelopment[382].

Machine learning algorithms have been studied across child and adolescent mental disorders[383], addressing questions relevant to diagnosis, treatment selection and prognosis. A systematic review[384] of studies on the use of machine learning in clinical practice in child and adolescent psychiatry found 33 relevant studies. Most examined ADHD and autism. The majority of studies focused on diagnostic applications. Results varied widely, reflecting differences in algorithms, datasets and outcome measures, with predictive performance ranging from moderate to high. Key limitations included small sample sizes, insufficient external validation, and the risk of overfitting.

AI also has the potential to help boost access to care[385] and strengthen therapeutic alliance[386]. This is particularly relevant in children and adolescents, in whom engagement with care providers is variable, and technology use is higher and more integrated into daily lives, while the anonymity provided by a digital environment[387] may help circumvent stigma. For instance, there is evidence suggesting that some adolescents are more likely to disclose sensitive information to a chatbot than to a human doctor[388].

In terms of clinical implementation, as mentioned, the tool *Canvas Dx* has received FDA approval to support the diagnosis of autism[342]. However, caution is warranted prior to clinical translation[389]. The rights of children and adolescents when developing emerging technologies need special consideration[380,390]. They can lack insight into what can be harmful, and are at risk of being more easily hurt by biased or unfair advice by AI technologies seeking

to exploit rather than assist them[391-393]. Based on recommendations from the United Nations and UNICEF[394], AI systems used for child and adolescent psychiatry must put the minor at the centre of ethical requirements such as data protection and transparency. Mental health professionals should make sure that the AI tools are compliant with the European Union General Data Protection Regulation, that sets standards for security, privacy and consent[395].

Considering future research developments, AI models aimed to support clinical practice for children and adolescents with mental health issues will need to be properly trained, and show adequate validation performance on an external test set, using data from relevant child and adolescent populations, prior to implementation. Of note, most available AI models have been trained on adult populations and could not learn the specific biological and psychological distinctions between children/adolescents and adults[396].

It is crucial to assess differential performance across vulnerable subgroups (e.g., race and ethnicity, gender, different age groups, poverty, living in metropolitan or rural areas, intellectual disability), and include users' point of view by participatory modelling approaches. All this could reduce potential discrimination and biases[397-399] that could lead to erroneous AI-based diagnoses and inaccurate treatment recommendations[392,400].

Generative AI also allows for chatbots that can discuss symptoms and provide information on resources. However, AI chatbots can sometimes "hallucinate", meaning that they provide incorrect information while presenting it confidently as if it were accurate[401]. This poses a particular concern for young populations. Such errors should be rare and non-harmful, and AI systems must undergo thorough testing before being implemented. Even after deployment, ongoing monitoring is essential, including regular random checks by humans, to detect and address any instances of AI-generated misinformation[402,403].

Literacy in AI must be developed in professionals working in child and adolescent mental health services, as well as in patients and families. If the outputs from the AI system are made available to the patient by the health care professional in an intelligible and interpretable manner, and the youth can understand how an automatically deployed decision was made, this could enable an empowerment of the patient and a real shared decision-making process[404,405]. This interpretability and explainability are key in allowing the modern black-box AI tools to complement clinicians in the task-sharing delivery of care, rather than replacing them.

Overall, the presence of AI in child and adolescent mental health management should not interfere with but rather strengthen their developmental process in a safe and beneficial way for their health. Implementation studies, following good practice guidelines[390,406] and embedded in regulatory frameworks[407], will likely help advance the field.

Cultural diversity and training in cultural competence

In response to mounting clinical and service delivery challenges, cultural competence has become one of the core principles of the children's community-based systems of care[408].

Cultural competence in child and adolescent psychiatry is regarded as the ability – streaming from a combination of behaviors, knowledge and attitudes – to effectively work with youth and families from diverse cultural backgrounds, understanding and respecting their beliefs, values and practices[408]. By addressing implicit biases and cultural barriers, culturally competent care ensures that services are tailored to meet the needs of diverse populations, leading to better communication, trust and outcomes in health care settings.

However, addressing cultural diversity through culturally sensitive care in child and adolescent psychiatry faces several challenges. First, training programs in cultural competence may inadvertently reinforce stereotypes by overgeneralizing cultural traits[409]. Second, there is a lack of consistency in defining and implementing effective training[410]. Third, many frameworks fail to address systemic inequalities and the influence of privilege and power imbalances in patient-provider relationships[410]. Fourth, the lack of a standardized approach to integrating cultural competence into clinical practice creates variability in care quality across settings. Fifth, evaluating the effectiveness of training and its impact on patient outcomes remains challenging, and the slow pace of demographic change within the professional workforce continues to affect the delivery of culturally competent care.

These challenges are compounded by a lack of robust research examining the long-term benefits of cultural competence on mental health outcomes for diverse youth and adult populations. Lower-resource environments also struggle to prioritize these initiatives due to competing demands, further exacerbating disparities in access to culturally informed care.

Transitioning from cultural competence to cultural humility in child and adolescent psychiatry represents a pivotal shift in improving care for diverse populations and may be a way to address the above challenges[411-413]. Unlike cultural competence, which focuses on acquiring specific knowledge about cultures, cultural humility emphasizes ongoing self-reflection, acknowledging biases, and maintaining a willingness to learn from the lived experiences of others[414]. This approach recognizes and seeks to address power imbalances in patient-provider relationships, fostering collaboration that empowers patients and nurtures trust[415].

By promoting lifelong learning and valuing diverse perspectives, cultural humility ensures that health care providers engage with individuals through openness and respect for personal differences[416]. This approach enhances communication and understanding, facilitating the development of more authentic, empathetic and patient-centered care. While the culturally competent psychiatrist may strive to master culture, the culturally humble psychiatrist embraces the process of not knowing, reframing it as an essential and empowering element of clinical practice[412]. Over time, this shift could strengthen the therapeutic alliance with youth and their families, reduce disparities, and support equitable health care practices across diverse communities.

One essential component of modern training in culturally sensitive child and adolescent psychiatry is a focus on cross-cultural aspects of developmental cultural neuroscience, which examines how cultural contexts influence the brain's structure, function and

maturation over time[417]. Incorporating such knowledge into psychiatric training may equip clinicians to interpret neurodevelopmental patterns through a cultural lens, allowing them to identify behaviors that may be adaptive in one cultural context but misunderstood or pathologized in another. This approach may not only improve diagnostic accuracy, but also foster culturally attuned treatment strategies that resonate with the lived experiences of diverse patients and families.

Equally important is equipping psychiatrists with the skills to effectively integrate culture-related information into both diagnostic assessments and treatment plans. For instance, a Dutch study revealed that many psychiatrists and residents were unfamiliar with the Cultural Formulation Interview, a structured set of questions in mental health care designed to help clinicians understand a patient's cultural background, beliefs and experience[418].

Moreover, training must prioritize ethnopsychopharmacology[419], a field that examines ethnic and racial variations in the pharmacokinetics and pharmacodynamics of psychotropic medications. Recognizing how genetic, environmental and cultural factors influence drug metabolism and response is essential for tailoring treatments to diverse populations.

In parallel, integrating cross-cultural evidence-based psychotherapies into training curricula ensures that clinicians are prepared to deliver interventions that are both empirically validated and culturally attuned[420,421]. Research shows that culturally adapted treatments tend to be more effective than non-adapted ones[422]. However, one challenge in assessing the empirical evidence for cultural adaptation lies in the fact that most trials of psychological interventions in LMICs fail to thoroughly document the specific adaptations made.

Cultural adaptation typically involves systematically modifying interventions and training materials to account for language, culture and context, aiming to align them with the users' cultural patterns, meanings and values[422]. To preserve fidelity to evidence-based treatments, it is generally recommended to retain the core components of the intervention, while making other adjustments to enhance acceptability, comprehensibility, relevance and completeness[423].

In sum, embracing cultural competence and humility promotes continuous professional development, helping psychiatrists adapt to evolving cultural dynamics. It also positions them as advocates for systemic changes to address health care disparities and foster equity. This approach enhances outcomes and empowers young patients and their families.

CONCLUSIONS

Mental disorders in children and adolescents are common conditions that can have a huge long-term negative impact on psychosocial functioning, overall health, and quality of life, especially if they go unrecognized and untreated. These disorders must be prioritized in public health, which is far from the current reality, even in high-income countries.

For instance, in the US, funding for child and adolescent mental health services and intervention research in the fiscal year 2015 accounted for only 2.1% of the total NIMH budget authority, and mental health research funds declined by 42% between 2005 and 2015[424]. In the UK, the Royal College of Psychiatrists estimated that, in the 2016/17 financial year, less than 5% of the total mental health budget was allocated to services for children and young people in many areas of the country[425].

Determinants of mental health in children and adolescents must be examined at multiple levels, with some factors extending beyond the individual and the health care system, requiring input from sociology and political sciences. For instance, the socioeconomic context of the family can either offer favorable opportunities for development or expose individuals to significant risks of potentially traumatic events or criminogenic environments. A neighborhood may be well-equipped with leisure, social and health services, or it may suffer from deprivation. There is a need to also consider the political conditions influencing individual choices to understand the barriers to changing individual behaviors, whether within a family system or at a personal level[426].

The existence of a sufficient and appropriate workforce in services involved in the prevention, diagnosis and management of youth mental health problems is another crucial aspect dependent on health policies and priorities, as well as on university and professional training, alongside students' motivation to pursue these careers. In certain countries, promotional campaigns for child and adolescent psychiatry have been launched to generate interest in these professions[427].

In recent years, initiatives from advocacy groups and patient participation in shaping the health care environment have noticeably increased. This trend is particularly significant in the context of autism spectrum disorder, and has spurred progress across research, therapeutic efforts, and broader social areas, including education and professional life. Awareness among the general public has grown. However, significant unmet needs remain for conditions such as conduct disorder, which are largely overlooked worldwide, as well as psychotic disorders, that continue to face persistent misrepresentations and stigma, leading to serious delays in recognition and care. Notable initiatives include the involvement of children and young people in mental health research and the development of health services. Still, there is a pressing need for the operationalization and evaluation of this involvement[428].

On a global scale, there is an urgent need to rebalance research funding, expand workforce training, and support interventions for children and adolescents with mental health problems. We hope that this paper, identifying and addressing the core challenges, possible solutions, opportunities, and future directions in child and adolescent psychiatry, will contribute to increase the public awareness of the urgent need for action in this field.

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REFERENCES

1. Kieling C, Buchweitz C, Caye A et al. Worldwide prevalence and disability from mental disorders across childhood and adolescence: evidence from the Global Burden of Disease study. JAMA Psychiatry 2024;81:347-56.
2. Solmi M, Radua J, Olivola M et al. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol Psychiatry 2022; 27:281-95.
3. Rey JM, Assumpção FB Jr, Bernad CA et al. History of child psychiatry. In: Rey JM (ed). IACAPAP e-textbook of child and adolescent mental health. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions, 2015:J10.
4. Rush B. Medical inquiries and observations upon the diseases of the mind, 4th ed. Philadelphia: Grigg, 1830.
5. Anonymous. L'Hôpital des Enfants-Malades, the world's first children's hospital, founded in Paris in 1802. Pediatrics 1981;67:670.
6. Parry-Jones WL. The history of child and adolescent psychiatry: its present day relevance. J Child Psychol Psychiatry 1989;30:3-11.
7. Maudsley H. The pathology of mind. A study of its distempers, deformities and disorder. London: Macmillan, 1895.
8. Griesinger W. Mental pathology and therapeutics. London: New Sydenham Society, 1867.
9. Emminghaus H. Die psychischen Störungen des Kindesalters. Tübingen: Laupp, 1887.
10. Binet A, Simon T. The development of intelligence in children. Paris: Schleicher, 1905.
11. Preyer W. The mind of the child: the development of his faculties from infancy to adolescence. New York: Appleton, 1889.
12. Stewart J. Child guidance in Britain, 1918-1955. London: Routledge, 2014.
13. Chess S, Hassibi M. Principles and practice of child psychiatry. Berlin: Springer, 1978.
14. MacKinnon LK, James K. The Milan systemic approach. Aust N Z J Fam Ther 1987;8:89-98.
15. Bradley C. The behavior of children receiving benzedrine. Am J Psychiatry 1937; 94:577-85.
16. World Health Organization. International classification of diseases, 6th revision (ICD-6). Geneva: World Health Organization, 1948.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 1st ed. Washington: American Psychiatric Association, 1952.
18. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 2nd ed. Washington: American Psychiatric Association, 1968.
19. Graham P, Minnis H, Nicholson M (eds). The development of child and adolescent psychiatry from 1960 until 1990. Glasgow: Centre for the History of Medicine of University of Glasgow, 2009.
20. Katz D. Triple Board Program. APA Medical Student Newsletter 2004;13:2.
21. Hill P, Rothenberger A. Can we – and should we – have a europsychiatry for children and adolescents? The work of the UEMS Section and Board for Child and Adolescent Psychiatry/Psychotherapy. Eur Child Adolesc Psychiatry 2005; 14:466-70.
22. Burns BJ. Mental health service use by adolescents in the 1970s and 1980s. J Am Acad Child Adolesc Psychiatry 1991;30:144-50.
23. Rutter M. Child and adolescent psychiatry: past scientific achievements and challenges for the future. Eur Child Adolesc Psychiatry 2010;19:689-703.
24. Cortese S, Purper-Ouakil D, Apter A et al. Psychopharmacology in children and adolescents: unmet needs and opportunities. Lancet Psychiatry 2024;11: 143-54.
25. Fusar-Poli P, Bauer M, Borgwardt S et al. European College of Neuropsychopharmacology Network on the Prevention of Mental Disorders and Mental Health Promotion (ECNP PMD-MHP). Eur Neuropsychopharmacol 2019;29: 1301-11.
26. Jablensky A. Psychiatric classifications: validity and utility. World Psychiatry 2016;15:26-31.
27. Stein DJ, Shoptaw SJ, Vigo DV et al. Psychiatric diagnosis and treatment in the 21st century: paradigm shifts versus incremental integration. World Psychiatry 2022;21:393-414.
28. Regier DA, Narrow WE, Clarke DE et al. DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. Am J Psychiatry 2013;170:59-70.
29. Basheer S, Tan SF, David R et al. Review article: The acceptability and effectiveness of standardised diagnostic assessment approaches in children and young people's mental health services – an updated systematic review. Child Adolesc Ment Health 2025;30:364-74.
30. Goodman R, Ford T, Richards H et al. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. J Child Psychol Psychiatry 2000;41: 645-55.
31. Sheehan DV, Sheehan KH, Shytle RD et al. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J Clin Psychiatry 2010;71:313-26.
32. Kaufman J, Birmaher B, Brent D et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36:980-8.
33. Brøndbo PH, Mathiassen B, Martinussen M et al. Agreement on diagnoses of mental health problems between an online clinical assignment and a routine clinical assignment. J Telemed Telecare 2013;19:113-9.
34. Högberg C, Billstedt E, Björck C et al. Diagnostic validity of the MINI-KID disorder classifications in specialized child and adolescent psychiatric outpatient clinics in Sweden. BMC Psychiatry 2019;19:142.
35. Maj M. Why the clinical utility of diagnostic categories in psychiatry is intrinsically limited and how we can use new approaches to complement them. World Psychiatry 2018;17:121-2.
36. Pine DS. Diagnosis, diagnostic formulation and classification. In: Thapar A, Pine DS, Cortese S et al (eds). Rutter's child and adolescent psychiatry and psychology, 7th ed. Hoboken: Wiley-Blackwell, 2025:19-30.
37. Cortese S, Solmi M, Michelini G et al. Candidate diagnostic biomarkers for neurodevelopmental disorders in children and adolescents: a systematic review. World Psychiatry 2023;22:129-49.
38. Cortese S, Bellato A, Gabellone A et al. Latest clinical frontiers related to autism diagnostic strategies. Cell Rep Med 2025;6:101916.
39. National Institute for Health and Care Excellence. Digital technologies for assessing attention deficit hyperactivity disorder (ADHD). London: National Institute for Health and Care Excellence, 2024.
40. Bellato A, Hall CL, Groom MJ et al. Practitioner review: Clinical utility of the QbTest for the assessment and diagnosis of attention-deficit/hyperactivity disorder – a systematic review and meta-analysis. J Child Psychol Psychiatry 2024;65:845-61.
41. Liu J, Teh WL, Tan RHS et al. Sleep disturbance as transdiagnostic mediator between adverse childhood experiences and psychopathology in children and adolescents: a structural equation modeling meta-analysis. JCPP Adv 2023;3:e12156.
42. Caspi A, Houts RM, Ambler A et al. Longitudinal assessment of mental health disorders and comorbidities across 4 decades among participants in the Dunedin Birth Cohort Study. JAMA Netw Open 2020;3:e203221.
43. Vasileva M, Graf RK, Reinelt T et al. Research review: A meta-analysis of the international prevalence and comorbidity of mental disorders in children between 1 and 7 years. J Child Psychol Psychiatry 2021;62:372-81.
44. Lahey BB, Krueger RF, Rathouz PJ et al. A hierarchical causal taxonomy of psychopathology across the life span. Psychol Bull 2017;143:142-86.
45. Kendler KS. The phenomenology of major depression and the representativeness and nature of DSM criteria. Am J Psychiatry 2016;173:771-80.
46. Kist JD, Vrijsen JN, Mulders PCR et al. Transdiagnostic psychiatry: symptom profiles and their direct and indirect relationship with well-being. J Psychiatr Res 2023;161:218-27.
47. Zimmerman M. Why hierarchical dimensional approaches to classification will fail to transform diagnosis in psychiatry. World Psychiatry 2021;20:70-1.
48. Lahey BB, Rathouz PJ, Van Hulle C et al. Testing structural models of DSM-IV

symptoms of common forms of child and adolescent psychopathology. J Abnorm Child Psychol 2008;36:187-206.
49. Kessler RC, Petukhova M, Zaslavsky AM. The role of latent internalizing and externalizing predispositions in accounting for the development of comorbidity among common mental disorders. Curr Opin Psychiatry 2011;24:307-12.
50. Caspi A, Houts RM, Belsky DW et al. The p factor: one general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci 2014;2:119-37.
51. Carragher N, Krueger RF, Eaton NR et al. Disorders without borders: current and future directions in the meta-structure of mental disorders. Soc Psychiatry Psychiatr Epidemiol 2015;50:339-50.
52. Michelini G, Barch DM, Tian Y et al. Delineating and validating higher-order dimensions of psychopathology in the Adolescent Brain Cognitive Development (ABCD) study. Transl Psychiatry 2019;9:261.
53. Michelini G, Carlisi CO, Eaton NR et al. Where do neurodevelopmental conditions fit in transdiagnostic psychiatric frameworks? Incorporating a new neurodevelopmental spectrum. World Psychiatry 2024;23:333-57.
54. Kotov R, Krueger RF, Watson D. A paradigm shift in psychiatric classification: the Hierarchical Taxonomy Of Psychopathology (HiTOP). World Psychiatry 2018;17:24-5.
55. Kotov R, Jonas KG, Carpenter WT et al. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): I. Psychosis superspectrum. World Psychiatry 2020;19:151-72.
56. Krueger RF, Hobbs KA, Conway CC et al. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): II. Externalizing superspectrum. World Psychiatry 2021;20:171-93.
57. Waldman ID, Poore HE, Luningham JM et al. Testing structural models of psychopathology at the genomic level. World Psychiatry 2020;19:350-9.
58. Watson D, Levin-Aspenson HF, Waszczuk MA et al. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): III. Emotional dysfunction superspectrum. World Psychiatry 2022;21:26-54.
59. Goodman R. The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry 1997;38:581-6.
60. Garrison WT, Earls F. The Child Behavior Checklist as a screening instrument for young children. J Am Acad Child Psychiatry 1985;24:76-80.
61. Jellinek MS, Murphy JM, Robinson J et al. Pediatric Symptom Checklist: screening school-age children for psychosocial dysfunction. J Pediatr 1988;112:201-9.
62. Boyle MH, Duncan L, Wang L et al. The 25-item Ontario Child Health Study Emotional Behavioural Scales - Brief Version (OCHS-EBS-B): test-retest reliability and construct validity when used as categorical measures. Can J Psychiatry 2022;67:305-14.
63. Salum G, Hoffmann MS. Transdiagnostic perspectives. In: Thapar A, Pine DS, Cortese S et al (eds). Rutter's child and adolescent psychiatry and psychology, 7th ed. Hoboken: Wiley-Blackwell, 2025:107-22.
64. Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: a tutorial paper. Behav Res Methods 2018;50:195-212.
65. Funkhouser CJ, Chacko AA, Correa KA et al. Unique longitudinal relationships between symptoms of psychopathology in youth: a cross-lagged panel network analysis in the ABCD study. J Child Psychol Psychiatry 2021;62:184-94.
66. Rouquette A, Pingault JB, Fried EI et al. Emotional and behavioral symptom network structure in elementary school girls and association with anxiety disorders and depression in adolescence and early adulthood: a network analysis. JAMA Psychiatry 2018;75:1173-81.
67. Kraemer HC. DSM categories and dimensions in clinical and research contexts. Int J Methods Psychiatr Res 2007;16 (Suppl. 1):S8-15.
68. Child Mind Institute. Creating a global standard for child and adolescent mental health. https://childmind.org.
69. Cuthbert BN. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry 2014;13:28-35.
70. Sanislow CA. Updating the Research Domain Criteria. World Psychiatry 2016; 15:222-3.
71. Pacheco J, Garvey MA, Sarampote CS et al. Annual research review: The contributions of the RDoC research framework on understanding the neurodevelopmental origins, progression and treatment of mental illnesses. J Child Psychol Psychiatry 2022;63:360-76.
72. Shah JL, Scott J, McGorry PD et al. Transdiagnostic clinical staging in youth mental health: a first international consensus statement. World Psychiatry 2020;19:233-42.
73. Sawrikar V, Macbeth A, Gillespie-Smith K et al. Transdiagnostic clinical staging for childhood mental health: an adjunctive tool for classifying internalizing and externalizing syndromes that emerge in children aged 5-11 years. Clin Child Fam Psychol Rev 2022;25:613-26.
74. Goffman E. Stigma and social identity. In: Anderson TL (ed). Understanding deviance: connecting classical and contemporary perspectives. London: Routledge, 2014:256-65.
75. Corrigan PW. Coming out proud to erase the stigma of mental illness. World Psychiatry 2022;21:388-9.
76. Markowitz FE. The effects of stigma on the psychological well-being and life satisfaction of persons with mental illness. J Health Soc Behav 1998;39:335-47.
77. Ferrie JF, Miller H, Hunter SC. Psychosocial outcomes of mental illness stigma in children and adolescents: a mixed-methods systematic review. Child Youth Serv Rev 2020;113:104940.
78. Global Coalition for Youth Mental Health. Perceptions of Youth Mental Health Report 2025: understanding the mental health impact of global challenges on Gen Z. New York: UNICEF / Global Coalition for Youth Mental Health, 2025.
79. Rohanachandra YM, Nanayakkara KASD. Stigma and stigma by association: findings from a child and adolescent mental health service (CAMHS), Sri Lanka. Sri Lanka J Psychiatry 2024;15:57-63.
80. Heflinger CA, Hinshaw SP. Stigma in child and adolescent mental health services research: understanding professional and institutional stigmatization of youth with mental health problems and their families. Adm Policy Ment Health 2010;37:61-70.
81. Fusar-Poli P, Estradé A, Esposito CM et al. The lived experience of mental disorders in adolescents: a bottom-up review co-designed, co-conducted and co-written by experts by experience and academics. World Psychiatry 2024;23:191-208.
82. Acker L, Knight M, Knott F. 'Are they just gonna reject me?' Male adolescents with autism making sense of anxiety: an interpretative phenomenological analysis. Res Autism Spectr Disord 2018;56:9-20.
83. Crockett MA, Núñez D, Martínez P et al. Interventions to reduce mental health stigma in young people: a systematic review and meta-analysis. JAMA Netw Open 2025;8:e2454730.
84. Waqas A, Malik S, Fida A et al. Interventions to reduce stigma related to mental illnesses in educational institutes: a systematic review. Psychiatr Q 2020; 91:887-903.
85. Yamaguchi S, Wu SI, Biswas M et al. Effects of short-term interventions to reduce mental health-related stigma in university or college students: a systematic review. J Nerv Ment Dis 2013;201:490-503.
86. Gronholm PC, Bakolis I, Cherian AV et al. Toward a multi-level strategy to reduce stigma in global mental health: overview protocol of the Indigo Partnership to develop and test interventions in low- and middle-income countries. Int J Ment Health Syst 2023;17:2.
87. Pereira TL, Wichaikhum OA, Nantsupawat A et al. Recognising the parental caregiver burden of children with mental disorders: a systematic mixed-studies review. Int J Ment Health Nurs 2024;33:1941-61.
88. Sowden E, Robinson D, Lovell K et al. Understanding the support needs of parents of children with obsessive-compulsive disorder: a qualitative descriptive study in the UK. BMC Psychiatry 2023;23:309.
89. Dinos S. Stigma creating stigma: a vicious circle. Psychiatr Bull 2014;38:145-7.
90. Cham CQ, Ibrahim N, Siau CS et al. Caregiver burden among caregivers of patients with mental illness: a systematic review and meta-analysis. Healthcare 2022;10:2423.
91. Piao J HY, Han C, Li Y et al. Alarming changes in the global burden of mental disorders in children and adolescents from 1990 to 2019: a systematic analysis for the Global Burden of Disease study. Eur Child Adolesc Psychiatry 2022;31:1827-45.
92. Racine N, McArthur BA, Cooke JE et al. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: a meta-analysis. JAMA Pediatr 2021;175:1142-50.
93. Centers for Disease Control and Prevention. Data and statistics on children's mental health. www.cdc.gov.
94. Rethink Mental Illness. The hidden toll of CAMHS waiting lists on young people's mental health. https://rethink.org.
95. World Health Organization. Mental health atlas 2020. Geneva: World Health Organization, 2021.
96. Radez J, Reardon T, Creswell C et al. Why do children and adolescents (not) seek and access professional help for their mental health problems? A systematic review of quantitative and qualitative studies. Eur Child Adolesc Psychiatry 2021;30:183-211.
97. Waid J, Kelly M. Supporting family engagement with child and adolescent mental health services: a scoping review. Health Soc Care Community 2020; 28:1333-42.
98. Babatunde GB, van Rensburg AJ, Bhana A et al. Barriers and facilitators to child and adolescent mental health services in low-and-middle-income countries: a scoping review. Glob Soc Welfare 2021;8:29-46.

99. Huff NR, Dunderdale L, Kellogg AJ et al. Factors related to help-seeking and service utilization for professional mental healthcare among young people: an umbrella review. Clin Psychol Rev 2024;114:102504.
100. Kirk S, Fraser C, Evans N et al. Perceptions of the key components of effective, acceptable and accessible services for children and young people experiencing common mental health problems: a qualitative study. BMC Health Serv Res 2023;23:391.
101. Werlen L, Gjukaj D, Mohler-Kuo M et al. Interventions to improve children's access to mental health care: a systematic review and meta-analysis. Epidemiol Psychiatr Sci 2019;29:e58.
102. Lenzer J. Is the United States Preventive Services Task Force still a voice of caution? BMJ 2017;356:j743.
103. Wissow LS, Brown J, Fothergill KE et al. Universal mental health screening in pediatric primary care: a systematic review. J Am Acad Child Adolesc Psychiatry 2013;52:1134-47.e23.
104. So M, McCord RF, Kaminski JW. Policy levers to promote access to and utilization of children's mental health services: a systematic review. Adm Policy Ment Health 2019;46:334-51.
105. Salerno JP. Effectiveness of universal school-based mental health awareness programs among youth in the United States: a systematic review. J Sch Health 2016;86:922-31.
106. Fusar-Poli P, Pillinger T, McCutcheon A et al. Real-world comprehensive care of people living with schizophrenia: recommendations across different settings and clinical stages. World Psychiatry 2026;25:231-64.
107. Patel V, Kieling C, Maulik PK et al. Improving access to care for children with mental disorders: a global perspective. Arch Dis Child 2013;98:323-7.
108. Iacobucci G. Fix "unfair" child mental health funding to protect our future health and prosperity, top paediatrician urges. BMJ 2025;390:r1580.
109. Long J, Zhang S, Chu L et al. Policies, resource allocation, and interventions for child and adolescent mental health in low- and middle-income countries in the Western Pacific Region: a scoping review. Lancet Reg Health West Pac 2025;62:101674.
110. Lu C, Li Z, Patel V. Global child and adolescent mental health: the orphan of development assistance for health. PLoS Med 2018;15:e1002524.
111. World Health Organization. Government expenditures on mental health as a percentage of total government expenditures on health (%). www.who.int.
112. Stelmach R, Kocher EL, Kataria I et al. The global return on investment from preventing and treating adolescent mental disorders and suicide: a modelling study. BMJ Glob Health 2022;7:e007759.
113. Hamersma S, Ye J. The effect of public health insurance expansions on the mental and behavioral health of girls and boys. Soc Sci Med 2021;280:113998.
114. World Health Organization. Mental health of children and young people: service guidance. Geneva: World Health Organization, 2024.
115. Degenhardt F. Child and adolescent psychiatry meets its challenges. Eur Child Adolesc Psychiatry 2022;31:699-700.
116. Royal College of Psychiatrists. CENSUS 2023. Workforce figures for consultant psychiatrist posts, SAS psychiatrist posts and a survey of private and independent psychiatrists. www.rcpsych.ac.uk.
117. McBain RK, Kofner A, Stein BD et al. Growth and distribution of child psychiatrists in the United States: 2007-2016. Pediatrics 2019;144:e20191576.
118. Substance Abuse and Mental Health Services Administration. Behavioral health workforce report. https://mamh-web.files.svdcdn.com.
119. HRSA Health Workforce. Behavioral health workforce projections, 2017-2030. https://bhw.hrsa.gov.
120. Mareva S, Chapman B, Hardwick R et al. The mental wellbeing of child and adolescent mental health service (CAMHS) workers in England: a cross-sectional descriptive study reporting levels of burnout, wellbeing and job satisfaction. Healthcare 2024;12:430.
121. Hoffmann JA, Attridge MM, Carroll MS et al. Association of youth suicides and county-level mental health professional shortage areas in the US. JAMA Pediatr 2023;177:71-80.
122. Shapiro DN. Increasing interest in child and adolescent psychiatry during medical school: launching a summer immersion experience for medical students. Acad Psychiatry 2022;46:70-4.
123. Kishore A, DiGiovanni M, Sun KL et al. Enhancing child and adolescent psychiatry recruitment through a medical student mentorship network: a qualitative study. Acad Psychiatry 2023;47:124-33.
124. Federal Student Aid. Public service loan forgiveness (PSLF). https://studentaid.gov.
125. Singh R, Leung S, Sawrikar V et al. Increasing youth peer workers' impact through integration: peer worker perspectives on best practice in youth mental health. Health Expect 2025;28:e70223.
126. Lee CM, Yonek J, Lin B et al. Systematic review: Child psychiatry access program outcomes. JAACAP Open 2023;1:154-72.
127. Brauer R, Alfageh B, Blais JE et al. Psychotropic medicine consumption in 65 countries and regions, 2008-19: a longitudinal study. Lancet Psychiatry 2021;8:1071-82.
128. Correll CU, Cortese S, Croatto G et al. Efficacy and acceptability of pharmacological, psychosocial, and brain stimulation interventions in children and adolescents with mental disorders: an umbrella review. World Psychiatry 2021;20:244-75.
129. Solmi M, Fornaro M, Ostinelli EG et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry 2020;19:214-32.
130. Rosland HG, Wergeland GJ, Holst L. Off-label use of psychotropic drugs in youth. BMC Psychiatry 2025;25:739.
131. Cortese S, McGinn K, Højlund M et al. The future of child and adolescent clinical psychopharmacology: a systematic review of phase 2, 3, or 4 randomized controlled trials of pharmacologic agents without regulatory approval or for unapproved indications. Neurosci Biobehav Rev 2023;149:105149.
132. Pasteuning-Vuhman S, de Jongh R, Timmers A et al. Towards advanced iPSC-based drug development for neurodegenerative disease. Trends Mol Med 2021;27:263-79.
133. Flear M. The EU Clinical Trials Regulation: key priorities, purposes and aims and the implications for public health. J Med Ethics 2016;42:192-8.
134. Huneke NTM, Amin J, Baldwin DS et al. Placebo effects in randomized trials of pharmacological and neurostimulation interventions for mental disorders: an umbrella review. Mol Psychiatry 2024;29:3915-25.
135. Huneke NTM, Cortese S, Solmi M. Understanding placebo mechanisms to reduce attrition in psychiatric trials. JAMA Psychiatry 2025;82:553-4.
136. Huneke NTM, Fusetto Veronesi G, Garner M et al. Expectancy effects, failure of blinding integrity, and placebo response in trials of treatments for psychiatric disorders: a narrative review. JAMA Psychiatry 2025;82:531-8.
137. Correll CU, Solmi M, Cortese S et al. The future of psychopharmacology: a critical appraisal of ongoing phase 2/3 trials, and of some current trends aiming to de-risk trial programmes of novel agents. World Psychiatry 2023;22:48-74.
138. Correll CU, Cortese S, Solmi M et al. Beyond symptom improvement: transdiagnostic and disorder-specific ways to assess functional and quality of life outcomes across mental disorders in adults. World Psychiatry 2025;24:296-318.
139. Stringaris A, Burman C, Delpech R et al. Comparing apples and oranges in youth depression treatments? A quantitative critique of the evidence base and guidelines. BMJ Ment Health 2025;28:1-9.
140. Chang Z, Ghirardi L, Quinn PD et al. Risks and benefits of attention-deficit/hyperactivity disorder medication on behavioral and neuropsychiatric outcomes: a qualitative review of pharmacoepidemiology studies using linked prescription databases. Biol Psychiatry 2019;86:335-43.
141. Li L, Zhu N, Zhang L et al. ADHD pharmacotherapy and mortality in individuals with ADHD. JAMA 2024;331:850-60.
142. Zhang L, Zhu N, Sjölander A et al. ADHD drug treatment and risk of suicidal behaviours, substance misuse, accidental injuries, transport accidents, and criminality: emulation of target trials. BMJ 2025;390:e083658.
143. Hemming K, Taljaard M. Reflection on modern methods: when is a stepped-wedge cluster randomized trial a good study design choice? Int J Epidemiol 2020;49:1043-52.
144. Park JJH, Detry MA, Murthy S et al. How to use and interpret the results of a platform trial: users' guide to the medical literature. JAMA 2022;327:67-74.
145. Pappalardo F, Russo G, Tshinanu FM et al. In silico clinical trials: concepts and early adoptions. Brief Bioinform 2019;20:1699-708.
146. Parellada M, Andreu-Bernabeu Á, Burdeus M et al. In search of biomarkers to guide interventions in autism spectrum disorder: a systematic review. Am J Psychiatry 2023;180:23-40.
147. Rosa C, Marsch LA, Winstanley EL et al. Using digital technologies in clinical trials: current and future applications. Contemp Clin Trials 2021;100:106219.
148. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annu Rev Clin Psychol 2008;4:1-32.
149. Garcia-Argibay M, Chang Z, Brikell I et al. Evaluating ADHD medication trial representativeness: a Swedish population-based study comparing hypothetically trial-eligible and trial-ineligible individuals. Lancet Psychiatry 2025;12:131-9.
150. European Medicines Agency and European Commission (DG Health and Food Safety). Action plan on paediatrics. Status/progress, December 2020. www.ema.europa.eu.
151. Ostinelli EG, Jaquiery M, Liu Q et al. Personalising antidepressant treatment for unipolar depression combining individual choices, risks and big data: the PETRUSHKA tool. Can J Psychiatry 2025;70:768-81.

152. Cortese S, Singh MK, Novins DK. The Neuroscience-based Nomenclature Child & Adolescent (NbN C&A) for psychotropic medications: innovation in progress. J Am Acad Child Adolesc Psychiatry 2022;61:1317-8.
153. Gosling CJ, Cortese S, Radua J et al. Umbrella-Review, Evaluation, Analysis and Communication Hub (U-REACH): a novel living umbrella review knowledge translation approach. BMJ Ment Health 2024;27:1-3.
154. Gosling CJ, Boisseleau L, Solmi M et al. Complementary, alternative and integrative medicine for autism: an umbrella review and online platform. Nat Hum Behav 2025;9:2610-9.
155. Gosling CJ, Garcia-Argibay M, de Prisco M et al. Benefits and harms of ADHD interventions: umbrella review and platform for shared decision-making. BMJ 2025;391:e085875.
156. Gosling CJ, Cartigny A, Mellier BC et al. Efficacy of psychosocial interventions for autism spectrum disorder: an umbrella review. Mol Psychiatry 2022; 27:3647-56.
157. Weisz JR, Kuppens S, Ng MY et al. What five decades of research tells us about the effects of youth psychological therapy: a multilevel meta-analysis and implications for science and practice. Am Psychol 2017;72:79-117.
158. Sonuga-Barke EJ, Brandeis D, Cortese S et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry 2013; 170:275-89.
159. Weisz JR, Venturo-Conerly KE, Fitzpatrick OM et al. What four decades of meta-analysis have taught us about youth psychotherapy and the science of research synthesis. Annu Rev Clin Psychol 2023;19:79-105.
160. Ayrolles A, Clarke J, Godart N et al. Early-onset anorexia nervosa: a scoping review and management guidelines. J Eat Disord 2024;12:182.
161. Weisz JR, Kuppens S, Ng MY et al. Are psychotherapies for young people growing stronger? Tracking trends over time for youth anxiety, depression, attention-deficit/hyperactivity disorder, and conduct problems. Perspect Psychol Sci 2019;14:216-37.
162. Weine S, Horvath Marques A, Singh M et al. Global child mental health research: time for the children. J Am Acad Child Adolesc Psychiatry 2020;59: 1208-11.
163. Purgato M, Cortese S. Editorial: Primum non nocere – are adverse events accurately reported in studies on psychological interventions for children? Child Adolesc Ment Health 2023;28:351-3.
164. Whiteside SP, Ale CM, Young B et al. The feasibility of improving CBT for childhood anxiety disorders through a dismantling study. Behav Res Ther 2015;73: 83-9.
165. Biagianti B, Conelea C, Brambilla P et al. A systematic review of treatments targeting cognitive biases in socially anxious adolescents. J Affect Disord 2020; 264:543-51.
166. Karyotaki E, Efthimiou O, Miguel C et al. Internet-based cognitive behavioral therapy for depression: a systematic review and individual patient data network meta-analysis. JAMA Psychiatry 2021;78:361-71.
167. Schleider JL, Weisz JR. Reducing risk for anxiety and depression in adolescents: effects of a single-session intervention teaching that personality can change. Behav Res Ther 2016;87:170-81.
168. Venturo-Conerly KE, Eisenman D, Wasil AR et al. Meta-analysis: The effectiveness of youth psychotherapy interventions in low- and middle-income countries. J Am Acad Child Adolesc Psychiatry 2023;62:859-73.
169. Merrill BM, Hare MM, Piscitello J et al. Diversity and representation in ADHD psychosocial treatment research: a comprehensive synthesis with data from over 10,000 participants. Clin Psychol Rev 2024;112:102461.
170. Soto A, Smith TB, Griner D et al. Cultural adaptations and therapist multicultural competence: two meta-analytic reviews. J Clin Psychol 2018;74:1907-23.
171. Craig SL, Eaton AD, Leung VWY et al. Efficacy of affirmative cognitive behavioural group therapy for sexual and gender minority adolescents and young adults in community settings in Ontario, Canada. BMC Psychol 2021;9:94.
172. Williams NJ, Beidas RS. Annual research review: The state of implementation science in child psychology and psychiatry: a review and suggestions to advance the field. J Child Psychol Psychiatry 2019;60:430-50.
173. Peters-Corbett A, Parke S, Bear H et al. Barriers and facilitators of implementation of evidence-based interventions in children and young people's mental health care – a systematic review. Child Adolesc Ment Health 2024;29:242-65.
174. Berger-Jenkins E, Monk C, D'Onfro K et al. Screening for both child behavior and social determinants of health in pediatric primary care. J Dev Behav Pediatr 2019;40:415-24.
175. Scudder A, Herschell AD. Building an evidence-base for the training of evidence-based treatments in community settings: use of an expert-informed approach. Child Youth Serv Rev 2015;55:84-92.
176. Bloomquist ML, Giovanelli A, Benton A et al. Implementation and evaluation of evidence-based psychotherapeutic practices for youth in a mental health organization. J Child Fam Stud 2016;25:3278-92.
177. Weisz JR, Kuppens S, Eckshtain D et al. Performance of evidence-based youth psychotherapies compared with usual clinical care: a multilevel meta-analysis. JAMA Psychiatry 2013;70:750-61.
178. Weisz JR, Krumholz LS, Santucci L et al. Shrinking the gap between research and practice: tailoring and testing youth psychotherapies in clinical care contexts. Annu Rev Clin Psychol 2015;11:139-63.
179. Freebairn L, Song YJC, Occhipinti JA et al. Applying systems approaches to stakeholder and community engagement and knowledge mobilisation in youth mental health system modelling. Int J Ment Health Syst 2022;16:20.
180. Subasri M, Cressman C, Arje D et al. Translating precision health for pediatrics: a scoping review. Children 2023;10:897.
181. McGough JJ, Sturm A, Cowen J et al. Double-blind, sham-controlled, pilot study of trigeminal nerve stimulation for attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2019;58:403-11.e3.
182. Conti A, Bozhilova N, Eraydin I et al. External trigeminal nerve stimulation in youth with ADHD: a randomized, sham-2 controlled, phase 2b trial. Nat Med 2026;32:582-90.
183. Sun CH, Mai JX, Shi ZM et al. Adjunctive repetitive transcranial magnetic stimulation for adolescents with first-episode major depressive disorder: a meta-analysis. Front Psychiatry 2023;14:1200738.
184. Cortese S, Solmi M, Gosling CJ. Editorial: Physical exercise as a treatment for anxiety and depression in children and adolescents? The devil is in the details. J Am Acad Child Adolesc Psychiatry 2026;65:143-5.
185. Vrijens B, De Geest S, Hughes DA et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012;73:691-705.
186. Edgcomb JB, Zima B. Medication adherence among children and adolescents with severe mental illness: a systematic review and meta-analysis. J Child Adolesc Psychopharmacol 2018;28:508-20.
187. El-Mallakh P, Findlay J. Strategies to improve medication adherence in patients with schizophrenia: the role of support services. Neuropsychiatr Dis Treat 2015; 11:1077-90.
188. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization, 2003.
189. Warnick EM, Gonzalez A, Robin Weersing V et al. Defining dropout from youth psychotherapy: how definitions shape the prevalence and predictors of attrition. Child Adolesc Ment Health 2012;17:76-85.
190. Charach A, Volpe T, Boydell KM et al. A theoretical approach to medication adherence for children and youth with psychiatric disorders. Harv Rev Psychiatry 2008;16:126-35.
191. Thongseiratch T, Chalermphol K, Traipidok P et al. Promoting medication adherence in children with attention deficit hyperactivity disorder: a mixed-methods systematic review with meta-analysis and qualitative comparative analysis. J Atten Disord 2024;28:139-50.
192. Ingoldsby EM. Review of interventions to improve family engagement and retention in parent and child mental health programs. J Child Fam Stud 2010; 19:629-45.
193. Torous J, Linardon J, Goldberg SB et al. The evolving field of digital mental health: current evidence and implementation issues for smartphone apps, generative artificial intelligence, and virtual reality. World Psychiatry 2025;24: 156-74.
194. Lehtimaki S, Martic J, Wahl B et al. Evidence on digital mental health interventions for adolescents and young people: systematic overview. JMIR Mental Health 2021;8:e25847.
195. Haine-Schlagel R, Walsh NE. A review of parent participation engagement in child and family mental health treatment. Clin Child Fam Psychol Rev 2015;18:133-50.
196. Pine AE, Baumann MG, Modugno G et al. Parental involvement in adolescent psychological interventions: a meta-analysis. Clin Child Fam Psychol Rev 2024;27:1-20.
197. Dadds MR, Collins DAJ, Doyle FL et al. A benchmarking study of father involvement in Australian child mental health services. PLoS One 2018;13: e0203113.
198. Haine-Schlagel R, Dickson KS, Shapiro AF et al. Parent mental health problems and motivation as predictors of their engagement in community-based child mental health services. Child Youth Serv Rev 2019;104:104370.
199. Mendez JL, Carpenter JL, LaForett DR et al. Parental engagement and barriers to participation in a community-based preventive intervention. Am J Community Psychol 2009;44:1-14.
200. Cardamone-Breen MC, Jorm AF, Lawrence KA et al. A single-session, web-based parenting intervention to prevent adolescent depression and anxiety disorders: randomized controlled trial. J Med Internet Res 2018;20:e148.

201. Finan SJ, Swierzbiolek B, Priest N et al. Parental engagement in preventive parenting programs for child mental health: a systematic review of predictors and strategies to increase engagement. PeerJ 2018;6:e4676.
202. King G, Currie M, Petersen P. Child and parent engagement in the mental health intervention process: a motivational framework. Child Adolesc Ment Health 2014;19:2-8.
203. Cortina MA, Shipman J, Saunders F et al. Embedding interagency working between schools and mental health specialists: a service evaluation of the Mental Health Services and Schools and Colleges Link Programme workshops. Clin Child Psychol Psychiatry 2019;24:906-20.
204. World Health Organization. Comprehensive mental health plan 2013-2030. Geneva: World Health Organization, 2021.
205. Wickersham A, Dickson H, Jones R et al. Educational attainment trajectories among children and adolescents with depression, and the role of sociodemographic characteristics: longitudinal data-linkage study. Br J Psychiatry 2021;218:151-7.
206. Murphy JM, Guzmán J, McCarthy AE et al. Mental health predicts better academic outcomes: a longitudinal study of elementary school students in Chile. Child Psychiatry Hum Dev 2015;46:245-56.
207. UK Department of Education. Me and my school: findings from the National Evaluation of Targeted Mental Health in Schools 2008-2011. https://assets.publishing.service.gov.uk.
208. Coffey S, Latta L, Mueller H et al. Collaboration, innovation, and time: a shared journey through child psychiatric consultation in the school setting. Psychiatr Serv 2019;70:631-4.
209. Fazel M, Hoagwood K, Stephan S et al. Mental health interventions in schools 1: Mental health interventions in schools in high-income countries. Lancet Psychiatry 2014;1:377-87.
210. Flaherty L. Models of psychiatric consultation to schools. In: Weist MD, Lever NA, Bradshaw CP et al (eds). Handbook of school mental health. Boston: Springer, 2013:283-94.
211. Marraccini ME, McGraw CB, Henderson Smith L et al. Information sharing between psychiatric hospitals and schools to better support adolescents returning to school following a suicide-related crisis. J Sch Psychol 2024;106:101343.
212. Flannery JS, Maza MT, Kilic Z et al. Cascading bidirectional influences of digital media use and mental health in adolescence. Adv Child Dev Behav 2023;64:255-87.
213. Lendrum A, Humphrey N, Wigelsworth M. Social and emotional aspects of learning (SEAL) for secondary schools: implementation difficulties and their implications for school-based mental health promotion. Child Adolesc Ment Health 2013;18:158-64.
214. Lyon AB, Bruns EJ. From evidence to impact: joining our best school mental health practices with our best implementation strategies. School Ment Health 2019;11:106-14.
215. Connolly A, Giles-Kaye A, Smith A et al. Barriers to supporting children's mental health in Australian primary schools: perspectives of school staff. Ment Health Prev 2024;33:200323.
216. Paton K, Gillam L, Warren H et al. How can the education sector support children's mental health? Views of Australian healthcare clinicians. PLoS One 2022;17:e0261827.
217. Sun CF, Correll CU, Trestman RL et al. Low availability, long wait times, and high geographic disparity of psychiatric outpatient care in the US. Gen Hosp Psychiatry 2023;84:12-7.
218. Mulraney M, Lee C, Freed G et al. How long and how much? Wait times and costs for initial private child mental health appointments. J Paediatr Child Health 2021;57:526-32.
219. Van Roosmalen M, Daniels M, Lawrence H. Clarifying an approach to consultation: the impact of a systemic consultation training for schools-based child and adolescent mental health services clinicians. Clin Child Psychol Psychiatry 2024;29:141-54.
220. Colomeischi AA, Duca DS, Bujor L et al. Impact of a school mental health program on children's and adolescents' socio-emotional skills and psychosocial difficulties. Children 2022;9:1661.
221. Haddock A, Ward N, Yu R et al. Positive effects of digital technology use by adolescents: a scoping review of the literature. Int J Environ Res Public Health 2022;19:14009.
222. Devi KA, Singh SK. The hazards of excessive screen time: impacts on physical health, mental health, and overall well-being. J Educ Health Promot 2023;12:413.
223. Primack BA, Shensa A, Sidani JE et al. Social media use and perceived social isolation among young adults in the U.S.. Am J Prev Med 2017;53:1-8.
224. The Times. Just 25 per cent of children play face-to-face daily, NSPCC finds. www.thetimes.com.
225. Buecker S, Horstmann KT. Loneliness and social isolation during the COVID-19 pandemic: a systematic review enriched with empirical evidence from a large-scale diary study. Eur Psychol 2021;26:272-84.
226. Kannan VD, Veazie PJ. US trends in social isolation, social engagement, and companionship – nationally and by age, sex, race/ethnicity, family income, and work hours, 2003-2020. SSM Popul Health 2023;21:101331.
227. Andrade FC, Erwin S, Burnell K et al. Intervening on social comparisons on social media: electronic daily diary pilot study. JMIR Ment Health 2023;10:e42024.
228. Branje S, de Moor EL, Spitzer J et al. Dynamics of identity development in adolescence: a decade in review. J Res Adolesc 2021;31:908-27.
229. Ballara NB. The power of social validation: a literature review on how likes, comments, and shares shape user behavior on social media. Int J Res Publ Rev 2023;4:3355-367.
230. Tibbs M, Deschenes S, van der Velden P et al. An investigation of the longitudinal bidirectional associations between interactive versus passive social media behaviors and youth internalizing difficulties. A within-person approach. J Youth Adolesc 2025;54:849-62.
231. Firth J, Torous J, López-Gil JF et al. From "online brains" to "online lives": understanding the individualized impacts of Internet use across psychological, cognitive and social dimensions. World Psychiatry 2024;23:176-90.
232. Ray G, McDermott CD, Nicho M. Cyberbullying on social media: definitions, prevalence, and impact challenges. J Cybersecurity 2024;10:026.
233. United Nations. The Annual Bullying Survey 2017: cyber-bullying, online behaviour and young people's digital lives. www.un.org.
234. Kim M, Ellithorpe M, Burt SA. Anonymity and its role in digital aggression: a systematic review. Aggress Violent Behav 2023;72:101856.
235. Jackson E, Boyes M, Blundell B et al. Managing cyberbullying among adolescents with neurodevelopmental disorders: a scoping review. Int J Speech Lang Pathol 2025;27:341-56.
236. Giumetti GW, Kowalski RM. Cyberbullying via social media and well-being: a review of the research. Curr Opin Psychol 2022;45:101314.
237. Firth J, Solmi M, Löchner J et al. Promoting healthy digital device usage: recommendations for youth and parents. World Psychiatry 2025;24:1-2.
238. Alotaibi N, Wilson CB, Traynor M. Enhancing digital readiness and capability in healthcare: a systematic review of interventions, barriers, and facilitators. BMC Health Serv Res 2025;25:500.
239. Liu C, You L, Li J et al. The effectiveness of longitudinal intervention programs for adolescent cyberbullying and its influencing factors: a three-level meta-analysis. J Affect Disord 2025;388:119654.
240. Mumtaz H, Riaz MH, Wajid H et al. Current challenges and potential solutions to the use of digital health technologies in evidence generation: a narrative review. Front Digit Health 2023;5:1203945.
241. Hoppen TH, Priebe S, Vetter I et al. Global burden of post-traumatic stress disorder and major depression in countries affected by war between 1989 and 2019: a systematic review and meta-analysis. BMJ Glob Health 2021;6:e006303.
242. United Nations Children's Fund. Two years of hellish war have devastated Gaza's children. www.unicef.org.
243. Goldson E. The effect of war on children. Child Abuse Negl 1996;20:809-19.
244. Lieberman AF, Knorr K. The impact of trauma: a developmental framework for infancy and early childhood. Pediatr Ann 2007;36:209-15.
245. Blackmore R, Gray KM, Boyle JA et al. Systematic review and meta-analysis: the prevalence of mental illness in child and adolescent refugees and asylum seekers. J Am Acad Child Adolesc Psychiatry 2020;59:705-14.
246. Trickey D, Siddaway AP, Meiser-Stedman R et al. A meta-analysis of risk factors for post-traumatic stress disorder in children and adolescents. Clin Psychol Rev 2012;32:122-38.
247. Slavich GM. Social safety theory: a biologically based evolutionary perspective on life stress, health, and behavior. Annu Rev Clin Psychol 2020;16:265-95.
248. Danese A, Martsenkovskyi D, Remberk B et al. Scoping review: Digital mental health interventions for children and adolescents affected by war. J Am Acad Child Adolesc Psychiatry 2025;64:226-48.
249. Sisk LM, Gee DG. Stress and adolescence: vulnerability and opportunity during a sensitive window of development. Curr Opin Psychol 2022;44:286-92.
250. Servili C. Children and young people's mental health: the case for action. Geneva: World Health Organization, 2025.
251. Dragioti E, Radua J, Solmi M et al. Global population attributable fraction of potentially modifiable risk factors for mental disorders: a meta-umbrella systematic review. Mol Psychiatry 2022;27:3510-9.
252. Solmi M, Dragioti E, Arango C et al. Risk and protective factors for mental disorders with onset in childhood/adolescence: an umbrella review of published meta-analyses of observational longitudinal studies. Neurosci Biobehav Rev 2021;120:565-73.

253. Arango C, Dragioti E, Solmi M et al. Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas. World Psychiatry 2021;20:417-36.
254. Fusar-Poli P, Solmi M, Brondino N et al. Transdiagnostic psychiatry: a systematic review. World Psychiatry 2019;18:192-207.
255. Schultze-Lutter F, Schmidt SJ, Theodoridou A. Psychopathology – a precision tool in need of re-sharpening. Front Psychiatry 2018;9:446.
256. Fusar-Poli P, Raballo A, Parnas J. What is an attenuated psychotic symptom? On the importance of the context. Schizophr Bull 2017;43:687-92.
257. Scott J, Graham A, Yung A et al. A systematic review and meta-analysis of delayed help-seeking, delayed diagnosis and duration of untreated illness in bipolar disorders. Acta Psychiatr Scand 2022;146:389-405.
258. Bertuccio P, Amerio A, Grande E et al. Global trends in youth suicide from 1990 to 2020: an analysis of data from the WHO mortality database. EClinicalMedicine 2024;70:102506.
259. Albaum C, Irwin SH, Muha J et al. Safety planning interventions for suicide prevention in children and adolescents: a systematic review and meta-analysis. JAMA Pediatr 2025;179:886-95.
260. Wright-Hughes A, Farrin AJ, Fonagy P et al. Systematic review and individual participant data meta-analysis: Reducing self-harm in adolescents: pooled treatment effects, study, treatment, and participant moderators. J Am Acad Child Adolesc Psychiatry 2025;64:997-1029.
261. Goh WS, Tan JHN, Luo Y et al. Risk and protective factors associated with adolescent depression in Singapore: a systematic review. Singapore Med J 2025;66:2-14.
262. Davico C, Graziano F, Rossi Ghiglione A et al. Preventing adolescent suicide: feasibility and preliminary outcome evaluation of a theatre-based gatekeeper training for teachers. Int J Environ Res Public Health 2024;21:1631.
263. Lee HA, Lee YJ, Kim KA et al. Development of a standardized suicide prevention program for gatekeeper intervention in Korea (Suicide CARE Version 2.0) to prevent adolescent suicide: version for teachers. Psychiatry Investig 2024;21:860-9.
264. Aggarwal S, Tham SG, Ibrahim S et al. Self-harm in children and young people who die by suicide: UK-wide consecutive case series. Br J Psychiatry 2025;227:593-600.
265. Blackman G, Byrne R, Gill N et al. How common is secondary psychosis? Estimates from a systematic review and meta-analysis. World Psychiatry 2025;24:145-6.
266. Simon KM, Levy SJ, Bukstein OG. Adolescent substance use disorders. NEJM Evid 2022;1:EVIDra2200051.
267. D'Souza DC. Cannabis, cannabinoids and psychosis: a balanced view. World Psychiatry 2023;22:231-2.
268. Di Forti M, Bond BW, Spinazzola E et al. A proof-of-concept analysis of data from the first NHS clinic for young adults with comorbid cannabis use and psychotic disorders. BJPsych Open 2024;11:e1.
269. Fusar-Poli P, Correll CU, Arango C et al. Preventive psychiatry: a blueprint for improving the mental health of young people. World Psychiatry 2021;20:200-21.
270. Fusar-Poli P. Integrated mental health services for the developmental period (0 to 25 years): a critical review of the evidence. Front Psychiatry 2019;10:355.
271. Oliver D, Shin JI, Fusar-Poli P. Population-level prevention of severe mental disorders. Neurosci Biobehav Rev 2025;178:106378.
272. Brodeur S, Oliver D, Ahmed MS et al. Why we need to pursue both universal and targeted prevention to reduce the incidence of affective and psychotic disorders: a systematic review and meta-analysis. Neurosci Biobehav Rev 2024;161:105669.
273. Mesman E, Vreeker A, Hillegers M. Resilience and mental health in children and adolescents: an update of the recent literature and future directions. Curr Opin Psychiatry 2021;34:586-92.
274. World Health Organization. Mental health. www.who.int.
275. Garmezy N. The study of competence in children at risk for severe psychopathology. In: Anthony EJ, Koupernik C (eds). The child in his family: children at psychiatric risk. New York: Wiley, 1974:77-97.
276. Luo S, Hu J, Zhang J et al. The correlation between resilience and mental health of adolescents and young adults: a systematic review and meta-analysis. Front Psychiatry 2025;16:1536553.
277. Meng X, Fleury MJ, Xiang YT et al. Resilience and protective factors among people with a history of child maltreatment: a systematic review. Soc Psychiatry Psychiatr Epidemiol 2018;53:453-75.
278. Mei Z, Cai C, Wang T et al. Interventions to promote resilience in children and adolescents: a systematic review and meta-analysis of randomized controlled trials. Gen Hosp Psychiatry 2025;96:295-306.
279. Dray J, Bowman J, Campbell E et al. Systematic review of universal resilience-focused interventions targeting child and adolescent mental health in the school setting. J Am Acad Child Adolesc Psychiatry 2017;56:813-24.
280. Kalisch R, Baker DG, Basten U et al. The resilience framework as a strategy to combat stress-related disorders. Nat Hum Behav 2017;1:784-90.
281. Ungar M, Theron L. Resilience and mental health: how multisystemic processes contribute to positive outcomes. Lancet Psychiatry 2020;7:441-8.
282. Jiang Y, Li X, Harrison SE et al. Effects of a multilevel resilience-based intervention on mental health for children affected by parental HIV: a cluster randomized controlled trial. J Child Fam Stud 2022;31:1094-105.
283. Jiang Y, Harrison SE, Li X. Resilience-based intervention to promote mental and behavioral health in children. Pediatr Clin North Am 2022;69:795-805.
284. Colizzi M, Lasalvia A, Ruggeri M. Prevention and early intervention in youth mental health: is it time for a multidisciplinary and trans-diagnostic model for care? Int J Ment Health Syst 2020;14:23.
285. Blessin M, Lehmann S, Kunzler AM et al. Resilience interventions conducted in Western and Eastern countries – a systematic review. Int J Environ Res Public Health 2022;19:6913.
286. Hodgins M, McHugh C, Hu N et al. Review of integrated care in youth mental health. Sydney: Headspace National Youth Mental Health Foundation, 2022.
287. Schultz C, Walker R, Bessarab D et al. Interdisciplinary care to enhance mental health and social and emotional wellbeing. In: Dudgeon P, Milroy H, Walker R (eds). Working together: Aboriginal and Torres Strait Islander mental health and wellbeing principles and practice, 2nd ed. Canberra: Commonwealth of Australia, 2014:221-42.
288. Kenwright M, Fairclough P, McDonald J et al. Effectiveness of community mental health nurses in an integrated primary care service: an observational cohort study. Int J Nurs Stud Adv 2024;6:100182.
289. McHugh C, Hu N, Georgiou G et al. Integrated care models for youth mental health: a systematic review and meta-analysis. Aust N Z J Psychiatry 2024;58:747-59.
290. Collins C, Hewson DL, Munger R et al. Evolving models of behavioral health integration in primary care. New York: New York Milbank Memorial Fund, 2010.
291. Asarnow JR, Rozenman M, Wiblin J et al. Integrated medical-behavioral care compared with usual primary care for child and adolescent behavioral health: a meta-analysis. JAMA Pediatr 2015;169:929-37.
292. Wissow LS, van Ginneken N, Chandna J et al. Integrating children's mental health into primary care. Pediatr Clin North Am 2016;63:97-113.
293. American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Collaborative and Integrated Care, AACAP Committee on Quality Issues. Clinical update: Collaborative mental health care for children and adolescents in pediatric primary care. J Am Acad Child Adolesc Psychiatry 2023;62:91-119.
294. Keynejad RC, Spagnolo J, Thornicroft G. Mental healthcare in primary and community-based settings: evidence beyond the WHO Mental Health Gap Action Programme (mhGAP) Intervention Guide. Evid Based Ment Health 2022;25:e1-7.
295. Centers for Medicare & Medicaid Services. CMS announces new model to advance integration in behavioral health. www.cms.gov.
296. Chaulagain A, Pacione L, Abdulmalik J et al. WHO Mental Health Gap Action Programme Intervention Guide (mhGAP-IG): the first pre-service training study. Int J Ment Health Syst 2020;14:47.
297. McGorry P, Bates T, Birchwood M. Designing youth mental health services for the 21st century: examples from Australia, Ireland and the UK. Br J Psychiatry 2013;202(Suppl. 54):s30-5.
298. Tuaf H, Orkibi H. Community-based programs for youth with mental health conditions: a scoping review and practical implications. Front Public Health 2023;11:1241469.
299. Chandra A, Minkovitz C. Factors that influence mental health stigma among 8th grade adolescents. J Youth Adolesc 2007;36:763-74.
300. Hopper T, Iwasaki Y. Engagement of 'at-risk' youth through meaningful leisure. J Park Recreat Adm 2017;35:20-33.
301. Orkibi H, Tuaf H. School engagement mediates well-being differences in students attending specialized versus regular classes. J Educ Res 2017;110:675-82.
302. Simmons MB, Coates D, Batchelor S et al. The CHOICE pilot project: challenges of implementing a combined peer work and shared decision-making programme in an early intervention service. Early Interv Psychiatry 2018;12:964-71.
303. Davidson L, Bellamy C, Guy K et al. Peer support among persons with severe mental illnesses: a review of evidence and experience. World Psychiatry 2012;11:123-8.
304. Flourish Australia. Major projects & funders. www.flourishaustralia.org.au.
305. Wellways. Youth Community Living Support Service. www.wellways.org.
306. LOFT Community Services. https://loftcs.org.

307. Headspace. https://headspace.org.au.
308. Rickwood D, Paraskakis M, Quin D et al. Australia's innovation in youth mental health care: the headspace centre model. Early Interv Psychiatry 2019;13:159-66.
309. Association Nationale des Maisons des Adolescents. https://anmda.fr.
310. YoungMinds. https://www.youngminds.org.uk.
311. Youth Move National. https://youthmovenational.org.
312. Patel V, Flisher AJ, Hetrick S et al. Mental health of young people: a global public-health challenge. Lancet 2007;369:1302-13.
313. Salazar de Pablo G. Editorial: Advancing equity, diversity and inclusion through culturally sensitive collaboration and training. Child Adolesc Ment Health 2024;29:331-2.
314. Sweet MA, Appelbaum MI. Is home visiting an effective strategy? A meta-analytic review of home visiting programs for families with young children. Child Dev 2004;75:1435-56.
315. Cibralic S, Wu WT, Ahinkorah BO et al. Systematic review and meta-analysis of home visiting interventions aimed at enhancing child mental health, psychosocial, and developmental outcomes in vulnerable families. BMC Pediatr 2025;25:314.
316. Mittmann G, Barnarb A, Krammer I. LINA – A social augmented reality game around mental health, supporting real-world connection and sense of belonging for early adolescents. Proceedings of the ACM on Human-Computer Interaction 2022;6:1-21.
317. Brunt TJ, Gale-Grant O. Telepsychiatry: what clinicians need to know about digital mental healthcare. BJPsych Adv 2023;29:230-8.
318. Chen JA, Chung WJ, Young SK et al. COVID-19 and telepsychiatry: early outpatient experiences and implications for the future. Gen Hosp Psychiatry 2020;66:89-95.
319. Harerimana B, Forchuk C, O'Regan T. The use of technology for mental healthcare delivery among older adults with depressive symptoms: a systematic literature review. Int J Ment Health Nurs 2019;28:657-70.
320. Kinoshita S, Cortright K, Crawford A et al. Changes in telepsychiatry regulations during the COVID-19 pandemic: 17 countries and regions' approaches to an evolving healthcare landscape. Psychol Med 2022;52:2606-13.
321. American Academy of Child and Adolescent Psychiatry Committee on Telepsychiatry & Committee on Quality Issues. Clinical update: Telepsychiatry with children and adolescents. J Am Acad Child Adolesc Psychiatry 2017;56:875-93.
322. Ali MM, West KD, Bagalman E et al. Telepsychiatry use before and during the COVID-19 pandemic among children enrolled in Medicaid. Psychiatr Serv 2023;74:644-7.
323. Lyu M, Zhao Q, Yang Y et al. Benefits of and barriers to telehealth for the informal caregivers of elderly individuals in rural areas: a scoping review. Aust J Rural Health 2022;30:442-57.
324. Gude J, Subhedar RV, Zhang MH et al. Emerging needs and viability of telepsychiatry during and post COVID-19 era: a literature review. Cureus 2021;13:e16974.
325. Kruse CS, Molina-Nava A, Kapoor Y et al. Analyzing the effect of telemedicine on domains of quality through facilitators and barriers to adoption: systematic review. J Med Internet Res 2023;25:e43601.
326. Bokolo AJ. Exploring the adoption of telemedicine and virtual software for care of outpatients during and after COVID-19 pandemic. Ir J Med Sci 2021;190:1-10.
327. Sanders C, Rogers A, Bowen R et al. Exploring barriers to participation and adoption of telehealth and telecare within the Whole System Demonstrator trial: a qualitative study. BMC Health Serv Res 2012;12:220.
328. Khan S, Ramtekkar U. Child and adolescent telepsychiatry education and training. Psychiatr Clin North Am 2019;42:555-62.
329. World Health Organization. How to plan and conduct telehealth consultations with children and adolescents and their families. Geneva: World Health Organization, 2021.
330. Molfenter T, Boyle M, Holloway D et al. Trends in telemedicine use in addiction treatment. Addict Sci Clin Pract 2015;10:14.
331. Brown NA. State Medicaid and private payer reimbursement for telemedicine: an overview. J Telemed Telecare 2006;12(Suppl. 2):S32-9.
332. Tian E, Ho MK, Chou OHI et al. Effectiveness of telepsychiatry interventions for youth with depressive and/or anxiety disorders: a systematic review with meta-analysis. Clin Child Psychol Psychiatry 2025;30:537-61.
333. Gabarron E, Denecke K, Lopez-Campos G. Evaluating the evidence: a systematic review of reviews of the effectiveness and safety of digital interventions for ADHD. BMC Psychiatry 2025;25:414.
334. Walder N, Frey A, Berger T et al. Digital mental health interventions for the prevention and treatment of social anxiety disorder in children, adolescents, and young adults: systematic review and meta-analysis of randomized controlled trials. J Med Internet Res 2025;27:e67067.
335. Myers K, Nelson EL, Rabinowitz T et al. American Telemedicine Association practice guidelines for telemental health with children and adolescents. Telemed J E Health 2017;23:779-804.
336. Gloff NE, LeNoue SR, Novins DK et al. Telemental health for children and adolescents. Int Rev Psychiatry 2015;27:513-24.
337. Holland M, Hawks J, Morelli LC et al. Risk assessment and crisis intervention for youth in a time of telehealth. Contemp Sch Psychol 2021;25:12-26.
338. Unzueta Saavedra J, Deaso EA, Austin M et al. Smartphone ecological momentary assessment and wearable activity tracking in pediatric depression: cohort study. JMIR Form Res 2025;9:e66187.
339. Janssen LHC, Verkuil B, van Houtum L et al. A closer look into the affect dynamics of adolescents with depression and the interactions with their parents: an ecological momentary assessment study. Eur Child Adolesc Psychiatry 2024;33:4259-72.
340. Whalen DJ, Silk JS, Semel M et al. Caffeine consumption, sleep, and affect in the natural environments of depressed youth and healthy controls. J Pediatr Psychol 2008;33:358-67.
341. Marciano L, Vocaj E, Bekalu MA et al. The use of mobile assessments for monitoring mental health in youth: umbrella review. J Med Internet Res 2023;25:e45540.
342. Megerian JT, Dey S, Melmed RD et al. Evaluation of an artificial intelligence-based medical device for diagnosis of autism spectrum disorder. NPJ Digit Med 2022;5:57.
343. Lee EY, Cho S, Ju R et al. Development of a social communication intervention mobile app for adolescents with autism spectrum disorder and social communication disorder: protocol for a pilot randomized clinical trial. JMIR Res Protoc 2025;14:e66419.
344. Lin J, Chang WR. Effectiveness of serious games as digital therapeutics for enhancing the abilities of children with attention-deficit/hyperactivity disorder (ADHD): systematic literature review. JMIR Serious Games 2025;13:e60937.
345. Choi H, Kim B, Kim I et al. Analysis of the status and future direction for digital therapeutics in children and adolescent psychiatry. J Korean Acad Child Adolesc Psychiatry 2023;34:192-203.
346. Kim S-C, Lee H. An analysis of the impact of digital therapeutic interventions on attention and working memory in children with attention-deficit/hyperactivity disorder: a randomized controlled trial. Appl Sci 2025;15:788.
347. Lee H, Lee S, Hwang M et al. Effectiveness of game-based digital intervention for attention-deficit hyperactivity disorder in children and adolescents: a systematic review and meta-analysis using Beard and Wilson's conceptualization of perception in experiential learning. Eur Child Adolesc Psychiatry 2025;34:3853-69.
348. Romero-Ayuso D, Toledano-González A, Rodríguez-Martínez MDC et al. Effectiveness of virtual reality-based interventions for children and adolescents with ADHD: a systematic review and meta-analysis. Children 2021;8:70.
349. Pu Y, Luo H. Using virtual reality technology to treat adolescent and young adult depression disorder: a systematic review and meta-analysis. Discov Psychol 2025;5:58.
350. Mittal P, Bhadania M, Tondak N et al. Effect of immersive virtual reality-based training on cognitive, social, and emotional skills in children and adolescents with autism spectrum disorder: a meta-analysis of randomized controlled trials. Res Dev Disabil 2024;151:104771.
351. Kollins SH, DeLoss DJ, Cañadas E et al. A novel digital intervention for actively reducing severity of paediatric ADHD (STARS-ADHD): a randomised controlled trial. Lancet Digit Health 2020;2:e168-78.
352. Kouroupa A, Laws KR, Irvine K et al. The use of social robots with children and young people on the autism spectrum: a systematic review and meta-analysis. PLoS One 2022;17:e0269800.
353. van Straten CL, Smeekens I, Barakova E et al. Effects of robots' intonation and bodily appearance on robot-mediated communicative treatment outcomes for children with autism spectrum disorder. Pers Ubiquit Comput 2018;22:379-90.
354. Robins B, Dautenhahn K. The role of the experimenter in HRI research – A case study evaluation of children with autism interacting with a robotic toy. Presented at the 15th IEEE International Symposium on Robot and Human Interactive Communication, Hatfield, September 2006.
355. Bevan Jones R, Stallard P, Agha SS et al. Practitioner review: Co-design of digital mental health technologies with children and young people. J Child Psychol Psychiatry 2020;61:928-40.
356. Spanakis P, Peckham E, Mathers A et al. The digital divide: amplifying health inequalities for people with severe mental illness in the time of COVID-19. Br J Psychiatry 2021;219:529-31.

357. Radovic A, Kirk-Johnson A, Coren M et al. Stakeholder perspectives on digital behavioral health applications targeting adolescent depression and suicidality: policymaker, provider, and community insights. Implement Res Pract 2022;3:26334895221120796.
358. Oudin A, Maatoug R, Bourla A et al. Digital phenotyping: data-driven psychiatry to redefine mental health. J Med Internet Res 2023;25:e44502.
359. McGorry PD, Mei C, Chanen A et al. Designing and scaling up integrated youth mental health care. World Psychiatry 2022;21:61-76.
360. Senior M, Fanshawe T, Fazel M et al. Prediction models for child and adolescent mental health: a systematic review of methodology and reporting in recent research. JCPP Adv 2021;1:e12034.
361. Fernandes BS, Williams LM, Steiner J et al. The new field of 'precision psychiatry'. BMC Med 2017;15:80.
362. Wang RC, Wang Z. Precision medicine: disease subtyping and tailored treatment. Cancers 2023;15:3837.
363. Cousins S. The great puberty shift. Lancet 2024;404:511-2.
364. McGorry PD, Mei C, Dalal N et al. The Lancet Psychiatry Commission on youth mental health. Lancet Psychiatry 2024;11:731-74.
365. Meehan AJ, Lewis SJ, Fazel S et al. Clinical prediction models in psychiatry: a systematic review of two decades of progress and challenges. Mol Psychiatry 2022;27:2700-8.
366. Salazar de Pablo G, Iniesta R, Bellato A et al. Individualized prediction models in ADHD: a systematic review and meta-regression. Mol Psychiatry 2024;29:3865-73.
367. Fu D, Guo HL, Hu YH et al. Personalizing atomoxetine dosing in children with ADHD: what can we learn from current supporting evidence. Eur J Clin Pharmacol 2023;79:349-70.
368. Umbricht D, Kas MJH, Dawson GR. The role of biomarkers in clinical development of drugs for neuropsychiatric disorders – A pragmatic guide. Eur Neuropsychopharmacol 2024;88:66-77.
369. Elzagallaai A, Barker C, Lewis T et al. Advancing precision medicine in paediatrics: past, present and future. Camb Prism Precis Med 2023;1:e11.
370. Uhlhaas PJ, Davey CG, Mehta UM et al. Towards a youth mental health paradigm: a perspective and roadmap. Mol Psychiatry 2023;28:3171-81.
371. Fusar-Poli P, Manchia M, Koutsouleris N et al. Ethical considerations for precision psychiatry: a roadmap for research and clinical practice. Eur Neuropsychopharmacol 2022;63:17-34.
372. Keri P, White LA, Oliver D et al. Empowering experts by experience to guide ethical precision psychiatry. Biol Psychiatry 2024;96:517-8.
373. Oliver D, Arribas M, Perry BI et al. Using electronic health records to facilitate precision psychiatry. Biol Psychiatry 2024;96:532-42.
374. Fedor S, Lewis R, Pedrelli P et al. Wearable technology in clinical practice for depressive disorder. N Engl J Med 2023;389:2457-66.
375. Walsh AEL, Naughton G, Sharpe T et al. A collaborative realist review of remote measurement technologies for depression in young people. Nat Hum Behav 2024;8:480-92.
376. Wu E, Torous J, Hardaway R et al. Confidentiality and privacy for smartphone applications in child and adolescent psychiatry: unmet needs and practical solutions. Child Adolesc Psychiatr Clin N Am 2017;26:117-24.
377. Martin-Sanchez F, Bellazzi R, Casella V et al. Progress in characterizing the human exposome: a key step for precision medicine. Yearb Med Inform 2020;29:115-20.
378. Choi KW, Wilson M, Ge T et al. Integrative analysis of genomic and exposomic influences on youth mental health. J Child Psychol Psychiatry 2022;63:1196-205.
379. Cortese. S. Research project: Personalising the pharmacological treatment of attention deficit hyperactivity disorder (ADHD) in children. www.southampton.ac.uk.
380. European Commission. White paper on artificial intelligence: a European approach to excellence and trust. Brussels: European Commission, 2020.
381. Ding H, Li N, Li L et al. Machine learning-enabled mental health risk prediction for youths with stressful life events: a modelling study. J Affect Disord 2025;368:537-46.
382. Chekroud AM, Bondar J, Delgadillo J et al. The promise of machine learning in predicting treatment outcomes in psychiatry. World Psychiatry 2021;20:154-70.
383. Dwyer D, Koutsouleris N. Annual research review: Translational machine learning for child and adolescent psychiatry. J Child Psychol Psychiatry 2022;63:421-43.
384. Till AC, Briganti G. Outcomes in machine learning models for child psychiatry: a systematic review of the literature. Psychiatr Danub 2025;37:79-84.
385. Chen T, Ou J, Li G et al. Promoting mental health in children and adolescents through digital technology: a systematic review and meta-analysis. Front Psychol 2024;15:1356554.
386. Mafi A. The risks and benefits of AI therapy tools. BMJ 2025;389:r821.
387. Gbollie EF, Bantjes J, Jarvis L et al. Intention to use digital mental health solutions: a cross-sectional survey of university students attitudes and perceptions toward online therapy, mental health apps, and chatbots. Digit Health 2023;9:20552076231216559.
388. Li X, Chen F, Ma L. Exploring the potential of artificial intelligence in adolescent suicide prevention: current applications, challenges, and future directions. Psychiatry 2024;87:7-20.
389. Wilhelm C, Steckelberg A, Rebitschek FG. Benefits and harms associated with the use of AI-related algorithmic decision-making systems by healthcare professionals: a systematic review. Lancet Reg Health Eur 2025;48:101145.
390. World Health Organization. Ethics and governance of artificial intelligence for health: WHO guidance, 1st ed. Geneva: World Health Organization, 2021.
391. Omiye JA, Lester JC, Spichak S et al. Large language models propagate race-based medicine. NPJ Digit Med 2023;6:195.
392. Mansfield KL, Ghai S, Hakman T et al. From social media to artificial intelligence: improving research on digital harms in youth. Lancet Child Adolesc Health 2025;9:194-204.
393. Academy of Medical Royal Colleges. Artificial intelligence in healthcare. London: Academy of Medical Royal Colleges, 2019.
394. United Nations Children's Fund. Policy guidance on AI for children. www.unicef.org.
395. European Union. General data protection regulation (GDPR). Brussels: European Parliament and Council, 2016.
396. Ciet P, Eade C, Ho ML et al. The unintended consequences of artificial intelligence in paediatric radiology. Pediatr Radiol 2024;54:585-93.
397. Markham S. Patient perspective on predictive models in healthcare: translation into practice, ethical implications and limitations? BMJ Health Care Inform 2025;32:e101153.
398. Gotzl C, Hiller S, Rauschenberg C et al. Artificial intelligence-informed mobile mental health apps for young people: a mixed-methods approach on users' and stakeholders' perspectives. Child Adolesc Psychiatry Ment Health 2022;16:86.
399. Voinov A, Jenni K, Gray S et al. Tools and methods in participatory modeling: selecting the right tool for the job. Environ Modell Softw 2018;109:232-55.
400. Shelmerdine SC, White RD, Liu H et al. Artificial intelligence for radiological paediatric fracture assessment: a systematic review. Insights Imaging 2022;13:94.
401. Aljamaan F, Temsah MH, Altamimi I et al. Reference hallucination score for medical artificial intelligence chatbots: development and usability study. JMIR Med Inform 2024;12:e54345.
402. Bianchi F, Kalluri P, Durmus E et al. Easily accessible text to image generation amplifies demographic stereotypes at large scale. arXiv 2022;2211.03759.
403. Hofmann V, Kalluri PR, Jurafsky D et al. AI generates covertly racist decisions about people based on their dialect. Nature 2024;633:147-54.
404. Galdo B, Pazos C, Pardo J et al. Artificial intelligence in paediatrics: current events and challenges. An Pediatr 2024;100:195-201.
405. Hassan N, Slight R, Bimpong K et al. Systematic review to understand users perspectives on AI-enabled decision aids to inform shared decision making. NPJ Digit Med 2024;7:332.
406. Cruz Rivera S, Liu X, Chan AW et al. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension. Nat Med 2020;26:1351-63.
407. European Parliament. EU AI Act: first regulation on artificial intelligence. www.europarl.europa.eu.
408. Pumariega AJ, Rothe E, Rogers K. Cultural competence in child psychiatric practice. J Am Acad Child Adolesc Psychiatry 2009;48:362-6.
409. Raval VV, Gopal B, Aggarwal P et al. Training in cultural competence for mental health care: a mixed-methods study of students, faculty, and practitioners from India and USA. Cult Med Psychiatry 2024;48:699-730.
410. Butler M, McCreedy E, Schwer N et al. Improving cultural competence to reduce health disparities. Rockville: Agency for Healthcare Research and Quality, 2016.
411. Trinh NH, Jahan AB, Chen JA. Moving from cultural competence to cultural humility in psychiatric education. Psychiatr Clin North Am 2021;44:149-57.
412. Patallo BJ. The Multicultural Guidelines in practice: cultural humility in clinical training and supervision. Train Educ Prof Psychol 2019;13:227-32.
413. Lekas HM, Pahl K, Fuller Lewis C. Rethinking cultural competence: shifting to cultural humility. Health Serv Insights 2020;13:1178632920970580.
414. Greene-Moton E, Minkler M. Cultural competence or cultural humility? Moving beyond the debate. Health Promot Pract 2020;21:142-5.
415. Ogunyemi D, Thind BS, Teixeira A et al. Integrating cultural humility into med-

ical education using a structured and interactive workshop. Adv Med Educ Pract 2024;15:575-83.
416. Foronda C, Baptiste DL, Reinholdt MM et al. Cultural humility: a concept analysis. J Transcult Nurs 2016;27:210-7.
417. Qu Y, Jorgensen NA, Telzer EH. A call for greater attention to culture in the study of brain and development. Perspect Psychol Sci 2021;16:275-93.
418. Hoshmand S, Knegtering H, Spoelstra SK. Cultural competence of mental health practitioners in the Netherlands. Int J Soc Psychiatry 2024;70:282-8.
419. Chen CH, Chen CY, Lin KM. Ethnopsychopharmacology. Int Rev Psychiatry 2008;20:452-9.
420. Kirmayer LJ. Cultural competence in psychotherapy. World Psychiatry 2025; 24:341-2.
421. Huey SJ Jr, Park AL, Galán CA et al. Culturally responsive cognitive behavioral therapy for ethnically diverse populations. Annu Rev Clin Psychol 2023;19:51-78.
422. Benish SG, Quintana S, Wampold BE. Culturally adapted psychotherapy and the legitimacy of myth: a direct-comparison meta-analysis. J Couns Psychol 2011;58:279-89.
423. Chowdhary N, Jotheeswaran AT, Nadkarni A et al. The methods and outcomes of cultural adaptations of psychological treatments for depressive disorders: a systematic review. Psychol Med 2014;44:1131-46.
424. Hoagwood KE, Atkins M, Kelleher K et al. Trends in children's mental health services research funding by the National Institute of Mental Health from 2005 to 2015: a 42% reduction. J Am Acad Child Adolesc Psychiatry 2018;57:10-3.
425. Royal College of Psychiatrists. The scandal of underfunded child and adolescent mental health services laid bare in new research from RCPsych. www.rcpsych.ac.uk.
426. Hofmann W. Going beyond the individual level in self-control research. Nat Rev Psychol 2024;3:56-66.
427. Vinchenzo P, Nabavi N, Tracy DK. 'Choose psychiatry' goes virtual: experiences and learning from the online 2020 National Psychiatry Summer School. BJPsych Bull 2022;46:181-7.
428. Totzeck C, van der Meer AS, Christiansen H et al. Systematic review: Patient and public involvement of children and young people in mental health research. Clin Child Fam Psychol Rev 2024;27:257-74.

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The dysconnection hypothesis of schizophrenia: a 30-year update

We introduced the dysconnection hypothesis of schizophrenia 30 years ago[1], with the advent of human brain mapping. Actually, one could argue that the basic idea emerged even before the notion of schizophrenia itself – in Bleuler's description of psychic disintegration and Wernicke's sejunction hypothesis.

At its inception, the dysconnection hypothesis made some strong claims about the functional anatomy of schizophrenia. In the preceding decades, functional theories of the disorder had focused on notions such as abnormal hemispheric lateralization, or empirical findings such as abnormal histopathology in particular brain regions. The switch of focus – from regional abnormalities to accounts based upon brain connectivity – spoke to the broad conceptualization of functional anatomy enshrined in the principles of functional segregation and integration[2]. Early brain imaging studies quickly established evidence for functional segregation in the brain (i.e., specialization of different brain regions) and subsequently addressed the more vexed issue of how specialized brain regions were integrated through their interconnections.

On this view, it was quite natural to think about schizophrenia as resulting from dysfunctional integration or connectivity. And indeed, aberrant functional connectivity was quickly identified in people with schizophrenia. Since that time, one could argue that the notion of dysfunctional connectivity – i.e., schizophrenia as a functional dysconnection syndrome – has been one of the most enduring mechanistic frameworks within schizophrenia research. So, does the dysconnection hypothesis simply posit a disintegration of coherent brain activity?

No. It was – and remains – a specific hypothesis that distinguishes between *disconnection* and *dysconnection*. The lexical distinction may be subtle, but the conceptual distinction is fundamental. On the one hand, disconnection invokes Geschwind's notion of disconnection syndromes, reminiscent of Wernicke's sejunction hypothesis, in which there are disruptions to the organs of connection – namely, the white matter tracts that connect brain regions. For example, schizophrenia may have been a pernicious form of leukodystrophy[3]. Alternatively, *dysconnection* implies that the pathology in question is not anatomical but involves a dysfunctional integration at the synaptic level. In terms of pathophysiology, one could conceive of dysconnection as a synaptopathy[4]. But what kind of synaptopathy?

The dysconnection hypothesis commits to a particular kind of synaptopathy – namely, a failure of neuromodulation (i.e., aberrant modulation of synaptic efficacy or postsynaptic gain). This commitment is inherited from the theoretical neurobiology of value-dependent learning, in which classical neurotransmitters – such as dopamine and acetylcholine – modulate associative plasticity and experience-dependent learning at the synaptic level. This way of thinking about learning and inference in the brain came to dominate systems neuroscience in the form of reward prediction errors, with clear links to dopaminergic theories of schizophrenia, e.g., the aberrant salience hypothesis.

However, things changed after the first decade, with a shift in cognitive neuroscience to the predictive processing paradigm. This shift was important for the dysconnection hypothesis, because it brought inference and sense-making into the compass of what would be later known as computational psychiatry. In brief, hierarchical predictive processing views the brain as a constructive organ, generating explanations for the causes of its sensorium.

In this setting, neuromodulation or postsynaptic gain control plays a key role. From the computational perspective, postsynaptic gain selects the neuronal messages that are sent to higher hierarchical levels. In other words – when looked at through the lens of computational neuroscience – postsynaptic gain encodes the precision or confidence afforded by neuronal messages. Psychologically, the implicit selection can be regarded as attentional selection (and deselection or sensory attenuation). This formulation had clear implications for a computational understanding of many psychopathologies, including autism and schizophrenia[5].

Physiologically, this focused attention on the mechanisms that determine postsynaptic gain, ranging from the role of fast-spiking inhibitory neurons – through voltage dependent N-methyl-D-aspartate (NMDA) receptor function – to classical neuromodulators that are, invariably, the target of psychomimetic, psychedelic and psychotherapeutic drugs. From the perspective of the dysconnection hypothesis, this placed great emphasis on cortical or synaptic gain control and the implicit encoding of confidence or precision.

Much of the attendant theoretical neurobiology was cast in terms of the Bayesian brain hypothesis and implicit Bayesian belief updating under uncertainty. This had a fundamental implication: it meant that one could talk about psychopathology as aberrant belief updating or false inference. In other words, one could link aberrant precision or gain control to a patient's perceptual inference and sense-making. It was then a natural step to cast the symptoms and signs of schizophrenia in terms of false inference.

For example, one can classify false inference in statistical terms, where type I errors correspond to inferring that something is there when it is not – as in hallucinations and delusions. Conversely, type II errors mean inferring that something is not there when it is – as in dissociative and neglect syndromes. All these aspects of psychopathology could then be explained by a failure to implement the right kind of precision or gain control in hierarchical predictive processing. This subsequently became a compelling line of research in its own right, with precision-based accounts of schizophrenia and beyond[6,7]. But what of the underlying pathophysiology and its aetiology?

As noted above, there are a myriad of synaptic and systemic mechanisms that mediate precision or cortical gain control in the brain[8]. Many licence a focus on key receptors and attendant psychopharmacology. Obvious examples include the NMDA receptor, due to its modulatory (nonlinear) characteristics, and its deployment on inhibitory interneurons that mediate synchronous gain. Likewise, a focus on classical ascending modulatory neurotransmitter systems seems fully justified. One interesting development over the past decade is a focus on markers of aberrant precision or

gain control, such as excitation-inhibition (E/I) balance[9].

From the perspective of the dysconnection hypothesis, the question is: what are the modulatory mechanisms that lead to a failure of cortical gain control or E/I balance? The mounting empirical evidence suggests a failure to modulate the recurrent (and often synchronous) exchange between fast-spiking inhibitory interneurons and (superficial) pyramidal cells in the cortex. Interestingly, the superficial pyramidal cells are – on a canonical reading of predictive coding architectures – responsible for passing prediction errors up cortical hierarchies. This evidence rests largely upon non-invasive electrophysiological studies – in conjunction with dynamic causal modelling – which allow one to pinpoint laminar specific and, at times, receptor-specific interactions at the level of neuronal populations. So, what next?

One could argue that incredible progress has been made over the past 30 years. For example, starting with the rather broad notion of dysfunctional connectivity, people are now talking about the functional genomics and molecular biology of ontogenetically characterized inhibitory interneurons, and their role in the canonical microcircuits that underwrite predictive processing. Having said this, the primary locus of pathology has yet to be identified. Are we talking about polygenic (or delayed epigenetic) mechanisms expressed at the level of synaptic modulation in canonical microcircuits? Or, are we looking at a synaptopathy in afferents to the sources of ascending modulatory neurotransmitter systems? Or both, or neither? These are important questions, because therapeutic interventions rest on understanding the mechanisms of pathogenicity, that matter at every level and to everyone concerned.

Karl Friston
Queen Square Institute of Neurology, University College London, London, UK

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1. Friston KJ, Frith CD. Clin Neurosci 1995;3:89-97.
2. Zeki S, Shipp S. Nature 1988;335:311-7.
3. Weinberger DR. J Neuropsychiatry Clin Neurosci 1993;5:241-53.
4. Obi-Nagata K, Temma Y, Hayashi-Takagi A. Proc Jpn Acad Ser B Phys Biol Sci 2019;95:179-97.
5. Adams RA, Stephan KE, Brown HR et al. Front Psychiatry 2013;4:47.
6. Powers AR, Mathys C, Corlett PR. Science 2017;357:596-600.
7. Friston K. Mol Psychiatry 2023;28:256-68.
8. Abbott LF, Varela JA, Sen K et al. Science 1997;275:220-4.
9. Jardri R, Hugdahl K, Hughes M et al. Schizophr Bull 2016;42:1124-34.

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Immuno-metabolic depression: challenges ahead for identification and intervention

Major depression is associated with an increased risk of cardiometabolic disorders such as obesity, cardiovascular disease, and diabetes. Although this can be partly explained by poorer lifestyle in depressed patients, underlying shared pathophysiological and genetic mechanisms play a role as well.

Depressed persons more often have systemic low-grade inflammation, with elevated levels of C-reactive protein (CRP), cytokines and glycoprotein acetyls, and metabolic syndrome abnormalities including abdominal obesity, dyslipidaemia, and insulin and leptin resistance[1]. Immuno-metabolic processes can lead to psychiatric disease acceleration (e.g., through dysfunction of reward and emotion regulating brain circuitry, and reduced neurogenesis and monoamine signalling)[2]. The same processes play a parallel role in the genesis and progression of subclinical and clinical cardiometabolic conditions.

Genetic correlation and shared genetic variants exist between immuno-metabolic traits and depression[3,4]. Furthermore, recent Mendelian randomization studies indicate that the genetic liability for depression is associated with an increased risk for cardiometabolic conditions, whereas no strong evidence is found for the reverse direction[5].

However, depression is arguably the most heterogeneous psychiatric condition. Heterogeneity exists in the depression symptom profile experienced, the environmental risk factors encountered, and the pathophysiology observed. Only 25-30% of depressed patients present with objective signs of low-grade inflammation and metabolic syndrome abnormalities[1]. The prominent symptom profile of depressed persons with immuno-metabolic dysregulations is distinct: they report more atypical, energy-related depressive symptoms such as hypersomnia, leaden paralysis, fatigue and hyperphagia, and anhedonia and reduced motivation[1,4]. So, there is a clustering of systemic low-grade inflammation, metabolic syndrome dysregulations, and atypical energy-related depressive symptoms and anhedonia. It is this clustering of specific symptoms with specific pathophysiology that could be indicated as immune-metabolic depression.

This is a dimensional phenomenon. Atypical energy-related symptoms have dose-response associations with inflammation indicators (CRP, interleukin-6, glycoprotein acetyls) and metabolic dysregulations (waist circumference, triglycerides, cholesterol, glucose, leptin). Currently, no consensus exists on how to classify immuno-metabolic depression, although pragmatic criteria have been explored. Twenty-six percent of 1,077 patients examined in the Netherlands Study of Depression and Anxiety (NESDA) have at least moderate atypical, energy-related symptom levels *as well as* a CRP level >1 mg/L, and this is applied as inclusion criterion for an ongoing study[6].

Why is the identification of immuno-metabolic depression clinically relevant? Immune-metabolic features have been related to poorer course, and (although the evidence is still limited) to a poorer response to standard antidepressants[1]. Importantly, treatments that directly target immuno-metabolic dysregulation could be use-

ful (augmentation) interventions for this specific group of patients.

Various anti-inflammatory medications – such as celecoxib, minocycline and infliximab – have been found to reduce depressive symptoms[1]. However, the initial evidence for the antidepressant effects of these medications came largely from trials in populations with somatic conditions, such as rheumatoid arthritis, in which persons with clinically overt diagnoses of depression were generally excluded. In clinically depressed patients, such trials are still limited – in terms of number of studies, included sample sizes, and consistency of effects.

The initial small-scaled anti-inflammatory trials with positive findings have been followed by larger studies with unclear beneficial effects, which may partly be due to not consistently selecting persons with evidence of underlying inflammation[7]. This raises an important unanswered question: in whom could adjunctive anti-inflammatory medication truly work? The original positive trials using minocycline and infliximab found beneficial effects in subgroups of depressed persons with CRP levels above 3 and 5 mg/L, respectively. Unfortunately, evaluation of consistent subgroup definitions is lacking. This is something that the Wellcome-funded ASPIRE project is currently attempting to address by meta-analyzing trials of anti-inflammatory drugs in depressed patients and exploring which consistent indicators mark depressed persons who benefit most from these treatments[7].

So far, CRP has been used as a rather crude stratification biomarker for inflammation. While this is a measure that can be readily assessed in routine clinical practice, it is unclear whether it is a sufficient and precise biomarker. The immune system is complex, and more research is needed on whether further differentiating depressed persons with a "lymphoid immunophenotype" (adaptive immune response) from a "myeloid immunophenotype" (innate immune response) is worthwhile, and on whether more detailed inflammatory signatures could better advance specific treatment options.

In addition, immune and metabolic functions are closely aligned and interacting. This raises the question whether selection criteria for immuno-metabolic augmentation approaches could benefit from adding metabolic biomarkers, and whether tested interventions should be extended to metabolism-modifying agents. For instance, the latest addition to diabetes and obesity care, glucagon-like peptide 1 receptor agonists (GLP1-RAs), represent a potentially relevant intervention for immuno-metabolic depression. These medications not only display effects on lipid metabolism, but also on inflammation, stress response and energy metabolism. In non-psychiatric, general populations, GLP1-RAs have not led to detrimental effects on psychiatric outcomes and have improved mental health-related quality of life[8].

Finally, we need to be aware that specific symptom dimensions – i.e., atypical, energy-related symptoms, low motivation and anhedonia – are associated with immuno-metabolic dysregulations. These symptoms are likely to be impacted most by immune-metabolic modulating interventions. Using global depression scales as primary outcome measures, as required by regulatory agencies, may be problematic, as these may be too crude and unprecise measures to pick up clinically relevant change in specific symptom dimensions. Consequently, relevant symptom dimension scales need to be further developed, utilized and accepted by regulatory agencies. This is needed to advance the science of precision psychiatry.

Even though it is too early to include immuno-metabolic interventions in our clinical depression guidelines, this does not mean that we can ignore immuno-metabolic health. In a recent network meta-analysis[9], current antidepressant medications had varying effects on cardiometabolic parameters such as weight, cholesterol, blood pressure and heart rate. Especially when caring for persons with immuno-metabolic depression, who are at increased risk for unfavorable physical health outcomes, potential somatic side effects of psychotropic medications need to be considered in treatment choices and monitoring.

Importantly, lifestyle interventions – such as physical exercise, behavioral activation, management of unhealthy eating, smoking cessation, and sleep hygiene – could further help not only to reduce depressive symptoms, but also to improve immuno-metabolic health.

Brenda W.J.H. Penninx
Department of Psychiatry, Amsterdam University Medical Center, Vrije University, Amsterdam, The Netherlands

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1. Penninx BWJH, Lamers F, Jansen R et al. Lancet Reg Health Eur 2024;48:101166.
2. Goldsmith D, Bekhbat M, Mehta ND et al. Biol Psychiatry 2022;93:405-18.
3. Bergstedt J, Pasman JA, Ma Z et al. Nat Cardiovasc Res 2024;6:754-69.
4. Pistis G, Strippoli MF, van Dalfsen JH et al. JAMA Psychiatry 2025;82:992-1001.
5. Berk M, Kohler-Forsberg O, Turner M et al. World Psychiatry 2023;22:366-87.
6. Zwiep JC, Milaneschi Y, Giltay EJ et al. Brain Behav Immun 2025;124:115-22.
7. Worrell C, Baune BT, Benedetti F et al. Lancet Psychiatry 2026;13:277-9.
8. Pierret ACS, Mizuno Y, Saunders P et al. JAMA Psychiatry 2025;82:643-53.
9. Pillinger T, Arumuham A, McCutcheon RA et al. Lancet 2025;406:2063-77.

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Somatic symptoms and sensory dysregulation are central to the clinical presentation of PTSD

Treatment guidelines for post-traumatic stress disorder (PTSD) have changed little in 20 years. In real-world settings, dropouts from exposure-based treatments are common, and remission is often incomplete. While many patients have a significant decrease in symptoms with currently recommended treatments, most are left with residuals of the disorder[1]. Hence, there is a need for a concep-

tual shift. Current treatments tend to focus on the impact of a specific trauma, but ignore critical elements of the phenomenology and neurobiology of traumatic stress.

Most traumatized patients do not suffer from the effects of one single trauma, but from the neurobiological consequences of cumulative traumatic experiences. Problems with affect regulation, concentration, and excessive reactivity interfere with being able to deal effectively with the ordinary demands of daily life. Particularly individuals with histories of child abuse (developmental trauma) tend to experience significant defects in a variety of transdiagnostic mental processes, including an inability to modulate or tolerate distress, being unable to notice internal states (alexithymia), and a lack of a coherent sense of self. All of these aspects have been shown to correlate with poor treatment outcome[2].

While the role of fear circuitry in PTSD has been well established, little attention has been paid to the central role of sensory processing and affect regulation in the pathophysiology of the disorder. Back in 1872, C. Darwin already described how intense emotions are registered in physical sensations – for instance, heartbreaking feelings in the chest and gut-wrenching sensations in the abdomen (mediated by the vagus nerve, which he called the pneumogastric nerve). Contemporary research has confirmed that traumatic re-experiencing is more than a memory or an emotion. It is a full body physiological and sensory reaction to images, sounds, touch and other internal or external sensory input. These physical sensations are poorly seriated in time and place, and are often experienced without context or insight as to their origins.

Trauma's neurobiological imprints vary significantly across the lifespan, shaped by neurodevelopmental stages, hormonal shifts, and the brain's evolving capacity to process threat. From infancy to late adulthood, the same traumatic event can ignite starkly different biological cascades – a reality underscored by mounting research into age-specific trauma responses[3] and our increasing understanding of critical periods of brain development.

Epidemiological studies consistently find that individuals with probable or subsyndromal PTSD report significantly higher rates of somatic symptoms – such as chronic pain, gastrointestinal complaints, cardiovascular symptoms, and fatigue – compared to those without PTSD. For example, in a population-based military sample, somatic disorder was present in 59.6% of those with probable PTSD, compared to only 5% in those without PTSD[4]. There is a direct correlation between the intensity of PTSD symptoms and the number and severity of somatic complaints, with a clear gradient observed in individuals exposed to multiple traumatic events[5]. These data suggest that somatic symptoms are not peripheral but core features of PTSD, that stem from trauma-induced biological changes.

The somatic symptoms associated with trauma exposure are due, at least in part, to dysregulated sensory processing and altered interoceptive capacities. The imprints of trauma often defy narrative. Instead, sensory fragments combined with intense emotional arousal or numbing bypass cognitive processing and are expressed as somatic states and behavioral reactivity[5].

Problems in discriminating whether sensory input is dangerous or safe are central features of PTSD[5]. Trauma survivors experience intrusive flashbacks not as coherent memories but as disjointed sensations: a flash of light, a muffled scream, the pressure of a hand. Significantly, in patients with PTSD, these sensory disturbances occur not only in response to trauma-related stimuli, but also to neutral sensory information, such as spatial navigation and scene perception[6]. In particular, children exposed to chronic trauma exhibit altered sensory modulation patterns and deficits in general sensory processing, independent of emotional context, which usually persist in adulthood[7].

Adults with histories of child abuse have elevated rates of autoimmune disorders, cardiovascular disease, and fibromyalgia – physical echoes of childhood hypothalamic-pituitary-adrenal (HPA) axis dysfunction[7]. Childhood trauma has been associated with reduced hippocampal volume, impairing memory integration, and a hyperreactive insula that magnifies bodily sensations (e.g., interpreting muscle fatigue as impending collapse)[7].

PTSD is associated with alterations in both the structure and function of sensory brain regions, such as lower gray matter volume in temporal, parietal and occipital regions, including the superior temporal gyrus, which helps integrate audiovisual information from emotional stimuli; the superior parietal gyrus, involved in dorsal visual processing stream for spatial and movement information; and the bilateral orbitofrontal gyrus, involved in guiding sensory attention and integrating inputs from sensory and limbic structures[6,7].

Altered connectivity between subcortical (e.g., amygdala, hippocampus) and cortical (e.g., prefrontal cortex, sensory cortices) regions impairs top-down (conscious) regulation, allowing bottom-up sensory and affective signals to predominate[5]. The resulting sensory overload further contributes to somatic distress, and promotes hypervigilance and feeling emotionally overwhelmed, as expressed in behavioral agitation, panic reactions and loss of impulse control[7].

On the other hand, hypo-responsivity, the result of emotional overmodulation, is associated with increased activation of medial prefrontal cortex and rostral anterior cingulate regions[8], reflected in dampening of bodily awareness, dissociative symptoms, numbness, and feeling detached from reality. A study comparing PTSD patients with and without the dissociative (depersonalization/derealization) subtype documented that the former group showed greater amygdala connectivity to prefrontal regions during resting state[8].

Somatic symptoms and lack of sensory regulation are central, not peripheral, to the clinical presentation of PTSD. They reflect complex neurobiological and psychological mechanisms[9]. Recognizing and addressing these somatic correlates is essential for comprehensive assessment and effective treatment of PTSD.

Traditional trauma-focused therapies, while effective for many, do not fully address the sensory dysregulation and somatic symptoms experienced by a substantial subset of patients. When considering whether emerging treatments – such as mindfulness approaches, stellate ganglion block, neurofeedback, and psychedelic-assisted psychotherapies – offer novel therapeutic benefits, it

is important to evaluate their effect on the somatic and sensory domains of PTSD, and to investigate which treatments can reverse or repair these long-term neurobiological imprints of trauma.

Bessel A. van der Kolk[1], Alexander C. McFarlane[2]
[1]Trauma Research Foundation, Brookline, MA, USA; [2]University of Adelaide, Adelaide, SA, Australia

1. Brewin CR, Atwoli L, Bisson JI et al. World Psychiatry 2025;24:52-80.
2. van der Kolk BA, Wang JB, Yehuda R et al. PLoS One 2024;19:e0295926.
3. Cross D, Fani N, Powers A et al. Clin Psychol 2017;24:111-24.
4. Nijdam MJ, Vermetten E, McFarlane AC. Acta Psychiatr Scand 2023;147:65-80.
5. McFarlane AC, Graham DK. J Psychiatr Res 2021;143:388-94.
6. Fleming LL, Harnett NG, Ressler KJ. Curr Opin Neurobiol 2024;84:102821.
7. Kearney BE, Lanius RA. Front Neurosci 2022;16:1015749.
8. Harricharan S, McKinnon MC, Lanius RA. Front Neurosci 2021;15:625490.
9. Burback L, Brult-Phillips S, Nijdam MJ et al. Curr Neuropharmacol 2024;22: 557-635.

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Rethinking the prediction and prevention of dropout in digital mental health

Interventions delivered by digital technologies – such as the Internet, smartphone apps, and chatbots – represent a promising means of increasing the availability of psychological treatments. A mature yet evolving body of evidence indicates that digital interventions can effectively target many psychiatric symptoms, whether delivered as stand-alone self-help programs, adjuncts to traditional in-person treatment, or relapse prevention tools[1].

Yet, digital interventions are characterized by high rates of early dropout or disengagement. In some trials, nearly half of participants never initiate use of their assigned digital intervention, or discontinue use entirely within the first 10 days[2]. Problems with engagement are even more profound in real-world settings. Early dropout is a critical concern, because it limits the potency of a digital treatment due to insufficient therapeutic content exposure, and undermines the validity of clinical trial findings. Preventing dropout is therefore a key priority.

Clinicians can play a central role in preventing early disengagement when digital health tools are integrated into a patient's care plan. A critical point for clinician intervention is at the beginning of treatment, as this is when early engagement trajectories can be established. Premature dropout from digital interventions typically occurs when patients have unclear expectations regarding optimal use, and limited understanding of how these tools can support treatment goals[3]. Moreover, without clear plans in place at treatment initiation, early difficulties may be interpreted as evidence that the digital intervention is burdensome, ineffective, or poorly suited to the user's needs, further contributing to disengagement.

Clinicians can mitigate this risk through intentional intake dialogue that clarifies when and how digital tools should be used, aligns demands with patient capacity, and defines the platform's role within the broader care plan. This may include explicitly articulating how digital interventions serve complementary functions, such as providing psychoeducational material outside of sessions or structured homework tasks that reinforce therapeutic work. Clinicians can also proactively anticipate likely barriers to sustained use, and work collaboratively with the patient to engage in early problem-solving aimed at addressing these challenges as they emerge, rather than waiting until patterns of non-use are established.

The earlier phase of treatment also represents a critical window for clinician support, as risk of dropout is highest during the first few weeks[2]. Disengagement during the initial treatment phase can be due to difficulty integrating the digital intervention into daily routines, uncertainty about whether initial effort is translating into progress, or skepticism about how the homework activities connect to in-session therapeutic work[3]. Clinicians can address these risks by front-loading support through brief, structured check-ins during early weeks of use. These check-ins can focus on collaboratively troubleshooting how the digital health tool fits into the patient's daily life, helping patients recognize early signs of skill acquisition even in the absence of clinical change, and explicitly linking completed digital homework tasks to in-session goals. By reinforcing relevance and strengthening the perceived value of continued use, early check-ins can support sustained engagement during this period of heightened dropout vulnerability.

The success of these engagement strategies, however, depends fundamentally on clinicians possessing adequate digital literacy. Patient-reported usability issues – including limited technological competency, navigation difficulties, or complications interpreting clinically relevant digital data – are often-cited contributors to early dropout[4], and therefore require clinician capacity to anticipate and address them. Without sufficient familiarity with the digital health tools they recommend, clinicians may struggle to troubleshoot technical barriers, help patients extract meaningful feedback from their data, or ensure that these interventions are being used optimally. Building digital literacy through credible training curricula[5] can equip clinicians with the skills needed to address patient-reported usability challenges, thereby ensuring that digital health tools are used in ways that support, rather than hinder, treatment goals.

While these clinician-led strategies offer immediately actionable ways to reduce early dropout, they rely extensively on clinician time, judgement, and manual monitoring, highlighting the need for complementary approaches that can support more efficient identification of disengagement risk. Achieving this efficiency calls for robust data-driven methods that are capable of accurately identifying which patients are likely or unlikely to disengage prematurely. Such predictive capabilities could support more precise allocation

of retention efforts and inform clinical decision-making on the suitability of digital interventions for individual patients.

Developing reliable, data-driven predictive algorithms capable of supporting automated personalization at the individual-patient level necessitates access to large volumes of data drawn from multiple sources. Algorithms trained on rich, heterogenous data are better positioned to detect subtle patterns and interactions that predict disengagement than those relying on sparse or single-modality inputs, which may overlook critical context-specific dropout risk factors and exhibit reduced predictive stability[6].

Digital health platforms are uniquely positioned to support this approach, as they can capture continuous multimodal data streams, including textual data derived from completed homework activities, usage metadata, passively sensed behavioral data, and temporally dense, high-frequency symptom ratings collected via repeated monitoring surveys. These data streams may capture distinct and complementary prognostic signals related to dropout that are not readily observable using traditional clinical baseline assessments (e.g., disruptions in sleep regularity inferred from passive smartphone data may signify accumulating fatigue that undermines engagement).

Crucially, collection and use of passively sensed and textual data requires explicit, informed user consent, which must be obtained transparently and in a manner that respects patient privacy and autonomy. Consent procedures should be designed to minimize burden and avoid undermining engagement, as overly complex or intrusive data requests could contribute to dropout[1]. Thus, multimodal data capture approaches should be implemented selectively, and carefully evaluated for their acceptability and impact on user engagement.

Despite the demonstrated value of integrating multimodal data streams to predict patient outcomes in other areas of psychiatry[7], this approach has not yet been systematically applied to the problem of predicting dropout from digital interventions. Existing work predicting early dropout has largely examined one or two data streams in isolation, with the strongest evidence supporting early usage metadata and textual features, which demonstrate modest predictive accuracy[8]. While informative, these studies are typically proof-of-concept, conducted on single datasets, and rarely subjected to external validation, thereby limiting their clinical relevance and readiness for real-world deployment.

Progress in this field demands systematic evaluation of whether multimodal data modelling can meaningfully improve the prediction of early dropout in digital mental health. Advances in predictive performance should be accompanied by rapid progression beyond proof-of-concept toward prospective and externally validated models tested in large, diverse samples, as this will be needed to establish generalizability and suitability for real-world deployment. Achieving this at pace will require coordinated, global collaboration among digital mental health researchers, including shared data infrastructures, harmonized data collection protocols, consensus on feature definitions, and improved standards for model reporting. Once multimodal predictive models are robustly validated, their clinical value can be assessed within implementation-focused trials that test whether algorithm-guided, just-in-time support can more effectively prevent early disengagement than non-adaptive digital interventions[6].

In conclusion, early dropout remains a critical barrier to realizing the potential of digital mental health interventions. Clinicians are central to encouraging patient engagement through supportive strategies implemented early in treatment. Harnessing data-driven predictive algorithms that integrate multimodal information can offer a means to augment these strategies with a level of precision far exceeding what manual monitoring can feasibly achieve.

If validated and implemented effectively, such algorithms could be embedded directly within digital health platforms to provide real-time risk alerts that prompt timely clinician intervention. By combining clinician expertise with data-driven prediction, this integrated approach holds promise for preventing early dropout and maximizing the therapeutic potential of digital interventions.

Jake Linardon
School of Psychology, Faculty of Health, Deakin University, Geelong, VIC, Australia

1. Torous J, Linardon J, Goldberg SB et al. World Psychiatry 2025;24:1-19.
2. Liu C, Torous J, Fuller-Tyszkiewicz M et al. JAMA Psychiatry 2026;83:43-50.
3. Boucher EM, Raiker JS. BMC Digit Health 2024;2:52.
4. Wisniewski H, Torous J. Acta Psychiatr Scand 2020;141:350-5.
5. Wisniewski H, Gorrindo T, Rauseo-Ricupero N et al. Digit Biomark 2020;4 (Suppl. 1):119-35.
6. Chekroud AM, Bondar J, Delgadillo J et al. World Psychiatry 2021;20:154-70.
7. Wang L, Wang C, Li C et al. NPJ Digit Med 2025;8:523.
8. Mylläri S, Saarni SE, Joffe G et al. Psychother Res 2026;36:387-402.

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Real-world comprehensive care of people living with schizophrenia: recommendations across different settings and clinical stages

Paolo Fusar-Poli[1-4], Toby Pillinger[5], Robert A. McCutcheon[5,6], Thara Rangaswamy[7], Laila Asmal[8], Swaran P. Singh[9], Dominic Oliver[1,6], Riccardo Stefanelli[3], Nicolas A. Crossley[6,10], Ary Gadelha[11], Carlos Lopez-Jaramillo[12], Byamah B. Mutamba[13], Majda Cheour[14,15], Marcelo Valencia[16], Laura Asher[17,18], Claudia Aymerich[19-23], Ana Catalan[5,19-22], Dong Keon Yon[24-28], Jae Il Shin[29,30], Marco Solmi[31-34], Stephen M. Lawrie[35], Kazione Kulisewa[36], Olga Karpenko[37], Dror Ben-Zeev[38], Samuele Cortese[39-42], Crick Lund[43,44], Oliver Howes[5,45], Peter Kéri[46], Charlene Sunkel[47], Ilaria Bonoldi[1,3], Stefano Damiani[3], Laura Fusar-Poli[3], Patrick D. McGorry[48,49], John M. Kane[50-52], Christoph U. Correll[34,50,53-55]

[1]Early Psychosis: Interventions and Clinical-Detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [2]OASIS Service, South London and Maudsley NHS Foundation Trust, London, UK; [3]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy; [4]Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University Munich, Munich, Germany; [5]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [6]Department of Psychiatry, University of Oxford, Oxford, UK; [7]Schizophrenia Research Foundation, Chennai, India; [8]Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; [9]Warwick Medical School, University of Warwick, Coventry, UK; [10]Department of Psychiatry, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile; [11]National Institute of Developmental Psychiatry for Children and Adolescents and National Center for Innovation and Research in Mental Health, São Paulo, Brazil; [12]Research Group in Psychiatry, Institute of Medical Research, Department of Psychiatry, Faculty of Medicine, University of Antioquia, Medellín, Colombia; [13]Butabika National Referral Mental Hospital, Kampala, Uganda; [14]Tunisian Center of Early Intervention in Psychosis, Department of Psychiatry "Ibn Omrane", Razi Hospital, Manouba, Tunisia; [15]Faculty of Medicine of Tunis, Tunis El Manar University, Tunis, Tunisia; [16]Division of Epidemiological and Psychosocial Research, National Institute of Psychiatry "Ramón de la Fuente", Mexico City, Mexico; [17]Nottingham Centre for Public Health and Epidemiology, School of Medicine, University of Nottingham, Nottingham, UK; [18]Institute of Mental Health, University of Nottingham, Nottingham, UK; [19]Department of Psychiatry, Basurto University Hospital, Bilbao, Spain; [20]Biobizkaia Health Research Institute, Barakaldo, Spain; [21]Department of Neuroscience, University of the Basque Country, Leioa, Biscay, Spain; [22]Spanish Network for Research in Mental Health, Carlos III Institute, Madrid, Spain; [23]Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [24]Center for Digital Health, Medical Science Research Institute, Kyung Hee University College of Medicine, Seoul, South Korea; [25]Department of Precision Medicine, Kyung Hee University College of Medicine, Seoul, South Korea; [26]Department of Regulatory Science, Kyung Hee University, Seoul, South Korea; [27]Department of Medicine, Kyung Hee University College of Medicine, Seoul, South Korea; [28]Department of Pediatrics, Kyung Hee University College of Medicine, Seoul, South Korea; [29]Department of Pediatrics, Yonsei University College of Medicine, Seoul, South Korea; [30]Severance Underwood Meta-Research Center, Institute of Convergence Science, Yonsei University, Seoul, South Korea; [31]Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada; [32]Regional Centre for Treatment of Eating Disorders and On Track: Champlain First Episode Psychosis Program, Department of Mental Health, Ottawa Hospital, Ottawa, ON, Canada; [33]Ottawa Hospital Research Institute Clinical Epidemiology Program, University of Ottawa, Ottawa, ON, Canada; [34]Department of Child and Adolescent Psychiatry, Charité - Universitätsmedizin, Berlin, Germany; [35]Department of Psychiatry, University of Edinburgh, Edinburgh, UK; [36]Kamuzu University of Health Sciences, Blantyre, Malawi; [37]Mental Health Clinic 1 "N.A. Alexeev", Moscow, Russia; [38]Behavioral Research in Technology and Engineering Center, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA; [39]School of Psychology, Faculty of Environmental and Life Sciences, Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK; [40]Department of Precision and Regenerative Medicine-Jonic Area, University of Bari "Aldo Moro", Bari, Italy; [41]Hampshire and Isle of Wight NHS Foundation Trust, Southampton, UK; [42]Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, NY, USA; [43]Centre for Global Mental Health, Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [44]A.J. Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health, University of Cape Town, Rondebosch, South Africa; [45]Institute of Clinical Sciences, Faculty of Medicine, Imperial College London, London, UK; [46]Global Alliance of Mental Illness Advocacy Networks - Europe (GAMIAN), Brussels, Belgium; [47]aves Mental Health, Paarl, South Africa; [48]Orygen, Parkville, VIC, Australia; [49]Centre for Youth Mental Health, University of Melbourne, Parkville, VIC, Australia; [50]Departments of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; [51]Institute of Behavioral Science, Feinstein Institutes for Medical Research, Manhasset, NY, USA; [52]Psychiatry Research, Zucker Hillside Hospital, Northwell Health System, Glen Oaks, NY, USA; [53]Department of Psychiatry, Zucker Hillside Hospital, Northwell Health, New York, NY, USA; [54]Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Northwell Health, New York, NY, USA; [55]German Center for Mental Health (DZPG), partner site Berlin, Berlin, Germany

The clinical management of a complex disorder such as schizophrenia remains a significant challenge worldwide. This disorder requires a comprehensive, integrated and personalized care that blends multiple approaches, and the real-world availability of multiple resources. We present here the first recommendations addressing the real-world comprehensive care for people with schizophrenia-spectrum psychoses across different approaches, clinical stages, and levels of available resources. The recommendations are based on a critical review of the scientific literature and a collaborative appraisal by numerous clinical academics actively treating people with schizophrenia worldwide, representing various countries and clinical settings, including those in the Global South. Experts by experience were also involved. Our recommendations indicate that the comprehensive care of schizophrenia should involve: a) early detection; b) measurement-based monitoring; c) pharmacological treatments; d) psychological interventions; e) psychosocial interventions (including supported employment, housing and education); f) management of somatic conditions; g) community care; h) inpatient care; i) peer support, self-help, and alternative healing methods; j) population-level prevention, and l) societal-level support. The overarching core recommendation is to implement evidence-based care that addresses disparities across high- to middle/low-resource settings, emphasizing early intervention (and prevention when possible), culturally-sensitive paradigms that leverage the local existing resources, and task-sharing models that involve non-professional health care workers and, if possible, traditional healers. In the future, we expect that scalable and resource-saving, evidence-based digital solutions will help extend and improve care quality and efficiency across all resource settings. However, none of this can be achieved without adequately focusing on and strengthening mental health funding, improving access to care, addressing social determinants of health, and recognizing that care for people at risk for or living with schizophrenia is uneven and in need of improvement across all settings.

Key words: Schizophrenia, real-world comprehensive care, middle/low-resource settings, early intervention, measurement-based monitoring, pharmacotherapy, psychosocial interventions, community care, population-level prevention, societal-level support

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Schizophrenia and related disorders have a global incidence rate of 18.66 per 100,000 person-years, translating into a median lifetime morbid risk (including the entire lifetime of a birth cohort, both past and future[1]) of about 0.72%. This is highly variable across different

countries[2], particularly in middle/low-resource settings, although high-quality incidence data in these latter settings are overall scarce[3]. Worldwide, about 20 million people live with schizophrenia[4].

Schizophrenia is a severe mental disorder, subjectively described by experts by experience as "*one of the most painful and upsetting existential experiences, so dizzyingly alien to our usual patterns of life and so unspeakably enigmatic and human*"[5]. Globally, this disorder is associated with an enormous familial[6] and socioeconomic[4] burden, and with 15.5 years (95% CI: 14.2-16.6) of potential life lost[7], translating into 73% of healthy life lost per year[8].

Key drivers of the burden related to schizophrenia are the early disease onset, with the highest incidence in adolescence or young adulthood[9], peaking in young people aged 12 to 35 years (meta-analytic median age at onset: 20.5 years)[10], and in most cases (about 80%)[11] a natural history progressing from premorbid vulnerable states (Stage 0) to clinical high-risk states (Stage I), first episode (Stage II), relapses (Stage III), and ultimately non-remitting chronic manifestations (Stage IV)[11,12]. Progression is variable, and a small subset of cases (about 20%[13]) may present without identifiable stages 0/I.

Additional drivers of schizophrenia-related burden include comorbid mental disorders (e.g., substance misuse, anxiety disorders and depression)[14,15], polysystemic somatic disorders (e.g., cardiovascular diseases and diabetes)[16-19], a complex etiopathology (with an interplay of genetic and environmental factors impacting the underlying neurobiology[20-22]), and cracks in the siloed somatic and mental health care systems, which are often exacerbated by arbitrary age-dependent service splits at the age of 18 years[23]. These drivers frequently lead to insufficient recovery and lifetime chronicity[11,24-26]. Moreover, the frequent and insufficiently treated concurrent physical diseases[16,27-30], and the increased suicide risk[31], reduce life expectancy by about 15 years[16,31].

Because of all these factors, the multidisciplinary, multi-stakeholder clinical management of schizophrenia remains a significant challenge worldwide. The treatment of such a complex disorder requires a comprehensive and integrated care that blends multiple approaches, encompassing mainstream pharmacological treatments with antipsychotic medications[32-35], psychosocial interventions such as supported employment/education, family support activities, and psychological treatments[36-38], as well as community and inpatient care, along with routine monitoring and interventions to address the concurrent somatic problems[39,40].

Comprehensive care for schizophrenia is recommended by most national and international clinical guidelines[41-46]. However, its applicability and implementation depend upon the real-world availability of clinical resources. Almost 80% of all patients with first-episode psychosis live in middle/low-resource settings, where mental health services are scarce[47]. Africa has the lowest number of mental health workers (0.9 per 100,000 population), mental health beds (2.5 per 100,000), and outpatient facilities (0.07 per 100,000)[48,49]. Most African countries lack a national health insurance scheme. In these settings, comprehensive care for schizophrenia is severely constrained by systemic and economic issues, grossly inadequate funding for mental health care, insufficiently trained professionals, and sociocultural barriers, compounded by ongoing political and social distress[50].

Consequently, up to 90% of people with schizophrenia in low-resource countries do not receive evidence-based treatment[51], and several of them end up incarcerated, homeless, chained, or institutionalized in long-stay hospitals, neglected or forgotten, and deprived of even the most basic elements of citizenship and human rights[52]. This highly problematic situation is complicated by the growing population in most middle/low-resource settings (a projected growth by 33% between 2017 and 2030[53]), which is expected to further increase the demand for mental health care in the coming years.

All these considerations underscore the need for an urgent customization of real-world recommendations for the management of schizophrenia, tailored to various regional, economic and local scenarios. We present here the first collaborative recommendations addressing real-world comprehensive care for schizophrenia-spectrum psychoses across high- and middle/low-resource settings, focusing on the various clinical stages of these conditions.

STRATIFYING RECOMMENDATIONS FOR REAL-WORLD COMPREHENSIVE CARE

This report is based on a critical review of the scientific literature and a collaborative appraisal by numerous clinical academics actively treating people with schizophrenia worldwide, representing various countries and clinical settings, including those in the Global South. Some experts by experience were also involved in reviewing the materials and sharing their feedback. We focus on schizophrenia-spectrum psychoses (i.e., affective-spectrum psychoses are not discussed), from now on referred to as schizophrenia, mostly in adult populations.

We adopted a consensus-based approach to provide pragmatic recommendations for the comprehensive care of schizophrenia that focused on the following domains: a) early detection; b) measurement-based monitoring; c) pharmacological treatments; d) psychological interventions; e) psychosocial interventions (including supported employment, housing and education); f) management of somatic conditions; g) community care; h) inpatient care; i) peer support, self-help, and alternative healing methods; j) population-level prevention; and l) societal-level support. These domains were primarily stratified across two broad settings (high- and middle/low-resource countries) and, whenever applicable, additionally stratified across the five above-mentioned clinical stages of schizophrenia (premorbid vulnerable states, Stage 0; clinical high-risk states, Stage I; first episode, Stage II; relapses, Stage III; non-remitting chronic stage, Stage IV).

The types of settings were defined according to the World Bank classification[54]. However, we do not intend to be prescriptive regarding specific countries, as we acknowledge that there may be places in middle/low-income countries that are very well-resourced, and places in high-income countries that are less well-resourced.

High-resource settings were defined as countries with a gross

national income per capita above $14,005 (e.g., the US, Canada, Australia, New Zealand, Western European countries, Russia, Oman and Saudi Arabia). These countries are generally characterized by low birth rates and population growth, high employment levels, high levels of education, well-developed social security systems, broad access to technology, advanced legal systems, and well-developed health care systems. Recommendations for these settings may focus more on the innovative potential associated with clinical research discovery and technologies, although access to and persistence of mental health care remain cross-resource level issues.

Middle-resource settings were defined as countries with a gross national income per capita between $1,146 and $14,005[54]. This definition encompasses a large proportion of the world population, and a very heterogeneous group of countries (e.g., Mexico, Brazil, Argentina, South Africa, Algeria, China, Ukraine, Belarus), that can be further subdivided into lower middle-income countries (gross national income between $1,146 and $4,515) and upper middle-income countries (gross national income between $4,516 and $14,005)[54]. Essentially, these countries are transitioning from agricultural-based economies (and their associated lifestyles) to diversified industrial economies. They have achieved significant improvements in human development, including education and health, but have typically substantial disparities within populations. These disparities are also reflected in health care services, with some groups of people benefiting from upper-income society services, while the majority does not. As such, these settings typically suffer from excessive centralization of scarce mental health resources[55].

Low-resource settings were defined as countries with a gross national income per capita below $1,146[54] (e.g., North Korea, Afghanistan, Syrian Arab Republic, Republic of Yemen, Guinea Bissau, Sierra Leone, Liberia, Mali, Burkina Faso, Niger, Chad, Sudan, Eritrea, Ethiopia, Somalia, Central African Republic, Democratic Republic of Congo, Madagascar, Uganda, Rwanda, Burundi, Malawi, Mozambique, Madagascar). These settings are characterized by severe inequalities, poor education, high unemployment, heavy reliance on agriculture, and rapid population growth. Recommendations for these settings will primarily need to address the presence of systemic, economic and health care constraints. However, economically deprived settings may be rich in other resources, such as community assets, and we will recommend how these can be drawn upon[56].

Our recommendations are guided by four overarching principles, which apply to all settings and clinical stages. First, we propose a rights-based approach to care that minimizes coercion and involuntary treatment. Aligning with the United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD)[57], we recognize that individuals living with schizophrenia remain full citizens at all stages of their disorder. We recommend that, even during acute psychosis, individuals are offered accessible communication about their rights and available options to the maximum extent possible. We also acknowledge that people with a diagnosis of schizophrenia are frequently stigmatized by public attitudes and media reporting[58,59]. We, therefore, include population-level actions to address these societal issues.

Second, we recommend a recovery-based approach. Core aspects of recovery-oriented care include fostering hope and facilitating self-determination, through supporting individuals living with schizophrenia to define their own goals[60]. Yet, we also acknowledge that false or overly optimistic expectations – especially when not matched by sufficient resources or system capacity – can cause harm to individuals and their families[61]. We highlight that recovery is a dynamic, individualized process, not a guaranteed system outcome, nor is it about making people "normal"[60].

Third, we promote an equity-focused approach to ensure that all individuals with schizophrenia, irrespective of their background or current circumstances, benefit from ongoing efforts. The prevalence of schizophrenia-spectrum disorders is significantly higher in refugees and other immigrants, people who are homeless, and prisoners, compared to the general population[62]. These groups experience higher rates of involuntary admissions[63] and worse mental and physical health outcomes[64]. In some settings, women with schizophrenia may be exposed to an increased risk of sexual violence[65]. We, therefore, highlight approaches to ensure the inclusion of, and address the needs of, specific vulnerable groups.

Fourth, we advocate for a person-centred approach across all components of care. This means that care should be customized to fit individuals' specific social and economic situations, beliefs, goals, physical and mental health comorbidities, while understanding that the social and cultural context shapes these characteristics [66]. We emphasize that truly integrated care should involve a coordinated collaboration across health and social care systems, nongovernmental organizations, the voluntary sector, traditional care providers, communities, and family systems.

Finally, we acknowledge that any mental health system is not infallible. It can fail, harm or exclude. We recognize that mental health services themselves can cause secondary trauma in people with psychosis through coercive practices or systemic failures[67]. By recognizing these constraints and risks, we hope to model the systemic humility required to create a culture of care that can truly promote recovery. Moreover, in the realization of our recommendations, we urge the systematic and meaningful integration of the voices of people living with schizophrenia across all phases, states and symptoms into care design, delivery and evaluation[68,69]. Hearing, understanding and integrating these voices, without filters or assumptions, offers the best chance of achieving a reasonably effective care for all.

EARLY DETECTION

High-resource settings

Clinical high-risk for psychosis

The vast majority (78% in a recent meta-analysis[13]) of patients with first-episode psychosis present prodromal manifestations before the onset of the disorder, whose early detection may lead to the prevention of transition to full-blown psychotic disorder and

improve outcomes[70].

The so-called clinical high-risk stage for psychosis (CHR-P) refers to individuals exhibiting attenuated psychotic symptoms, or brief limited intermittent psychotic episodes, or high genetic risk for psychosis (e.g., a first-degree relative with a psychotic disorder) plus a marked decline in psychosocial functioning[71,72]. Most individuals with CHR-P have neurocognitive impairments[73], mental health comorbidities such as anxiety and mood disorders[74,75], substance misuse[76], and physical comorbidities[74]. Suicidality is also increased[77]. The prevalence of CHR-P features is about ten times higher in clinical samples (19.2%) than in the general population (1.7%)[78].

In high-resource settings, the detection of a CHR-P state should be delivered by specialized services[79], which involve a multidisciplinary team consisting of psychiatrists, clinical psychologists, counselors, case managers, and nurses. CHR-P care is currently recommended by several national and international guidelines[80-82]. It is also expanding, including in the Global South[83].

Most CHR-P services receive young people with a putative risk of psychosis from health-related organizations such as mental health services and general health care services[84,85]. CHR-P care can also be integrated with primary care by offering a "soft entry" or "one-stop shop" for youth health care, which minimizes barriers to access[86]. These latter units are organized as a dedicated team of clinical and non-clinical (e.g., peer workers) personnel, providing a comprehensive range of care for the youth and their family, encompassing mental health, physical health, support related to alcohol and other drug use, and vocational support[86]. While these youth mental health models originated in Australia (e.g., headspace[87]), they are expanding to several countries[88,89].

The detection of CHR-P should be based on a semi-structured interview such as the Comprehensive Assessment of At-Risk Mental States (CAARMS)[90] or the Structured Interview for Psychosis-Risk Syndromes (SIPS)[91]. The use of these instruments requires intensive psychometric training, that can be delivered remotely through digital platforms. Administering the full CAARMS interview (60 items in total) takes on average one hour and a half, which may pose logistic challenges even in high-resource settings. To fill this gap, a recent study has validated a mini-CAARMS (23 items) and an ultra-mini CAARMS (12 items), which have demonstrated an excellent accuracy compared to the full version[92].

A complete psychiatric assessment is needed to identify mental health comorbidities (that do not exclude a CHR-P state) and to evaluate the risk for self-harm and suicidal behavior. Concomitant physical conditions should also be timely detected.

First-episode psychosis

The detection of first-episode psychosis is based on eliciting the core symptoms of schizophrenia[93]: delusions (fixed false beliefs resistant to reasoning, e.g. paranoid delusions); hallucinations (perceptions without external stimuli, most commonly auditory); disorganized speech (e.g., incoherence, derailment); grossly disorganized or catatonic behavior (e.g., agitation, immobility, or peculiar posture); negative symptoms (affective flattening, alogia, avolition, anhedonia, asociality); and cognitive symptoms (impaired attention, memory, processing speed, social cognition, and executive functioning). The use of the Composite International Diagnostic Interview (CIDI)[94,95], a clinician-rated tool whose administration takes about 120 min, can be advised in order to make a diagnosis of schizophrenia according to the ICD or DSM, along with the Positive and Negative Syndrome Scale (PANSS)[96] – possibly in its 6-item version (PANSS-6)[97,98], whose administration takes about 15 min – for assessing symptom severity.

It is essential to establish the speed of onset, duration, and functional impact of symptoms, in order to distinguish a first-episode psychosis from a CHR-P stage. An associated aim is to exclude alternative diagnoses (other psychiatric disorders or physical conditions with brain involvement), identify comorbid mental health conditions (e.g., depression, substance misuse), assess prognostic factors (e.g., duration of untreated psychosis, DUP), obtain a family history (genetic predisposition to schizophrenia), assess social history (e.g., support network, housing), establish baseline physical health, evaluate risk (to health, self, others, and from others), consider the necessary level and intensity of care, and assess capacity to consent to treatment.

Clinical investigations (see Table 1) can support the identification of any physical health condition that may be contributing to the altered mental state – e.g., thyrotoxicosis, autoimmune conditions such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, acute drug intoxication/withdrawal, infections (either neurological or systemic), malnutrition, rheumatological diseases, and neurological diseases[99,100].

Early detection has grown within clinical staging frameworks [101,102] to target the highest therapeutic malleability of the unfolding schizophrenia process, with an increased potential for averting the progression of the disorder and strengthening functional recovery [70,103]. At the first presentation of psychosis, treatment may need to be initiated before a diagnosis of schizophrenia has been unequivocally established.

The benefits of early detection and intervention are multifaceted, encompassing clinical and social realms[11,104]. Available meta-analyses indicate that early intervention in schizophrenia, compared to treatment as usual, is consistently associated with improvement in several outcomes: all-cause treatment discontinuation (risk ratio, RR=0.70), at least one psychiatric hospitalization (RR=0.74), involvement in school or work (RR=1.1), total symptom severity (standardized mean difference, SMD=–0.32), positive symptom severity (SMD=–0.22), and negative symptom severity (SMD=–0.28)[105]. These effects are inconsistently maintained until approximately two to five years post-intervention[106], although non-random attrition effects (e.g., cases with worse outcomes are more likely to be retained in the prior early intervention group) and non-adherence-related relapses that level off differences in outcomes may be partly responsible.

Before starting antipsychotic treatment, the following measures should be obtained: body mass index, waist circumference, blood pressure, hemoglobin A1c (HbA1c), fasting glucose, lipids, prolactin (especially when starting prolactin-raising antipsychotics such

Table 1 Clinical investigations recommended in high-resource settings for excluding physical health conditions in the differential diagnosis of schizophrenia

Blood tests

- Full blood count
- Hemoglobin A1c and fasting glucose
- Fasting lipid profile
- Liver function tests
- Parathyroid hormone and calcium
- Serum electrolytes and creatinine
- Infection screen: HIV and syphilis (if encephalitis is suspected, include infectious encephalitis serology)
- Thyroid function tests
- Vitamin B12 and folate
- Antinuclear antibody and erythrocyte sedimentation rate may be considered as a screen for possible autoimmune disorders
- If encephalitis is suspected, include neuronal surface antibody testing

Urine drug screen

- Detect recent use of psychoactive substances (e.g., cannabis, cocaine)

Brain imaging

- Magnetic resonance imaging or computer tomography scan if structural abnormalities (e.g., tumors, hydrocephalus) are suspected

Cerebrospinal fluid examination

- Indicated if infectious, autoimmune or paraneoplastic encephalitis is suspected

Electroencephalogram

- Indicated if seizure activity or encephalitis is suspected

Electrocardiogram

- Check QTc if antipsychotic medication with QTc-prolonging effects is to be initiated

as amisulpride, first-generation antipsychotics, risperidone and paliperidone), liver function tests, urea and electrolytes, and full blood count[107]. Pragmatically, if a fasting glucose sample cannot be obtained, a random sample can be taken initially as a screening measure; if the result is abnormal, a fasting measure is prioritized. Given the risk of psychiatric medications interfering with cardiac electrophysiology[100], a baseline electrocardiogram is recommended, especially when other cardiac risk factors are present or when the antipsychotic initiated is known to prolong QTc (particularly amisulpride, sertindole, ziprasidone)[32].

There are treatment access gaps and regional differences in providing early intervention services even within high-resource settings[108]. The long-term sustainability of positive effects and the need for tailored interventions for patients with treatment-resistant illness require further research[109,110] (see below).

Relapsing and non-remitting psychosis

After initial remission, timely detection of an individual's "early warning signs" for relapse is a core clinical step. Early warning signs manifest subtly and may not be consistently recognized by the individuals or their family members, making routine monitoring essential. Common early signs of relapse include social withdrawal, increased irritability, sleep disturbances, and changes in personal hygiene or daily functioning. These signs often precede the re-emergence of full psychotic symptoms, such as delusions or hallucinations.

Early detection of relapse in schizophrenia involves establishing a close partnership between patients, their families, and health care providers. By developing and implementing personalized "relapse prevention plans", clinicians can make timely revisions of treatment, such as adjusting medication regimens, increasing the number of therapy sessions, or enhancing community-based support.

Another essential step is early detection of treatment resistance, defined as the experience of ongoing psychotic symptoms despite treatment with at least two antipsychotic medications at adequate dose, of a sufficient duration, and with an appropriate adherence [110]. Treatment resistance should be identified as soon as possible, ideally within the first six months of treatment initiation, to allow for the earlier use of clozapine (see below), which is much needed to improve long-term outcomes.

Middle/low-resource settings

The clinical staging model and its associated early detection and intervention approaches are underdeveloped in middle/low-resource settings. We acknowledge that in these settings it may not be feasible to set up specialized services that stratify across the different clinical stages of psychosis, when even basic care for mental disorders is lacking[47]. Limited access to formal mental health services is one of the reasons why many individuals first seek care from traditional and faith healers (see below).

An analysis of clinical staging in psychosis literature found a stark under-representation of studies from middle/low-resource settings [111]. Another recent review of current early detection and intervention provision in middle/low-resource settings found that, while some services and programs exist, very few provide comprehensive care packages comparable to those in high-resource settings [112]. We recommend that evidence generated in high-resource settings should not be simply "translocated" to middle/low-resource settings, given the enormous cultural and contextual differences, adding to the substantial lack of well-resourced mental health infrastructures.

Clinical high-risk for psychosis

The CHR-P approach is not fully consolidated for middle-resource countries and is just emerging in low-resource settings. Although still a fledgling research and clinical field globally, some CHR-P care has been implemented in different continents, albeit only sparingly in African countries[83]. For example, the Washing-

ton Early Recognition Center Affectivity and Psychosis (WERCAP) Screen has been used to assess young people aged 14-25 years in low-resource settings[113] in order to estimate the risk for developing a psychotic disorder.

In some low-resource countries, the feasibility to detect a CHR-P state and conduct prospective cohort studies in youth with this condition has been documented (e.g., the Tunisian Early Intervention in Psychosis project[114,115]). Within these initiatives, some instruments have been translated and validated (e.g., the CAARMS), thereby providing an initial set of assessment tools for emerging psychosis.

Recommendations for future clinical practice in this area include the design of more culturally appropriate tools for assessing CHR-P, as well as the transcultural validation of existing CHR-P assessment instruments in middle/low-resource settings[116]. For example, while Indonesia has begun prioritizing CHR-P care, early data indicate the need for significant adaptation and cultural contextualization of the CHR-P criteria and assessment tools in that setting[117].

It is also recommended that CHR-P services be developed in middle/low-resource settings by building them within youth mental health programs[118]. Given the large number of young people and the increasing prioritization of youth mental health in these settings[102,119], embedding CHR-P approaches within comprehensive youth services[120] could enhance early intervention without significantly straining mental health systems. However, we acknowledge that settings with scarce health care resources should prioritize the detection and treatment of individuals with a first episode of psychosis over the implementation of CHR-P care.

First-episode psychosis

Detecting the first episode of schizophrenia is particularly challenging in middle/low-resource settings. Assessment and diagnosis should be primarily clinical[121], focusing on the core symptoms listed above. Initial assessments in these settings may be more effective when targeting psychosis broadly, including mood disorders with psychotic features and substance-induced psychosis. Given the lack of resources, it makes more sense in these settings to target psychotic disorders as a broader diagnostic group rather than narrowing strategies to the diagnostic category of schizophrenia[122,123]. This approach facilitates real-world assessment beyond strict diagnostic criteria, and streamlines levels of care according to the broader associated disability.

The initial diagnosis of psychosis can be made in different settings. One opportunity lies within specialist services, which are typically located in major urban areas[48,124-126], involving face-to-face contact with a psychiatrist or a health care assessor who has been trained and supervised (through telemedicine when available)[127]. However, another opportunity is to expand the early detection of a first episode of psychosis in more remote and rural areas by implementing task-sharing models[128]. These models can potentially improve early case detection in settings where access to specialists is limited, and many individuals first seek help from non-specialists, e.g., peers, faith-based groups, or traditional healers. In the absence of task-sharing models, faith-based groups or traditional healers are more likely to delay access to mental health care[129].

Task-sharing is an effective approach, allowing community and/or primary health care workers to deliver mental health services under the supervision of specialists. Those trained for the early detection of psychosis may include community health workers, networks of community volunteers outside of health care, and traditional and faith-based healers (see below). Collaboration with the latter can particularly facilitate the detection of a first episode of psychosis while building trust between communities and mental health services[130]. Training to early detection of psychosis should include culturally adapted diagnostic material that integrates narrative-based diagnostic vignettes and locally grounded concepts of mental distress relating to first-episode psychosis[131].

Task-sharing models of care centred on the community are key to reducing reliance on specialist services while enabling scalable delivery of care for first-episode psychosis in low-resource settings [132]. The World Health Organization (WHO) Mental Health Gap Action Programme (mhGAP) is the most widely disseminated task-sharing model[133]. Examples of task-sharing models of care for psychosis in middle/low-resource settings that have been validated by randomized controlled trials (RCTs) include the TaSCS (task-shared care for people with severe mental disorders) in Ethiopia [134], the COSIMPO (collaborative shared care to improve psychosis outcome) in Nigeria and Ghana[135], and the COPSI (community care for people with schizophrenia) in India[136].

Relapsing and non-remitting psychosis

There is a lack of regionally representative data that undermines the ability to customize recommendations for detecting relapsing and non-remitting stages of psychosis in low-resource settings[137].

In middle-resource settings, some attempts have been made[138]. Using evidence-based practices, some guidelines have been developed for the detection of relapsing and non-remitting schizophrenia, which recommend the prompt assessment of relapse together with the implementation of psychoeducation and involvement of relatives[138]. However, these recommendations are not widely known, and identification of relapsing and non-remitting schizophrenia patients remains primarily based upon idiosyncratic approaches.

MEASUREMENT-BASED MONITORING

High-resource settings

Clinical high-risk for psychosis

Measurement-based monitoring of CHR-P individuals should be done at least every six months, aiming to map their likelihood of developing a first episode of schizophrenia. The same instruments recommended for the detection of CHR-P (e.g., the CAARMS, the

mini-CAARMS or the ultra-mini CAARMS) should be used, along with an overall psychiatric assessment (ideally by a standardized tool such as the CIDI). Physical health should also be regularly monitored, as well as the risk for self-harm and suicidal behavior.

The probability of transitioning from a CHR-P stage to first-episode psychosis (73% of which are schizophrenia-spectrum psychoses[139]) cumulates to 0.20 (95% CI: 0.19-0.21) at two years and 0.35 (95% CI: 0.32-0.38) at 10 years[140]. Stratified across CHR-P subgroups[141], transition to psychosis is higher in individuals presenting with brief limited intermittent psychotic symptoms (about 10% of cases)[142-146] than in those presenting with attenuated psychotic symptoms (85% of cases) and in those with familial risk.

The likelihood of developing psychosis in the whole CHR-P group is substantially higher than the observed incidence rate in the general population (0.317% at 10 years[147]). Moreover, most individuals at CHR-P who do not transition to psychosis continue to display other mental health problems or functional impairment [148,149], and only 41% remit at two years[148]. These problems are typically already present at baseline, and the CHR-P state does not constitute, *per se*, a risk stage for the development of other non-psychotic mental disorders[148-150] (e.g., for detecting individuals at risk of bipolar disorders, additional interviews would be needed, such as the Semistructured Interview for Bipolar At Risk States, SIBARS[151]).

A variety of neurocognitive deficits (e.g., impaired processing speed, verbal and visual memory, attention) and biomarkers (e.g., reduced hippocampal volume) have been reported to predict transition from CHR-P to psychosis[152]. However, these markers are not adopted in the routine clinical assessment of CHR-P and should be the focus of further research.

First-episode psychosis and relapsing/non-remitting psychosis

The PANSS[96] and the Brief Psychiatric Rating Scale (BPRS)[153] are widely used tools for monitoring symptom severity in schizophrenia. A 25% reduction in PANSS/BPRS score signifies a minimal clinical response, while a 40-50% reduction reflects a robust response[154]. A major barrier to using the PANSS in day-to-day clinical practice is the time required to conduct an assessment. To address this, the shorter PANSS-6 may be considered[97,98,155].

Reassessment of symptom severity should occur within a short period (e.g., one week) after starting antipsychotic medication, and the dose should be increased or adjusted based on response and tolerability. Assuming good adherence, an individual's first antipsychotic medication should be given at a therapeutic dose for at least 2-4 weeks[156]. Recent meta-analyses suggest that a less than minimal response (<20% PANSS/BPRS reduction) at even 2 weeks suggests that the antipsychotic can/should be changed[156,157]. At this point, if significant positive symptoms persist, a switch to an alternative antipsychotic should be discussed (see the pharmacological treatment section for more in-depth guidance).

Symptom domain-specific tools which can be considered are the Scale for the Assessment of Negative Symptoms (SANS)[158], the Screen for Cognitive Impairment in Psychiatry (SCIP)[159], and the Calgary Depression Scale for Schizophrenia[160]. Treatment-emergent side effects should also be monitored, preferably using a self-report instrument such as the Glasgow Antipsychotic Side-Effect Scale (GASS)[161].

Body weight, waist circumference, and blood pressure should be checked weekly for 6 weeks, and at a minimum 4 weeks after antipsychotic initiation. Fasting glucose and lipids, HbA1c and liver function tests should be re-checked and reviewed routinely at 3 months, one year, and annually thereafter (6-monthly in people at high risk for or with metabolic syndrome)[39]. In patients started on an antipsychotic with QTc-prolonging potential, at least one additional electrocardiogram should be obtained at steady-state antipsychotic dose.

For the monitoring of social functioning, a tool that has been validated in clinical populations of individuals with schizophrenia is the Specific Level of Functioning (SLOF)[162], a clinician-, patient- or informant-rated scale exploring the subdomains of physical functioning, personal care skills, interpersonal relationships, social acceptability, activities, and work skills. For the assessment of quality of life, validated instruments such as the Heinrichs-Carpenter Quality of Life Scale (QLS)[163], the Schizophrenia Quality of Life Questionnaire 41 (S-QoL 41)[164], and the Schizophrenia Quality of Life Scale (SQLS)[165] can be considered.

Various digital health technologies designed to monitor symptoms of schizophrenia or prevent relapse (e.g., the CareLoop[166]) are emerging. However, they require further evidence of clinical effectiveness before they can be incorporated into routine clinical practice. Digital applications may also be used to promote active and healthy lifestyle behaviors, predict cardiometabolic disease risk in people with psychotic disorders[167], and support antipsychotic prescription decisions[168].

Middle/low-resource settings

It is acknowledged that measurement-based monitoring of individuals with psychosis is challenging in middle- and particularly low-resource countries, outside specific research settings[169]. While assessment tools such as the PANSS, BPRS and SANS may be used in such research settings[170-173], they are not commonly utilized in routine clinical care due to a lack of resources and training.

To ensure that care is meaningful and impactful, culturally relevant measures should be ideally adopted, but they are not available to date. The PANSS-6 is a brief clinician-rated tool for the monitoring of positive and negative symptoms of schizophrenia, whose administration takes about 15 min. However, it has not been validated for use in middle/low-resource settings, and this specific validation should be prioritized. The Calgary Depression Scale for Schizophrenia is a clinician-rated tool for the assessment of depressive symptoms in psychotic patients whose administration takes about 20 min, which has been validated for use in middle/low-resource settings[174,175]. The WHO-Five Well-Being Index (WHO-5) is a self-rated tool for the assessment of well-being that takes just one minute to administer and has been validated in these settings[176,177].

Emerging findings from sub-Saharan Africa suggest that many individuals with psychosis and their caregivers have access to mobile technologies and are interested in leveraging digital platforms for psychoeducation and illness management support[178]. These digital innovations could be integrated into task-sharing monitoring systems, supported by structured reminders[179,180], which have shown potential to improve medication adherence and reduce treatment dropout.

In middle/low-resource settings, digital systems may also potentially facilitate effective coordination between mental health specialists and community health workers[181]. For example, short message service reminders might be considered to help maintain engagement, particularly for those at high risk of disengaging from care[182]. However, ensuring digital health access equity and overcoming insufficient digital and language skills are basic prerequisites for harnessing this potential.

PHARMACOLOGICAL TREATMENTS

High-resource settings

Pharmacotherapy plays a key role in the treatment of people living with schizophrenia. Several general principles should guide pharmacological treatment. It is crucial to involve patients in shared decision-making throughout treatment, ensuring that they understand the potential benefits and risks of each option. Factors such as age, sex, ethnicity and physical health influence drug metabolism and safety profiles, requiring careful personalized selection and regular review of treatments. Early efficacy and safety of antipsychotics often predict longer-term outcomes[156,157,183]; therefore, clinicians should proactively address side effects or lack of efficacy. The optimal treatment strategy varies significantly across different stages of illness.

Clinical high-risk for psychosis

The available research evidence suggests that exposure to antipsychotics in CHR-P individuals is associated with a higher risk of developing psychosis, probably because it indexes the most severe cases, that are in the process of transitioning to psychosis[184]. Cannabidiol, a non-intoxicating constituent of cannabis, is currently under investigation, given its high tolerability and potential for an antipsychotic effect[185].

It is essential to note that clinical approaches to CHR-P states can deliver benefits beyond the prevention of psychosis onset. We recommend treating other comorbid conditions, including non-psychotic mental disorders, substance use, and physical diseases, aiming to improve recovery, functional status, and quality of life. The use of certain antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), may be considered if comorbid depression or anxiety significantly contributes to the individual's risk profile. These medications can help stabilize mood and reduce stress, potentially mitigating risk factors that exacerbate prodromal symptoms of psychosis[186].

We acknowledge that some second-generation antipsychotics at a dosage lower than the minimum effective one may be considered for a small subset of CHR-P individuals, in the presence of behavioral disturbances (e.g., "symptoms severely disorganizing or dangerous" according to the SIPS definition[143]) or persistent attenuated positive symptoms that lead to functional disability and failure to recover[187]. It is important to note, however, that even low-dose antipsychotics can increase the risk for adverse cardiometabolic outcomes, particularly in this young population[188-190].

The use of antipsychotics at a dosage equal to or above the minimum effective one should be reserved only for those individuals who have made a full transition to a first episode of psychosis.

First-episode psychosis

When an individual presents with a clear-cut first episode of psychosis, early and effective pharmacological intervention can make a significant difference in both short- and long-term outcomes. A delay in antipsychotic prescription at doses equal to or above the minimum effective one should only be considered when symptoms are clearly related to substance use or a medical condition, and do not pose safety concerns.

The goals at this stage typically include rapid symptom reduction, prevention of immediate relapse, and minimizing side effects, which can impact treatment adherence. It is crucial to involve individuals diagnosed with schizophrenia in decision-making wherever possible[42,191-195]. They should be informed about potential treatment options, as well as the associated risks and benefits. As treatment progresses, it is essential to maintain a shared decision-making approach when evaluating the effectiveness of treatment and considering adjustments to pharmacological therapy.

Treatment should be individualized whenever possible, taking into account the current symptom profile, the patient's views on potential side effects, and his/her preferences regarding the route of administration, yet in the context of adequate psychoeducation about these options. This process should be careful, as various individual-level factors (e.g., age, sex, ethnicity, and physical health) impact pharmacokinetics and, therefore, should influence dosing[196,197].

A regular treatment review is crucial. Treatments should be optimized, changed or augmented where needed. An early response (i.e., within 2-4 weeks) to treatment is a good indicator of longer-term effects, and decisions to address side effects or lack of efficacy should be made as soon as possible[156].

Antipsychotics with a lower overall side effect burden include partial dopamine agonists, such as aripiprazole, brexpiprazole and cariprazine, which may, therefore, be a suitable choice for the first-line treatment, depending on the patient's views[32,168]. If during the initial intervention a more sedating treatment is required, it may be preferable to co-administer a benzodiazepine, rather than initiating a sedative antipsychotic such as olanzapine, since the latter

often shows a greater risk of metabolic harm[198-201]. An exception may be a deliberate, time-limited approach, in which the sedating and cardiometabolically problematic antipsychotic is only given for 1-2 weeks, while the less sedating and cardiometabolically more neutral antipsychotic dose is optimized. If a medication with an adverse metabolic profile is necessary, adjunctive strategies should be employed concurrently to mitigate adverse effects (see below).

In the first episode of psychosis, treatment should be started at a low but effective dose, with reassessment occurring soon (e.g., after 2 weeks) thereafter to assess efficacy and side effects, with careful dose changes made accordingly[193].

RCTs and real-world data have shown that long-acting injectable antipsychotics (LAIs) are superior to oral antipsychotics in reducing the risk of non-adherence, relapse and hospitalization, while increasing functional outcomes[202]. Real-world data have also suggested that the use of LAIs is associated with a decreased risk of overall mortality, suicide-related mortality, and mortality due to natural causes[203]. The administration of LAIs should be discussed with patients early in treatment, not only in cases of non-adherence[44,204-207].

Non-adherence to pharmacological treatments is a frequent and underestimated phenomenon in clinical practice[208]. Antipsychotic plasma levels may be useful here. Pill counts or staff/carer reports can also be informative[193,209-214], but the use of LAIs is the only reliable way to know exactly when a patient becomes non-adherent.

An individual's initial antipsychotic should be administered for at least 2-4 weeks (assuming it is tolerable). If significant positive symptoms remain present and adherence has been adequate, a switch to an alternative antipsychotic should be discussed with the patient. A switch to a compound with a distinct pharmacological profile, including potential side effects, may be considered. If the initially used antipsychotic is a partial dopamine receptor agonist, switching to risperidone, amisulpride or olanzapine are potential options (with care taken to attenuate potential side effects, particularly the metabolic syndrome that can be induced by olanzapine).

Switching strategies should be based on the half-life of each medication, and aim to maintain a minimum therapeutic level of D2 receptor occupancy that corresponds to the minimum effective dose[215,216], as illustrated in Table 2. If positive symptoms do not respond adequately to a second medication, taken at an adequate dose, with good adherence, then treatment with clozapine should be discussed with the patient[217-222], instead of engaging in antipsychotic polypharmacy for first-episode psychosis.

Antipsychotic polypharmacy has an insufficient efficacy evidence base and may produce substantial harms[223-226], as shown by a recent meta-analysis[225]: increased risk of relapse (RR=1.42) and psychiatric hospitalization (RR=1.24), worse global functioning (SMD=0.31), more adverse events (extrapyramidal symptoms: RR=1.63; dystonia: RR=5.91; anticholinergic use: RR=1.91; longer QTc interval: SMD=0.24), and greater all-cause mortality risk (RR=1.19). Polypharmacy is a global concern, with an average frequency of antipsychotic polypharmacy of 33% in people with schizophrenia-spectrum disorders[225].

Table 2 Minimum effective dose per day of second-generation antipsychotics for treating a first episode of psychosis

Amisulpride	300 mg
Aripiprazole	10 mg
Asenapine	10 mg
Brexpiprazole	2 mg
Cariprazine	1.5 mg
Iloperidone	4 mg
Lurasidone	40 mg
Olanzapine	5 mg
Paliperidone	3 mg
Quetiapine	250 mg
Risperidone	2 mg
Ziprasidone	40 mg

The optimal duration of treatment following a first episode of psychosis and an initial resolution of symptoms remains uncertain[227,228], leading to broad variations in guidelines regarding whether and when to consider antipsychotic tapering and discontinuation. If an individual experiences complete remission of symptoms and functional recovery for at least two years, discontinuation may be considered and discussed with the patient, although long-term continuation is also an option[227]. Both risks and benefits of discontinuation should be considered, given that, even at this stage, there remains a substantially increased risk of relapse[34].

If ongoing risk factors for relapse are present – such as family history of schizophrenia, ongoing substance use, a particularly poor premorbid adjustment, or significant concerns regarding risk associated with psychotic exacerbation – one may discuss ongoing antipsychotic medication even in the context of extended remission. If the choice to discontinue medication is made, one should also deliver individualized psychoeducation to both the patient and carers regarding risk factors and early signs of relapse.

The optimal duration over which to taper antipsychotic medication also remains unclear, but a gradual tapering over at least six months allows for the assessment of any potential concerns emerging during the period[229]. Follow-up and careful assessment of symptoms by specialist health care professionals should occur both during the tapering period and after discontinuation, as the risk of relapse significantly increases during this period[230].

During the initial episode, care should be taken to adequately treat symptom domains beyond just positive symptoms. Much of the disability associated with schizophrenia relates to negative and cognitive symptoms[231-234]. In the presence of negative symptoms, secondary causes (such as the side effects of antipsychotic medication, depressive symptoms, positive symptoms, and medical illness) should be considered and addressed where possible[235]. If positive symptoms are sufficiently controlled, a gradual reduction in antipsychotic dose (remaining within the therapeutic range) may be considered[230,236], but the risk for relapse can be increased if doses are too low[34,237-239].

If a switch to another antipsychotic is thought to be a suitable option, a partial dopamine receptor agonist may be most likely to show benefit, with cariprazine, in particular, having shown benefits compared to risperidone in the management of negative symptoms[32,240,241]. Additionally, low-dose amisulpride (50-300 mg/day) may be an option[240]. There is also some evidence that antidepressant or aripiprazole augmentation in the absence of clear depressive symptoms may show a modest effect in treating negative symptoms[242,243].

Until recently, all licensed drugs with antipsychotic activity displayed an affinity for the postsynaptic dopamine D2 receptor[244,245]. It has recently been demonstrated that a drug with negligible D2 affinity and high muscarinic M1/M4 agonism, xanomeline, in combination with the peripherally restricted anticholinergic trospium to buffer pro-cholinergic peripheral side effects, is associated with an antipsychotic effect in people with chronic schizophrenia[246], supposedly via reduced presynaptic dopamine release. However, xanomeline-trospium has not yet been tested in first-episode schizophrenia. Investigating where this new medication should be placed in current treatment algorithms is a crucial current question[246-249].

Relapsing psychosis

Despite successful acute treatment in a first episode of schizophrenia, relapse remains a significant risk, especially in the first few years following remission. One of the most common reasons for early relapse is suboptimal medication adherence or premature antipsychotic discontinuation.

If a patient experiences a relapse despite being on an antipsychotic, the first step is to assess adherence and dosage as well as substance misuse[250]. In some cases, increasing the dose within the therapeutic range can restore symptom control. However, if side effects are the primary reason for non-adherence, switching to another antipsychotic with a more tolerable side-effect profile is advised[34]. If adherence is unclear, a trial of a LAI should be considered as early as possible[217,251].

Cognitive dysfunction remains a major unmet need in schizophrenia treatment, although there is hope that efficacious treatments for this domain may soon be available[252,253]. Postsynaptic dopamine receptor blocking antipsychotics have minimal efficacy for improving cognition, especially in stable patients[254], and may even exacerbate cognitive impairment[255], with a high anticholinergic burden, in particular, being associated with poor cognitive performance[256].

Anticholinergic burden, sedative side effects, and antipsychotic dosage should therefore be reviewed, and attempts made to reduce these where possible, but the potential for an increased relapse risk also needs to be considered[239,257,258]. Furthermore, obesity, metabolic syndrome, diabetes mellitus and hypertension are associated with poorer cognition in people with schizophrenia[259], which is why less cardiometabolically problematic antipsychotics are preferred, and a healthy lifestyle, especially aerobic exercise, which can improve cognition, is recommended[260].

Non-remitting psychosis and treatment resistance

Treatment resistance, which occurs in about 20% of patients with first-episode schizophrenia and up to 40% of those with multi-episode schizophrenia[261], should be promptly identified and addressed. Clozapine remains the gold-standard medication for treatment-resistant schizophrenia[44,262]. This drug can effectively reduce hospitalization risk and persistent positive symptoms, and improve overall functioning[220,263]. However, clozapine has a unique and complex side-effect profile that necessitates careful monitoring: in addition to rare and severe side effects such as agranulocytosis and myocarditis, it is also associated with a range of common side effects such as weight gain, hypersalivation and constipation, all of which can cause distress, reduce adherence, and potentially endanger health[110,264].

Clozapine dose should be gradually increased based on efficacy and tolerability, aiming for a dose associated with a plasma level of at least 350 ng/ml, if a therapeutic response is not observed before then[110,265,266]. If response is not observed after 12 weeks, an increase to 550 ng/ml may be attempted[267]. If symptomatic response remains insufficient, then augmentation with aripiprazole, or electroconvulsive therapy (ECT), may be discussed[266,268-271].

ECT is particularly recommended for severe, life-threatening symptoms, such as catatonia and suicidal behavior, and may be used in clozapine-resistant cases[272]. Although high-quality RCT data targeting symptomatic improvement provide insufficient evidence for the use of antipsychotic polypharmacy, including for the augmentation of clozapine[268], nationwide real-world data have favored low- and medium-dose aripiprazole augmentation of clozapine for the prevention of hospitalization[269].

Middle/low-resource settings

Pharmacological interventions remain the primary and most widely available treatment modality for managing schizophrenia in middle/low-resource settings. Although most clinical considerations discussed for high-resource settings also apply here, including the involvement of individuals diagnosed with schizophrenia in decision-making, this section focuses only on specific customizations needed for middle/low-resource settings.

Facility-based biomedical management in which patients are prescribed antipsychotic drugs is the predominant model of care for persons with schizophrenia in most low-resource settings[273]. However, availability (from country regulation to market provision) and costs of antipsychotics, particularly when self-funded, represent substantial barriers. For example, first-generation antipsychotics remain the mainstay of pharmacotherapy for psychosis management in several low-income countries[274-276]. Some second-generation formulations, such as LAIs, are only occasionally reported in the existing literature on antipsychotic treatments for people with schizophrenia in Africa[277].

On the other hand, several middle-resource settings have supplies of both first- and second-generation antipsychotics[278], with some countries (e.g., Tunisia) also having access to second-gen-

eration partial dopamine agonists, such as cariprazine. In these countries, the number of psychotropics available on the market has gradually increased, providing a great variety of treatment options for prescribers[279].

Use of generic bioequivalent compounds should be encouraged, as they can reduce financial barriers for patients, and ensure that a wider population can benefit from effective therapies[280]. As discussed later, it is also urgent to reduce financial barriers and improve accessibility to second-generation antipsychotics[281] with a more favourable side-effect profile compared to first-generation antipsychotics.

Even when some of the second-generation antipsychotics are available, access is highly variable, particularly between urban and rural areas. This situation has resulted in a treatment gap of approximately 80-90% in some rural regions in low-resource countries[282]. The lack of a sufficient number of psychiatrists and mental health workers, together with some socio-cultural factors addressed below [283-285], has further increased this pharmacological gap for schizophrenia in many parts of middle/low-resource settings.

A second issue is to better clarify the side effects of antipsychotics in these populations. There is very limited evidence on the use of antipsychotic treatment for schizophrenia in some low-resource populations. Knowledge on antipsychotic usage mostly focuses on European countries, the US and China, and cannot be readily generalized to sub-Saharan African populations, given the significant differences in racial and ethnic make-up[286].

A systematic review identified only three reports in African countries other than South Africa addressing the impact of antipsychotics on people with schizophrenia[287]. However, qualitative research from Ethiopia suggests that medication side effects (particularly relating to first-generation antipsychotics) are a barrier to treatment adherence, as well as having an impact on functioning and livelihoods[128]. All phase 2 and 3 trials in the US currently include substantial subsamples of African American participants, who share similar genetic endophenotypes. However, regional genetic, lifestyle, nutritional and environmental factors may limit the direct applicability of data to sub-Saharan populations.

A third critical issue is to reduce the problem of polypharmacy (i.e., the concurrent prescription of more than one antipsychotic). In low-resource settings (e.g., some African countries), the frequency of antipsychotic polypharmacy in schizophrenia reaches 40.6% [288]. In middle-resource settings (e.g., India), it similarly reaches nearly 44%[287]. Depot and oral first-generation antipsychotics are the most commonly prescribed polypharmacy combinations in Africa[288].

Such high frequencies of antipsychotic polypharmacy are of concern, since the benefits of this treatment strategy are not supported by meta-analytic evidence[224]. On the contrary, as noted above, antipsychotic polypharmacy is associated with worse clinical outcomes, as well as with more adverse events[225]. In low-resource settings, it is also associated with higher treatment cost, longer hospitalizations, and increased alcohol use[288] compared with antipsychotic monotherapy[278,287,289].

It is also important to monitor other psychotropic medications that are frequently co-prescribed with antipsychotics. Mood stabilizers and anticholinergics are the most commonly prescribed co-medications with antipsychotics in South Africa[288], indicating high-dose antipsychotic approaches and a resultant high prevalence of extrapyramidal symptoms, that is associated with future risk of tardive dyskinesia[290] and cognitive impairment[235]. Given these findings, there is a pressing need to promote the use of minimum effective doses of antipsychotics and avoid antipsychotic polypharmacy at high dosages[180]. Adhering to our recommendations formulated for high-resource settings becomes even more essential when resource constraints apply[44].

A further recommendation is to implement and scale up the use of LAIs in medium/low-resource settings, as they have shown substantial benefits in people with schizophrenia across all stages [202]. A study conducted across 15 Asian countries found that only about 17% of antipsychotic prescriptions included LAIs[291]. Recent evidence demonstrates that it is possible to combine LAIs with a customized adherence enhancement intervention to advance the care of people with early-stage psychosis in low-resource settings (e.g., Tanzania[292] and Nigeria[180]).

A final recommendation is to expand and support the early recognition of treatment resistance in schizophrenia[293]. This early recognition, which is already insufficient in high-resource settings, is even more neglected in middle/low-resource countries[294]. Clozapine, the only approved medication for treatment-resistant schizophrenia, is hardly ever prescribed in low-resource settings[295] and infrequently prescribed in middle-resource settings (although this is also related to its reduced availability).

PSYCHOLOGICAL INTERVENTIONS

High-resource settings

Clinical high-risk for psychosis

Psychological therapies are recommended as first-line interventions in people with CHR-P. These include cognitive behavioral therapy (CBT) and integrated psychological interventions (combining elements such as personalized CBT, social skills training, and sometimes cognitive remediation or family psychoeducation) [296,297]. These approaches aim to reduce symptoms, improve social skills, recognize dysfunctional thoughts, and lower levels of anxiety and depression, often associated with distress experienced in the CHR-P phase[298].

Earlier meta-analytic evidence suggested that psychological interventions, such as CBT, halve the likelihood of transitioning from a CHR-P stage to a first episode of psychosis (RR=0.54 at 12 months) [299]. However, an updated network meta-analysis showed no evidence of significantly superior efficacy of any one intervention over the others at 6 and 12 months[300]. A subsequent independent pairwise meta-analysis by the Cochrane group confirmed that available interventions did not show any clear differences in effect for preventing transition to psychosis[301]. However, these meta-analyses report large confidence intervals and, therefore, high uncertainty. For example, the needs-based interventions typically used as con-

trol conditions in CHR-P clinics are expected to be quite effective in themselves and may dilute the comparative efficacy of experimental interventions.

This lack of demonstrable preventive advantages for specific interventions could also be a consequence of one-size-fits-all approaches in treating individuals at CHR-P, who are intrinsically heterogeneous. Significant effects for specific subgroups may not have been detected, and CBT may be particularly effective for some subgroups. Further interventions are under development.

First-episode psychosis and relapsing/non-remitting psychosis

The psychological intervention with the most consistent evidence base for schizophrenia in high-resource settings is cognitive behavioral therapy for psychosis (CBTp). This therapy helps individuals identify and challenge distorted beliefs about their psychotic experiences. It also reduces distress associated with symptoms, improves coping strategies[41,302], and may have an impact on both positive and negative symptoms[303], particularly if the latter are associated with antipsychotic treatment.

Another approach recommended in high-resource settings is cognitive remediation therapy. This therapy uses structured exercises to enhance cognitive skills, targeting cognitive deficits – such as poor memory, attention, and executive functioning – which are common in schizophrenia. It can significantly improve global cognition and functioning. Benefits are more pronounced with longer treatment durations and integration into psychiatric rehabilitation programs, such as vocational or educational programs[304,305].

International efforts to implement cognitive remediation therapy in diverse health care systems reveal challenges concerning training and cost-effectiveness. Effective strategies include high-level governmental support and integration with rehabilitation services[306].

Middle/low-resource settings

In many middle/low-income settings, access to psychological interventions for schizophrenia remains very limited, due to a lack of trained mental health professionals and a scarce awareness about non-pharmacological treatments.

Psychological interventions should be developed or adapted to fit the cultural and social context. They should be accessible to all individuals who may benefit, irrespective of their beliefs or explanatory models. Culturally congruent societal or systems-level interventions addressing stigma (see below) may also promote access to these therapies[307,308].

Task-sharing models can address both the lack of specialist mental health workers and culturally sensitive barriers, and optimize the delivery of psychological interventions for psychosis. These models can leverage lay health workers, peer support workers and nursing staff who undergo ad-hoc training to implement culturally adapted refinements of psychological interventions[309,310].

In countries such as India, Nepal and Pakistan, task-sharing and culturally sensitive psychological interventions delivered by community health workers have been found to be both feasible and effective for schizophrenia[311]. For example, an RCT conducted in Pakistan evaluated brief culturally adapted CBT for psychosis combined with treatment as usual compared with the latter treatment alone[312]. Adaptations utilized culturally appropriate idioms to explain concepts related to symptoms and causes[312], such as referring to religious teachings, speaking in the native language, and involving carers and family. The acceptability and effectiveness of the intervention was documented[312].

A core potential in this area relates to digital interventions. One example is the Schizophrenia Research Foundation (SCARF) Tele-Psychiatry Program (STEP) in India[313]. This offers affordable and accessible options for online psychotherapy and general mental health care through mobile apps, improving access to rural and underserved areas.

These initiatives can be extremely useful in addressing the treatment gaps discussed above, while combating stigma by providing discreet support. Digital platforms can not only deliver culturally sensitive CBT, addressing the unique challenges of the large population[314], but at the same time help individuals maintain medication adherence and offer psychoeducation. Digital care options also offer flexible and cost-effective support for caregivers[315].

There is very limited evidence on the effectiveness of psychological interventions for schizophrenia in low-resource settings[48]. An earlier meta-analysis on psychological treatments for psychosis identified around 40 studies across the globe, including only two studies from low-resource settings[316]. An updated meta-analysis confirmed a lack of available data from those settings[317].

However, a recent study has demonstrated that it is possible to implement cognitive remediation therapy in Togo and Benin as part of a broader psychological intervention for schizophrenia. Cognitive performance and real-world functioning improved in patients receiving that therapy compared to treatment as usual[318]. This initiative highlights the potential for integrating various psychological interventions to enhance treatment outcomes in low-resource settings, although standardized protocols, cultural adaptations, and consistent outcome measures are needed to improve the reliability of future studies[319].

PSYCHOSOCIAL INTERVENTIONS

High-resource settings

Psychosocial interventions should play a crucial role in the comprehensive care of people with schizophrenia in high-resource settings, complementing pharmacological treatment and targeting functional recovery.

Clinical high-risk for psychosis

Psychoeducation for individuals with CHR-P and their care-

givers can improve long-term outcomes and possibly help to prevent transition to full-blown psychosis[320]. However, despite routinely being recommended as a critical component of treatment for individuals with CHR-P, the methods by which psychoeducation is delivered in the real world are heterogeneous and should be a focus for future research aiming at their operationalization[321].

Multidisciplinary support for individuals with CHR-P should include case managers who can provide psychosocial and vocational interventions to address functional decline[85]. These interventions should include support in re-engaging with education, facilitating stable housing, and securing employment or other financial support.

First-episode psychosis and relapsing/non-remitting psychosis

Psychoeducational interventions for people with established schizophrenia are designed to enhance patients' and caregivers' understanding of the condition, thereby improving their ability to manage the illness. Psychoeducation enhances medication adherence, reduces relapse rates, and reduces the length of hospital admission[322]. Family therapy, which usually emphasizes psychoeducation and structured support, provides another platform to educate relatives about the symptoms of mental illness, and improves communication within family networks, reducing relapse rates[323].

Supported employment and education, and stable housing are cornerstones of recovery-oriented care for individuals with psychotic disorders in high-resource settings (see Henderson et al[324] in this journal for further details). Employment programmes such as Individual Placement and Support (IPS) are highly effective in helping individuals achieve competitive, sustained employment [325]. IPS focuses on rapid job placement based on patient preferences, on-the-job training, and continuous support from employment specialists. Unlike traditional vocational rehabilitation, IPS does not require individuals to meet specific prerequisites, such as being symptom-free, which increases accessibility.

Supported housing models prioritize independent living and offer, depending on the individual's needs, case management, health care access, and psychosocial support. These models may include permanent supportive housing or transitional housing programs. Supported housing reduces emergency service use while improving quality of life and adherence to treatment in people with schizophrenia[326].

Educational support can also help individuals with schizophrenia resume or complete formal education, which may be disrupted by the illness. People with schizophrenia who complete education have better functional outcomes and social integration, and lower rates of relapse[327].

Middle/low-resource settings

We acknowledge that there is insufficient evidence for psychosocial interventions in middle/low-resource settings to stratify our recommendations across clinical stages.

Overall, it is recommended to implement multicomponent recovery-oriented psychosocial interventions, which are increasingly recognized in these settings as crucial for addressing the complex needs of individuals with severe mental illness, promoting recovery and aiding reintegration into society[328,329]. However, resource-limited health systems barely provide other essential aspects of mental health care for psychosis outside of the psychopharmacological approach[273,330].

Multicomponent psychosocial interventions include psychoeducation, supported employment/education, and supported housing programs[38]. These interventions integrate care and livelihoods to better address the broader social determinants of health in middle/low-resource settings. However, they are typically delivered by non-governmental organizations, and their population-level coverage is low.

In middle/low-resource settings, psychosocial interventions should be based on task-sharing models. These offer an effective framework for delivering community-based support through non-specialist providers following practical training and with specialist supervision[128,331]. Psychosocial task-sharing models of care for middle/low-resource settings have been increasingly validated over the past few years[309,310]. For example, culturally relevant and simplified family psychoeducation can be delivered through community health workers and lay counsellors[131]. Existing family psychoeducation and counselling manuals for psychoses developed in other settings can be adapted to local contexts or newly developed through participatory methods, ensuring that they are culturally relevant to the communities they serve[131].

A study conducted in Nigeria showed that caregivers of individuals with schizophrenia who received structured psychoeducation experienced a greater reduction in burden than those who received "care as usual"[332]. Psychoeducation is most effective when combined with psychosocial support, including support for employment/education and housing, thereby enhancing functional outcomes[333,334].

Another recent trial conducted in a rural district of Ethiopia evaluated a community-based rehabilitation intervention, delivered alongside primary care, for individuals with schizophrenia. The care package was implemented by lay workers over a 12-month period, comprising home visits (psychoeducation, adherence support, family intervention, support for returning to work and community life, and crisis management) and community mobilization. The intervention was effective in reducing disability among people with schizophrenia[335].

Interestingly, when early intervention services that offer state-of-the-art psychopharmacological treatment along with psychosocial support can be implemented in middle/low-resource settings and are accessible (e.g., India), they seem to be associated with better outcomes for schizophrenia[336], compared to high-resource settings (e.g., Canada), likely because of a higher involvement of families.

Supported employment, education and housing have been implemented more frequently in middle-resource countries, and are specifically recommended for those settings. These programs help individuals with schizophrenia obtain meaningful jobs, improve

socio-occupational functioning, and eventually improve outcomes[337]. For example, India's Supported Education Programme supports students with schizophrenia during their academic reintegration[338]. Assisted living enhances the quality of life by allowing individuals with schizophrenia to maintain autonomy, engage socially, and participate in daily activities, leading to a reduction in psychotic symptoms compared to hospital care[339].

These results are particularly interesting, as they open up new treatment perspectives. At the same time, we acknowledge that implementing supported employment/education in these settings may face substantial obstacles: vocational training initiatives in India are hindered by workplace stigma[340], while China's vocational programs face funding challenges[341].

MANAGEMENT OF SOMATIC CONDITIONS

High-resource settings

People with schizophrenia die 15-20 years earlier than members of the general population[7], and most of this excess mortality is due to physical health conditions, predominantly cardiometabolic disease[342-345]. The explanation for this increased physical comorbid burden is multifactorial: poor mainstreaming with the general health system, adverse lifestyle factors, poorer health care access, and side effects of antipsychotics all contribute[168,346,347]. Importantly, people with CHR-P and antipsychotic-naïve individuals experiencing a first episode of psychosis may already present with systemic alterations[348], including immune dysfunction and metabolic disturbance, which may increase cardiovascular disease risk[168, 349-351].

To target these problems, routine cardiometabolic monitoring and lifestyle advice (healthy diet, promotion of physical activity, and tobacco cessation) are essential, and should be provided to all patients, including people with CHR-P[40,352,353]. "Prophylactic" metformin may be offered when starting antipsychotics with a poor cardiometabolic profile (i.e., olanzapine or clozapine)[354], at an initial dose of 500 mg once daily and subsequent increments every two weeks up to 1 g twice daily with food, dependent on tolerability[355]. This approach has been shown to attenuate antipsychotic-induced weight gain in both first-episode psychosis and chronic schizophrenia[354].

Thresholds for treating antipsychotic-induced weight gain are provided in Table 3. Available treatment strategies include a switch to an antipsychotic with a more benign metabolic profile[356], adjunctive metformin treatment[357], or adjunctive treatment with a glucagon-like peptide-1 receptor agonist[358].

For raised cholesterol levels, lifestyle advice should be provided. In cases of significantly increased cardiovascular disease risk (e.g., QRISK3 score greater than 10%[359]), a statin should be offered[39]. Metformin should be considered for HbA1c levels between 5.7% and 6.5% and/or fasting glucose between 5.5 and 7 mmol/L. In the case of HbA1c ≥6.5%, random glucose ≥11 mmol/L, or fasting glucose ≥7 mmol/L, a diabetes specialist review should be arranged[39,360]. In the case of raised blood pressure, an antihypertensive should be offered, in line with guidance for the general population[39]. These interventions can be undertaken in conjunction with primary care services, but drug-drug interactions between medications prescribed for schizophrenia and for somatic comorbidities need to be considered[361,362].

Table 3 Thresholds for treating antipsychotic-induced weight gain

Interventions should be offered if any, or multiple, of the following three criteria are met:

- ≥5% weight gain within 3 months after medication initiation
- Body mass index ≥30 kg/m^2 for individuals of Caucasian background, or ≥27.5 kg/m^2 for those of Asian, Middle Eastern, Hispanic, Black African or African-Caribbean family backgrounds
- ≥1 component of the metabolic syndrome alongside body mass index ≥27 kg/m^2 for individuals of Caucasian heritage, or alongside ≥24.5 kg/m^2 for those of Asian, Middle Eastern, Hispanic, Black African or African-Caribbean family backgrounds

Use of antipsychotics may be associated with prolongation of the QTc interval and cardiac arrhythmia. The relative risk of QTc prolongation differs across antipsychotic agents, and is generally dose-related[100]. In cases of mild QTc prolongation (>440 ms for men, >470 ms for women; under <500 ms for both), clinicians should consider adjusting and switching potentially involved psychiatric medications where feasible. Other causes of QTc prolongation (e.g., electrolyte imbalance) should also be addressed. High-risk QTc prolongation (>500 ms) or demonstration of abnormal T-wave morphology should prompt an immediate discussion with cardiology staff, and the involved psychiatric agent should be stopped. If ongoing psychotropic treatment is necessary, an agent with lower QTc prolongation risk should be selected[100], preferably antipsychotics with meta-analytically documented lack of QTc elevation, such as lurasidone, aripiprazole, brexpiprazole, cariprazine, paliperidone and lumateperone[32,363].

Antipsychotics may be associated with a variety of neuromotor side effects, including akathisia, dystonia, parkinsonism, and tardive dyskinesia[364-367]. When extrapyramidal side effects emerge, medication adjustment, specifically dose reduction or switching agent, is recommended. For akathisia, propranolol is the adjunctive agent most routinely recommended, with doses up to 80 mg daily[99,100,368]. Low-dose mirtazapine (15 mg once daily) may also be effective[99,100]. Only beta-blockers (primarily propranolol) and 5-HT2A antagonists (primarily mirtazapine) have network meta-analytic evidence to support efficacy for akathisia[369,370], albeit with low confidence.

For tardive dyskinesia, in addition to medication rationalization, some guidelines recommend discontinuation of concurrent anticholinergics[99]. When switching, olanzapine, clozapine or partial dopamine agonists (e.g., aripiprazole) are recommended. First-line adjunctive treatment includes a reversible vesicular monoamine transporter 2 inhibitor[99,100], such as valbenazine or deutetrabenazine, and second-line treatment involves vitamin E, each supported by meta-analytic evidence[371,372].

Although hyperprolactinaemia may be observed in antipsychotic naïve people with first-episode psychosis[350], it is most com-

monly seen in association with antipsychotic treatment. Indeed, the incidence ranges for antipsychotic-induced hyperprolactinemia are 18-72% in men and 42-93% in women[373-376]. In the case of symptomatic hyperprolactinaemia (e.g., galactorrhoea, gynecomastia or amenorrhea in women; decreased libido, erectile dysfunction or anorgasmia in men), the possibility of switching to a partial dopamine agonist should be discussed[100]. Alternatively, adjunctive low-to-mid dose aripiprazole (5-15 mg once daily) can be considered[100,377]. Patients should be counselled on the risks of untreated asymptomatic hyperprolactinaemia, including reduced bone mineral density and, for women, a significantly increased association with breast cancer[378-380].

Middle/low-resource settings

We acknowledge that there are very limited data on the prevalence of somatic conditions in people with schizophrenia in middle/low-resource settings. Some studies indicate significantly higher multi-morbidity in people with psychosis from these settings compared to high-resource ones[17], as well as an association between underweight and schizophrenia, which may relate to excess mortality[381].

Overall, management of somatic conditions associated with schizophrenia is poor across most low-resource settings, and inadequate across middle-resource settings. Receiving treatments for somatic conditions typically requires multiple visits to non-mental health services, leading to treatment failures and suboptimal care for common conditions such as hypertension and diabetes mellitus.

Contrary to these existing practices, routine physical health assessments should be integrated into mental health care through feasible, low-cost screening measures to address comorbidities, such as cardiometabolic risks, as recommended for high-resource settings. Future task-shared models embedded within primary health care facilities could provide a practical framework for integrating mental and physical health care in middle/low-resource settings[134]. Introducing low-risk second-generation antipsychotics should also be facilitated, to reduce the incidence of cardiometabolic disease[39,168].

COMMUNITY CARE

High-resource settings

In most high-resource settings, the mid-20th century saw a shift towards reducing inpatient psychiatric care. This transition was driven by the development of effective antipsychotic treatments and the notion that the large asylums themselves exacerbated disability among individuals with schizophrenia. The process of deinstitutionalization aimed to integrate these individuals into society through community-based care. Initiatives by governments and mental health organizations led to the establishment of community mental health teams (CMHTs) to enhance access to outpatient care and support for individuals residing in the community[382].

The following decades made it apparent that, for many individuals with schizophrenia, independent community living was a significant challenge. In some contexts, community resources focused more on patients who were less severely ill than those with schizophrenia who needed more intensive services. Homelessness, substance use, social isolation, and criminalization of this population emerged in several contexts. While CMHTs tend to form the core of community services in many high-resource settings, several specialist community services have also been developed to address significant treatment gaps[383].

Clinical high-risk for psychosis

As discussed above, we recommend specialist community services for early detection and intervention in CHR-P individuals. These services have been operational in many contexts for over two decades, either as standalone units or integrated in broader youth mental health care[79].

These services focus on specialist assessment of CHR-P states and the provision of care that focuses on the presenting problems to delay or alter progression to a first episode of psychosis. As noted above, CHR-P services can also reduce the DUP by enabling earlier detection and intervention.

When individuals under CHR-P care develop a full-threshold psychotic disorder, they are typically transferred to an early intervention in psychosis (EIP) team for more intensive support, thus ensuring continuity of care. We recommend this model to be extended to as many contexts as possible in high-resource countries.

First-episode psychosis

In the 1990s, EIP programs emerged in Australia and the UK, with a view that more intensive intervention at illness onset could both reduce the DUP and improve recovery rates. The core components of EIP services include proactive engagement, comprehensive assessment, multidisciplinary care, and personalized recovery planning. These services typically operate on a three-year frame.

In high-resource settings, people with a first episode of schizophrenia should be primarily cared for in the community by these services. Key elements of EIP care include rapid access to treatment to reduce the DUP, low-dose antipsychotic treatment strategies, provision of psychological therapies including CBT and family therapy, vocational and educational support, physical health monitoring, and assistance with reducing substance use.

As noted above, meta-analyses have consistently demonstrated superiority of EIP care over treatment as usual in terms of several outcomes, including hospitalization, symptom severity and remission, and overall functioning[105].

Despite the effectiveness of EIP care, challenges remain, including variability in service provision, workforce constraints, and issues surrounding the transition out of EIP services once the structured care ends. Many individuals still require ongoing support,

yet post-EIP care options remain inconsistent, often resulting in disengagement and relapse. Strengthening the continuity of care beyond EIP services remains a key priority in optimizing long-term outcomes for individuals with schizophrenia.

Relapsing psychosis

A substantial proportion of individuals with schizophrenia disengage from community treatment due to cracks in the health care system, a high burden of negative symptoms, or a lack of illness insight. The first recommendation is to establish care continuity between inpatient treatment, day hospitals, and community care units to ensure proper follow-up and treatment.

These individuals could be supported by assertive community treatment (ACT)[384] outreach teams, which ensure a higher staff-to-patient ratio and employ experienced staff who provide intensive, individualized care, helping individuals manage symptoms, adhere to treatment, and access housing, employment, and social support. By working closely with patients and actively engaging those withdrawing from care, these teams aim to prevent hospitalization and the disengagement of patients with a high-risk profile.

Legal mechanisms are used in some high-resource settings to mandate community treatment, which is primarily designed for individuals with repeated non-adherence to treatment and subsequent high-risk behaviors. In the UK, Australia, Canada and New Zealand, these approaches are termed "community treatment orders". In the US, similar arrangements are provided by "assisted outpatient treatment" laws. The evidence for the effectiveness of these approaches is limited[385,386]. It has, however, been argued that, as with LAIs[387], randomized clinical trial evidence tends to underestimate benefits, as those most likely to benefit are often excluded from trials due to their limited capacity to consent.

When psychotic symptoms are particularly severe, more intensive community treatment may be indicated, delivered by home treatment and crisis resolution teams[388]. These teams aim to avert hospitalization of individuals during acute exacerbations of symptoms. They are highly recommended, as they deliver intensive, short-term interventions, including multiple daily visits for medication supervision and psychosocial support. Intensive home treatment significantly reduces inpatient readmission rates and total inpatient days for people living with schizophrenia[389-392]. This approach may enhance patient autonomy and improve social outcomes, ultimately leading to a better quality of life[392].

Non-remitting psychosis

For individuals with chronic psychosis and high levels of disability, specialist services such as rehabilitation teams and clozapine clinics have been developed. Rehabilitation teams focus on individuals with persistent functional impairments, providing long-term care in residential or supported living settings. These teams integrate vocational training, social skills interventions, and structured psychosocial support to promote independent living where possible.

Specialist clozapine services cater to individuals with treatment-resistant schizophrenia, ensuring optimized management of clozapine therapy. These services monitor side effects, support adherence, and manage associated complications such as neutropenia and metabolic syndrome.

Overall, while community-based care has significantly transformed the management of schizophrenia in the past decades, substantial challenges remain in ensuring that the most vulnerable individuals receive appropriate and sustained support. The evolution of specialized community services reflects ongoing efforts to address care gaps and improve outcomes for individuals across all stages of illness.

Middle/low-resource settings

It is recommended that community-based care for schizophrenia is also implemented in middle/low-resource settings[393].

In low-resource settings, the focus should mostly be on primary care. A trained workforce, including primary care clinicians, should be involved in the management of patients with schizophrenia. Education tailored to professionals and suitable for various levels of care should be readily available and integrated into routine practice[394].

Given the shortage of staff and infrastructure, efforts to scale up community care for schizophrenia should focus on task-sharing delivery by trained non-specialists. As family members are typically the main sources of support, they should be involved in care models to ensure acceptability and feasibility. Collaborative approaches to primary health care, also involving educated faith healers in some contexts, may improve outcomes for individuals with schizophrenia, as well as reduce harmful practices[395].

As previously noted, it is also recommended to involve service users and caregivers in designing and monitoring these task-sharing community services for schizophrenia, ensuring that care remains relevant and responsive to real-world needs[181]. It is increasingly recognized that services must be of high quality, alongside greater availability, to improve patient outcomes.

In middle-resource settings, additional layers of care can be added, such as community-based residential care, mental health teams that conduct outreach work, and basic psychosocial rehabilitation programs integrated with primary care[396]. In some middle-resource countries (e.g., India), community care has received an impetus from the national and district mental health programmes, which mandated the training of primary care physicians in mental health. Over the next few decades, several non-governmental organizations will implement evidence-based community care programs, especially in rural and remote areas[397]. These organizations have engaged diverse stakeholders, including community and religious leaders, local administrators, self-help and family groups, teachers and physicians.

Another example is China, which has included community-based follow-up services for patients with psychosis in national basic public health services. In many other middle-resource coun-

tries, the scope of community care for schizophrenia is expanding, including protection of human rights, mental health of youth and the elderly, and health promotion and education.

INPATIENT CARE

High-resource settings

Hospitalization remains necessary when an individual's symptoms are of such severity that treatment in the community is no longer feasible. Therefore, inpatient care is still a critical aspect of the mental health system for patients with schizophrenia in high-resource settings.

Most inpatient services do not distinguish between the stages of the disorder. Inpatient admission will rarely be appropriate for CHR-P individuals. There have been attempts to develop specialist inpatient units for individuals with first-episode psychosis, but these are uncommon, and individuals with early psychosis, relapses, or chronic illness are typically admitted to the same setting[398]. Youth inpatient units are generally lacking even in high-resource settings.

General adult wards should be used to stabilize and treat severe symptoms. Wards should focus on assessment, resolution of acute crises, medication adjustment, and the development of a strategy to enable successful discharge. Depending on the pressure on inpatient beds, these beds may primarily be reserved for those with severe psychotic symptoms and accompanying suicidality, aggression, or disorganized behavior[399].

Inpatient care should typically involve a multidisciplinary team. Nursing plays a central role in providing 24-hour supervision, administering medication, offering general support, and monitoring both physical and mental health. Psychiatrists oversee treatment planning, often lead ward rounds, and adjust pharmacological treatment. Social workers address community factors that may have contributed to admission and assist with discharge planning, whereas psychologists may provide assessment and brief psychotherapeutic interventions. Structured activities may also be available, including group therapies, occupational therapy, creative therapies, and more general recreation[399].

Psychiatric intensive care units are available in some countries, such as the UK, and provide even greater intensity of support compared to acute wards. They are intended for individuals with schizophrenia who present with particularly disorganized or aggressive behaviors. In these wards, the staff-to-patient ratio is usually greater, and experienced multidisciplinary teams include nurses trained in de-escalation techniques[399].

Middle/low-resource settings

Given the limited availability of community-based services, psychiatric hospitals remain a primary source of care for people with schizophrenia in middle/low-resource settings. Inpatient psychiatric units are generally scarce and centralized in capital cities and major towns. Outside these areas, mental health services are often unavailable, inaccessible, or too expensive for patients and their families. People with schizophrenia (e.g., in Ethiopia or Indonesia) may be restrained physically by family members as a strategy to manage (or hide) their illness in the absence of other support[400,401].

The general principles that we outlined for high-resource settings should apply also to middle/low-resource countries: hospitalization in psychiatric units should be reserved for acute cases, with systems developed for transition from inpatient to community-based care. Post-discharge follow-up should be implemented through task-shared outreach teams.

A core recommendation, strongly endorsed by the WHO World Mental Health Report[402], is to support deinstitutionalization and move away from custodial care towards care in the community. This process requires careful planning and preparation, as well as phased implementation that considers risks, given that deinstitutionalization is technically challenging and complex[402]. As highlighted in the WHO report, deinstitutionalization is not merely about discharging people from institutions, but requires transforming the lives and mindsets of all people involved, empowering individuals with lived experience and their families, and establishing a shared vision to humanize care, based on the rights-centred principles described above (e.g., autonomy and full citizenship)[402]. Operationally, deinstitutionalization involves simultaneously increasing discharges, reducing admissions, and scaling up care in the community in line with each resident's individual needs, to prevent neglect and homelessness, ensuring that resources follow patients into community support[402].

We also recommend improving the quality of care in existing psychiatric inpatient units in middle/low-resource settings. In fact, in most low-resource settings, descriptive data on the quality of care offered in inpatient psychiatric services are limited. For example, medical screening for patients admitted to psychiatric units in some low-resource settings (e.g., Malawi) appeared to be minimal or poorly documented[403]. In these settings, most patients had no record of a physical examination, vital signs, or standard laboratory screening tests, and few had documentation of co-occurring physical illnesses[403].

Additional concerns relate to the potential for human rights abuse in large mental hospitals. Overcrowding, inadequate staff, unhygienic conditions, insufficient supervision and monitoring, and poor follow-up of discharged patients are some of the drawbacks of such hospitals[404,405]. Consequently, in many middle-resource settings (e.g., India and China), many patients live with their families, while involuntary hospitalization represents a mainstream admission pathway[406]. It has also been repeatedly pointed out that, in many middle/low-resource settings, hospitalization is not always associated with clinical events related to the history of schizophrenia, but rather indexes social control attitudes[407].

These concerns are amplified by activists who have documented cases in which compulsory admission has led to abuses, ranging from the use of psychiatric methods to suppress political dissent to the sexual and physical abuse of individuals in the custody of mental health professionals.

Compulsory institutionalization has often been used to man-

age people with schizophrenia in the absence of rights-centred approaches[408]. Beyond the recommendations already provided, we support the WHO QualityRights initiative, which aims to address the above issues, improving human rights conditions in mental health facilities[409].

We think that the objective should be to implement brief admissions in inpatient psychiatric units placed in general hospitals, ensuring continuity with community-based care after discharge[410].

PEER SUPPORT, SELF-HELP, AND ALTERNATIVE HEALING METHODS

High-resource settings

Peer support, i.e. the provision of social and emotional support by individuals who have shared similar health conditions, has been promoted as a valuable tool for fostering recovery among people living with mental disorders, including schizophrenia[411], and is sometimes available in high-resource settings. It employs a strength-based approach, focusing on recovery and resilience rather than pathology, and aims to inspire individuals to take an active role in their recovery process[412]. A recent meta-analysis examining the impact of peer support on individuals with schizophrenia found that it was associated with some benefits in terms of clinical, functional and personal recovery[413].

While peer support approaches tend not to be explicitly stratified by illness stage, there are situations in which they should be particularly taken into consideration, as individuals are likely to be able to relate more easily to people who have shared similar experiences (e.g., CHR-P states). Broader youth mental health services are particularly suited to facilitate peer work and support[86].

Self-help has tended to be less emphasized in schizophrenia compared to mood disorders. A range of interventions, often taking advantage of digital devices, have been developed. They typically involve guided use of psychological techniques to address ongoing difficulties. Recent meta-analyses have suggested benefits across symptom domains, although most trials have methodological shortcomings[414,415].

Alternative healing treatments are increasingly being explored as adjunctive approaches to managing schizophrenia in high-resource settings, particularly for patients who do not respond adequately to conventional antipsychotic medications. For example, mindfulness-based interventions have shown promise in improving psychosocial function, insight[416], and cognition[417]. However, the heterogeneity of mindfulness-based protocols, and some methodological limitations in the studies require cautious interpretation of the results before these approaches can be recommended.

Middle/low-resource settings

Peer support and self-help should be integrated into psychosocial interventions in middle/low-resource settings, based on growing evidence of their acceptability, feasibility and effectiveness[61,418,419]. The World Bank Disease Control Priorities (DCP-3) specifically recommend peer support and self-help to address drawbacks in the implementation of interventions for psychosis in these settings[420], although local cultural adaptations are needed[421].

Traditional healers and faith-based entities often play a significant role in dealing with people with schizophrenia in middle- and especially low-resource settings[422]. In some middle-resource settings (e.g., India), 30-54% of individuals with psychosis first consult spiritual leaders and Ayurvedic practitioners[423-425]. In China, traditional medicine, including acupuncture and herbal remedies, is typically employed in the care of psychosis[426]. Other settings, such as Indonesia, integrate spiritual and herbal therapies with rituals. In Brazil, psychoactive plants and shamanistic traditions are used to address the needs of patients with psychosis. In sub-Saharan Africa, people are more likely to endorse spiritual or magico-religious etiologies of their psychotic symptoms, and seek alternative care options that are consistent with their belief systems[427].

It has been suggested that combining traditional healing practices with mainstream mental health care may improve community engagement and reduce stigma[428,429]. However, the primary concern is the need to ensure the safety of traditional healing[430]. For example, some traditional and faith healers may believe that psychotic disorders are expressions of spiritual possessions, curses, or moral failings, and use approaches that may be harmful, such as shackling, chaining, fasting and beating[431]. Moreover, seeking help from these traditional healers may contribute to a longer DUP[432], which is a significant predictor of poor outcome[433].

Efforts such as the WHO Global Centre for Traditional Medicine in India reflect a global commitment to integrating traditional approaches into modern health systems for the benefit of patients with schizophrenia. Similar initiatives have been reported in Burkina Faso, Ghana, Kenya, Nigeria, Malawi, South Africa and Zimbabwe, with a positive involvement of traditional models of care such as the controlled use of herbal medications, rituals, and prayers[422,431].

We recommend extending ongoing efforts to develop culturally sensitive and contextually appropriate mental health interventions that bridge traditional healing and local health systems[61,434]. For example, the implementation of a psychiatric service near a religious healing site seems to be a practical and acceptable manner to make psychiatric mental health care more accessible to patients with psychotic disorders[431].

A pragmatic challenge to collaborations between mental health services and traditional healers is overcoming the mutual sense of distrust and superiority over the other provider group, as well as the incompatibility of belief systems[435]. However, a recent trial conducted in sub-Saharan African countries (i.e., Ghana and Nigeria) tested the safety and effectiveness of an intervention which included manualized collaborative care delivered by trained traditional healers and primary health care providers[395]. The study found that this collaboration led to improved outcomes and greater reductions in overall care costs in patients with psychotic disorders[395]. The study also demonstrated that healers can be trained and monitored to substantially reduce the use of harmful practices.

This model offers an unprecedented prospect of scaling up care to this vulnerable population in settings with very limited health care resources[395].

POPULATION-LEVEL PREVENTION

There are no published randomized controlled trials demonstrating the effectiveness of a population-level preventive intervention for schizophrenia[436]. This situation is likely due to the relatively low prevalence of the disorder in the general population[437], and the long latency between the time of exposure to many risk factors and the onset of the disorder[438]. This means that any proposed trial investigating a population-level preventive intervention requires large sample sizes and a long duration of follow-up, thereby inflating the complexity and cost.

Therefore, for our recommendations, we focus on modifiable risk factors with robust evidence for their association with psychosis, and then illustrate how these risk factors can be addressed at a population level, acknowledging uncertainty surrounding the effectiveness of interventions.

Neurodevelopment and neuroinflammation

People with schizophrenia are more likely to present with neurodevelopmental risk factors, which can be displayed as impaired olfactory identification ability, minor physical abnormalities, low premorbid intelligence and/or non-right-handedness[22]. The etiology of these neurodevelopmental abnormalities can, at least partially, be attributed to obstetric complications[439]. Being born in winter and spring is also more common in people with schizophrenia[440], likely due to increased likelihood of perinatal infections. These infections can lead to changes in the fetal or newborn environment, which in turn can influence the course of brain development[441], introducing vulnerability[442,443].

Accordingly, population-level prevention of neurodevelopmental abnormalities relies on addressing obstetric complications and perinatal infections. This can be achieved by improving the provision of perinatal care, increasing access to family planning services, increasing access to maternal vaccination, and improving infection control.

Improving the provision of perinatal care is a layered and complex process. For example, increasing access to prenatal checkups is essential, but is reliant on both availability of services and maternity leave policies that enable pregnant women to attend them. Combining early and frequent prenatal checkups with screening for high-risk pregnancies (e.g., women with hypertension, diabetes mellitus, vitamin D deficiency, or anaemia) can improve prevention of obstetric complications and thereby reduce psychosis risk[440]. This approach can be further supported by ensuring the skilled training of obstetric clinical staff in safe delivery practices, ideally in line with an internationally agreed-upon core package of care[444].

Lifestyle interventions that promote frequent exercise and healthy nutrition can also be used at a population level to reduce the incidence of hypertension, diabetes mellitus, vitamin D deficiency, and anaemia[445-447]. If identified, symptomatic management of hypertension with labetalol[448], of gestational diabetes mellitus with insulin or metformin[449], of vitamin D deficiency with increased sun exposure and vitamin D supplementation, and of anaemia with iron supplementation, is recommended.

The prevalence of hypertension during pregnancy is substantially higher in Africa and South-East Asia (respectively, 334.9 and 136.8 per 100,000 women of childbearing age)[450]. Gestational diabetes mellitus is more common in South East Asia (25.9%) and Northern America and the Caribbean (20.7%)[450]. Vitamin D deficiency in pregnant women is more frequent in South-East Asia (87%) and Western Pacific (83%)[451]. The prevalence of anaemia is higher in South Asia and Western sub-Saharan Africa (respectively, 41,646 and 40,977 per 100,000 women)[452]. Countries with higher prevalence of these risk factors should consider greater investment in relevant policies and tailored interventions.

Shorter inter-pregnancy intervals can increase the risk of certain obstetric complications, such as preterm birth and low birthweight, which in turn can increase the risk of neurodevelopmental abnormalities and perinatal infection. These factors, and the consequent psychosis risk, can be addressed by increasing access to family planning services and contraceptives. This is an unmet need in low- and middle-resource countries[453], particularly in sub-Saharan Africa.

Expanding access to maternal vaccination is crucial to reduce the risk of perinatal infections and the associated neuroinflammation, which can lead to neurodevelopmental complications. Maternal influenza and tetanus, diphtheria and pertussis vaccines are effective and safe, and are recommended during pregnancy[454,455].

In certain settings, additional infectious exposures can pose a perinatal risk due to their associated neuroinflammatory processes. For example, it is imperative to reduce potential exposure to mosquito-borne diseases, in particular malaria, through vector control strategies, such as insecticide-treated nets.

Psychosocial stress

Stressors experienced during early life can increase risk for psychosis[439]. These can include parenting risk factors (e.g., childhood trauma), inequality (e.g., low socioeconomic status), and experiencing discrimination (e.g., regarding ethnicity and/or immigrant status)[22].

Interventions to identify and reduce childhood trauma, inequality and discrimination are crucial to reduce their downstream effects on the incidence of psychosis. While societal-level support is addressed in the next section, we address here the core population-level approaches.

Parenting interventions

Childhood trauma is a risk factor not only for psychosis but also for other non-psychotic mental disorders, as well as for physi-

cal diseases, with one of the strongest "transdiagnostic" evidence bases[21,27]. Universal prevention programmes targeting parents are effective at improving parenting skills and reducing childhood trauma across low-, middle- and high-resource countries[456]. These interventions appear to be most effective when targeting parents of children at an early age[457]. They also reduce behavioral problems in children[456], which are linked to an increased risk of experiencing psychotic-like experiences[458], that can later lead to the onset of psychosis.

Reducing inequality

Economic inequality is significantly associated with psychosocial stress, stressful life events[459,460] and, therefore, the incidence of psychosis[461]. It is shown to affect mental health across the entire population, not just those who are most disadvantaged[460], providing scope for population-level effects if addressed.

Policies should be implemented that invest in interventions to improve socioeconomic equity, which can potentially reduce the incidence of psychotic disorders at the population level[459,462]. Guaranteed income programmes have been shown to improve mental health[463] and reduce mental health-related hospitalizations[464]. These programmes demonstrate more substantial mental health benefits in middle/low-resource settings[464], and in low-income populations within high-resource settings[465]. Interventions of this type need to be performed at scale, otherwise their impact will be limited. Some studies, such as Moving to Opportunity, have shown mental health and social benefits of moving families from underprivileged neighborhoods to higher-income ones[466].

Improving the physical quality of neighborhoods by planting trees, reducing litter, and landscaping vacant land can also have mental health benefits[467], with increased exposure to green space specifically reducing psychosis risk[468].

Interventions need to be community-driven, with continued engagement from local residents, to succeed[469]. In addition, they must be supported by multiple funding streams that reflect a common goal and a commitment to achieving long-term success and sustainability. Multifaceted approaches, aligning multiple sectors, are essential to promote equity[470].

While there is evidence for the effectiveness of these interventions for mental health generally, research on their effectiveness for preventing psychosis is limited. However, these interventions should theoretically be effective by reducing chronic psychosocial stress, which is an established risk factor for psychosis[439,468,471].

Reducing discrimination

Experiencing discrimination can enhance levels of psychosocial stress, leading to an increase in psychosis risk. This means that individuals from marginalized groups (e.g., people from ethnic minority backgrounds, migrants, the homeless, and sexual minorities) are at higher risk for psychosis, both in high- and middle/low-resources settings.

Therefore, reducing discrimination against ethnic minorities, migrants and other marginalized groups is essential for population-level prevention. Specific interventions that are recommended to address discrimination are discussed in the next section.

Cannabis use

Frequent use of high-potency cannabis – i.e., with high Δ9-tetrahydrocannabinol (THC) concentrations – increases psychosis risk[472], particularly during childhood and adolescence[473-475]. Eradicating cannabis use could prevent 10-12% of new psychosis cases worldwide[21,476]. This varies between countries, with more scope for prevention seen in specific high-resource settings (e.g., the US, Canada), as well as some middle/low-resource settings (e.g., Nigeria, Zambia[21]), because of either high prevalence or high THC concentrations in these settings.

We recommend integrating school-based interventions to educate adolescents about cannabis and the potential harms associated with its use[477,478]. These interventions can be delivered online, increasing scalability and reducing associated costs.

At a societal level, cannabis policy can be a significant driver of cannabis use within a population. Adopting a public health-oriented approach to legalization is essential to mitigate against potential harms. An example of this is seen in Canada, which has banned cannabis advertising, mandated plain packaging, and enforced taxation based on THC potency[479].

In legal markets, we also recommend implementing the standard cannabis unit to inform cannabis users[480]. Similar to the standard alcohol unit, this can be used on packaging to provide individuals with guidance on the potency of cannabis products and accordingly tailor their use. The standard cannabis unit is 5 mg THC, a meaningful dose for frequent cannabis users, but low enough to minimize harms associated with a single dose, particularly in cannabis-naïve users who are most at risk[481].

SOCIETAL-LEVEL SUPPORT

High-resource settings

Improving mental health literacy and addressing stigma

Globally, individuals with schizophrenia face a high level of discrimination, in part related to the stigma associated with the disorder[59], which can extend into self-stigma[482].

At the population level, campaigns aimed to reduce stigma and discrimination against people with schizophrenia have been conducted, and their impact has been evaluated. A good example is the Open the Doors programme launched by the World Psychiatric Association, which was implemented in 20 countries encompassing Europe, North and South America, Africa and Asia[483]. Another example is the Time To Change programme in the UK[484], targeting both common and severe mental illness. Both programmes aimed to improve mental health literacy and challenge people's discrimi-

natory beliefs. Notably, a positive outcome of both programmes was a reduction of people's desire for social distance from individuals with schizophrenia[483,484].

Educational anti-discrimination initiatives in schools, possibly including a component of direct contact with people with lived experience of severe mental illness, could be promoted in high-resource settings. Programmes targeting media professionals should also be considered, since available research evidence suggests that, while media guidelines concerning coverage of suicide have been successful to some extent[485,486], prejudice against people with schizophrenia seems to persist[59,324,487]. Colleagues of other medical disciplines represent another important target, since it is well documented that their discriminatory attitudes against people with schizophrenia contribute to the decreased access of these people to screening procedures and health care[28,29]. Discriminatory attitudes and behaviors within the mental health professions should also be identified and proactively addressed[488]. At a societal level, stigma against individuals with schizophrenia can also be addressed by modifying laws whose content promotes discrimination of these people (e.g., concerning access to the right to vote)[324].

Improving access to mental health care

Even in high-resource settings, accessing mental health care poses significant challenges for socially disadvantaged groups, primarily due to systemic barriers and social stigmatization. These groups, including ethnic minorities, people stigmatized due to their sexual orientation, and those living in poverty, often face unique obstacles that exacerbate mental health disparities. These disparities often mean that minority groups may find it harder to access specialist CHR-P or EIP services, and are more likely to enter the mental health system via compulsory detention[489,490].

Ethnic minority groups are also less likely to receive evidence-based treatments for schizophrenia[3]. Furthermore, in some countries, such as the US, a lack of insurance coverage also contributes to the treatment gap, preventing many people from seeking or receiving adequate care for schizophrenia[491]. On the other hand, racial prejudice and difficulties in communication may lead to an incorrect diagnosis of schizophrenia in some ethnic groups[492,493].

Promoting cultural competence and combating prejudice among mental health professionals, along with implementation of measures reducing health inequalities at the systemic and organizational level, should be prioritized in high-resource settings.

The funding of mental health services, even in high-resource settings, is often inadequate. Underfunded systems cannot provide the necessary interventions to deliver robust care, resulting in suboptimal patient outcomes.

Reducing coercion in mental health services

Reducing coercion in mental health services involves three layers. The first is to pay systematic attention to all relevant rights and incorporate them into national laws, policies and programmes [324,408], aligning mental health legislation more closely with the UN Convention on the Rights of Persons with Disabilities[57]. The second is engaging experts by experience both in individual treatment choices and in policy-making[408]. The third is to expand community-based care and support, which are explicitly intended to avoid the need for hospital admission[408]. The examples of home treatment and crisis resolution teams are established templates that have been found to effectively reduce the rate of coercion for individuals developing a first episode of schizophrenia[388,389].

A further effective approach, supported by meta-analytic evidence, involves the making of *advance statements*, a written statement setting out how individuals would wish to be treated, or not to be treated, should their ability to make decisions become significantly impaired as a result of their mental disorder[408,494] (see Swartz and Swanson[495] in this journal for further details).

Middle/low-resource settings

Improving mental health literacy

We recommend addressing the limited mental health education and poor awareness which represent a barrier to care for many patients affected with schizophrenia in middle/low-resource settings[496]. Specifically, a lack of insight into the disorder hampers engagement with available treatment services. Beliefs about psychosis being a form of divine or spiritual punishment are still prevalent in some African communities, with schizophrenia being often conceived as the consequence of wicked acts committed by the individual sufferer or his/her relatives[116]. These beliefs may lead to a severely prolonged DUP and should be addressed[497].

For example, in a middle-resource country such as Mexico, relatives of mental health patients gathered and created an association called "Voice for Mental Health"[498,499]. Some of them travelled to the US and received psychoeducation about mental illness from their National Alliance for Mental Illness (NAMI) counterparts. They developed a "From Family to Family" community program for other relatives of the association to learn about psychosis and how to solve problems with their ill relatives.

A dynamic interaction exists between the individuals recognizing symptoms as those of psychosis, accepting the need for treatment, and seeking the support of caregivers to access or pay for care[497]. Acknowledging this interplay, while promoting the integration of mainstream and traditional/religious care in parallel, is likely to increase acceptability and engagement. It is also important to note that, beyond the role of personal beliefs, individuals with psychosis in middle/low-resource settings are primarily interested in finding (or desperate for) effective support, and the major obstacles are represented by stigma, lack of care provision, unreliable medication supplies, and poverty[500,501].

Addressing stigma

We recommend addressing stigma, which represents a substan-

tial barrier to care in medium/low-resource settings. Name-calling, ridicule and chastisement are the types of things that people with schizophrenia frequently encounter in these settings[496]. Stigma devalues and disfavours people with mental health conditions and often prevents them from accessing treatment, and also leads to social exclusion and reduced ability to meet role expectations such as marriage and employment[502].

People may fear that family and friends will avoid them or treat them differently, or that disclosing a psychotic condition will lead to adverse perceptions and behaviors at work[496]. Self-stigma[482] is also common among people with psychosis in middle/low-resource settings, and is mediated by the attitudes of caregivers[497,503]. Notably, stigma may be high even among individuals with schizophrenia who are already receiving care in mental health services [504, 505].

Mental health professionals working in middle/low-resource settings need to be aware that stigma may impede treatment engagement. Overcoming this issue should be a priority, leveraging a framework that includes a multistep approach. Initially, awareness about schizophrenia should be raised[22], particularly among youth predisposed to increased challenges and whose attitudes are more pliable, by dispelling misconceptions and demystifying psychosis. Subsequently, social contact in the population should be promoted by delivering testimonies from individuals who have lived the experience[5]. Involving people with lived experience of psychosis in the training of primary care workers is a promising approach for reducing stigma that is acceptable and feasible[506].

Expanding advocacy groups to include community leaders, priests, and traditional healers should help challenge misconceptions and promote mental health literacy. These individuals, who hold influential roles within their communities, can help address systemic barriers, reduce stigma, and bridge the gap between traditional healing methods and mainstream care for psychosis[395]. Finally, active community engagement supports continuity of care and is especially critical in rural areas[134], where interest must be garnered in identifying needs and providing care support[50,116,507].

Deploying adequate mental health funding

Despite the increasing recognition of mental health as a critical component of public health, the allocation of government funding for mental health services in middle/low-resource settings remains largely insufficient[508]. On average, African governments allocate less than $0.50 per capita to mental health care, which is well below the recommended $2 per capita for low-resource countries[496]. Furthermore, data recorded in health management systems of these settings do not typically include records of schizophrenia, which contributes to an underappreciation of the disease burden. An additional problem is that the majority of mental health budgets for the care of schizophrenia are often spent on psychiatric hospitals, with limited tracking and allocation of funds to community-based mental health services.

Financing schizophrenia care in middle/low-income countries should involve different and complementary strategies. These countries could consider tax expansions for investment in health, targeting the sugar-sweetened beverage industry, plastic shopping bags, the gambling and betting industry, and the tobacco and alcohol industries[50]. Concurrently, by leveraging "policy windows" that align mental health initiatives with broader health policy opportunities (e.g., early intervention initiatives), the sustainable integration of psychosis care into national health systems[131] can be pursued. It is also essential to mobilize new financing from the private sector at affordable terms, such as public-private partnerships or venture capital[50]. The evaluation and establishment of long-term financial grants should be considered to support individuals with schizophrenia[181]. Organizations of experts with lived experience should be integrated into this new care planning[509].

Furthermore, a policy framework should be implemented to track mental health, allocating investments for countries to monitor and evaluate progress toward the established benchmarks. For example, the WHO Assessment Instrument for Mental Health Systems (AIMS) indicators can be adapted to review national mental health funding[510].

An ongoing discussion with policy makers should inform these initiatives, to convey the crucial evidence that every $1 invested in targeting schizophrenia is estimated to return $4 in improved health and productivity in low-resource settings[511].

Improving access to mental health care

In resource-limited settings, organizing care pathways and improving access to care are particularly critical. Implementing a clear and structured map from community to primary to tertiary care, supported by regional emergency units within general hospitals, would enhance system efficiency and optimize the use of resources. The utilization of available community and health resources should be emphasized rather than creating new structures. Non-health-related pathways to care in specific groups should also be considered, particularly in more isolated communities, such as traditional healers or religious services[512].

An associated core problem is the lack of qualified staff to take care of patients affected by schizophrenia. While the WHO recommends a ratio of psychiatrists to the population of 1:10,000, many low-income countries are far from approaching this standard. For instance, in Uganda, there are only 53 psychiatrists countrywide, translating to 0.12/100,000[513]. The long-standing shortage of well-trained mental health professionals has been, over the past years, further compounded by the massive brain drain that plagues these settings. Training more psychiatrists requires integrating psychiatric care with primary care, increasing clinical capacity with digital patient management systems, and shifting some responsibilities to allied health care workers, such as community health care workers, as discussed above[181].

In this context, we recommend fostering new innovative educational strategies that empower low-resource institutions to develop best training practices. This goal may be supported through international calls currently released by some mental health funders (e.g., Wellcome Trust). Another example is the African Mental

Health Research Initiative, which aims to build research capacity and develop evidence-based training curricula for mental health professionals, including those dealing with psychosis in sub-Saharan Africa[514].

A recent clinical research initiative is the development of the Kenya Psychosis-Risk Outcomes Study, a 5-year project in Kenya funded by the US National Institutes of Health, designed to harmonize with the Accelerating Medicines Partnership Schizophrenia (AMP SCZ)[515]. The study will recruit over 100 CHR-P and 50 healthy participants and conduct multiple clinical and biomarker assessments over 2 years. Capacity building and training of health care professionals on preventive practices is a key component of the study[515].

Other barriers that should be overcome to improve access to care in middle/low-income settings include broader systemic issues, such as psychotropic medication supply chains that are erratic. Addressing these issues would require central policy interventions to streamline medication procurement and distribution processes[130].

Buying prescribed medicines adds to the burden of costs for food and accommodation, which are an everyday struggle for people with schizophrenia and their families. For example, even in those middle/low-resource settings where mental health care is free at the point of delivery (e.g., Uganda), the costs of accessing such care can be prohibitive. A major financial contributor is lost productivity, as carers accompany patients to far-distance services, incurring transportation costs. In some middle-resource countries (e.g., India), almost a quarter of households seeking treatment for a relative with schizophrenia incur catastrophic debt due to out-of-pocket expenditure in accessing public care[516].

Social protection programming, cash transfers, microfinancing, and other interventions targeting poverty are largely absent from the current literature on schizophrenia. These practices may exist, but have not yet been evaluated or documented in peer-reviewed academic literature. Therefore, recommendations in middle/low-resource settings should primarily aim to raise awareness of and find ways to address the pervasive impact of social determinants of health, such as poverty. These factors may exert their influence through various mechanisms that could serve as actionable targets, such as limited access to transportation for appointments[517] or food insecurity. Leveraging existing government social support programs can play a critical role in addressing the needs of these vulnerable patients[518].

SUMMARY AND CONCLUSIONS

Schizophrenia usually emerges early in life and causes enormous personal, familial and socioeconomic burden. Its management remains a significant challenge worldwide, with a significant impact of the illness stage and of resource levels across and within countries and settings where care is delivered. Based on a critical review, involving clinicians, researchers, and people with lived experience, we present the first recommendations for real-world comprehensive care of people with schizophrenia. These recommendations consider multi-level and multi-stakeholder approaches, different stages of the disorder, and diverse levels of available resources, including countries in the Global South.

In summary, recommendations for management of people living with schizophrenia include the following domains:

- Comprehensive care, encompassing: a) early detection; b) measurement-based monitoring; c) pharmacological treatments; d) psychological interventions; e) psychosocial interventions; f) management of somatic conditions; g) community care; h) inpatient care; i) peer support, self-help, and alternative healing methods; j) population-level prevention, and l) societal-level support.
- Customization of comprehensive care to various regional and local scenarios, adapting evidence from high-resource settings to middle/low-resource ones, given enormous cultural, contextual and economic differences.
- Integration of clinical staging in the delivery of comprehensive care.
- Accessible, adapted communication about people's rights and available options, even in acute care scenarios, to the maximum extent possible, to implement person-centred care.
- Systematic and meaningful integration of the voices of people living with schizophrenia across all phases, states and symptoms into care design, delivery and evaluation.
- Recovery-oriented care, including fostering hope and facilitating self-determination.
- Optimizing access to and persistence of care.
- Early intervention approaches across all resource settings.
- Scalable measurement-based assessments used for diagnosis and monitoring.
- Psychoeducation of people with schizophrenia, family members/carers, and the general public.
- Education about and promotion of healthy lifestyle behaviors.
- Training and leveraging of non-medical staff, including peers, to improve access to care and care provision.
- Integration of and task-sharing with traditional healers in settings where their influence can be maximized in a positive way.
- Choice of effective pharmacological treatments with the least harm potential, considering LAIs and clozapine as early as needed.
- Implementation of psychological, psychosocial, and societal-level interventions to prevent deterioration, treat symptoms, and improve functioning and quality of life.
- Assessment, monitoring and management of psychiatric and physical comorbidities, and treatment of adverse effects of medications.
- Prompt detection and management of relapses, through psychoeducation, quick initiation/adjustment of treatments, and involvement of family members.
- Integration of digital health care options that are going to develop further.
- Strengthening mental health funding.
- Addressing social determinants of mental health.

Focusing on these areas, the overarching core recommendation is to implement evidence-based care that addresses disparities across high- to middle/low-resources settings, emphasizing early intervention (and prevention when possible), culturally-sensitive paradigms that leverage the local existing resources, and task-sharing models that involve non-professional health care workers.

In the future, we expect that scalable and resource-saving, evidence-based digital solutions will help extend and improve care quality and efficiency across all resource settings. However, none of this can be achieved without strengthening mental health funding and improving access to care, which is critical for reducing the global burden of schizophrenia, particularly in middle/low-resources settings, recognizing that care for people at risk for or living with schizophrenia is uneven and in need of improvement across all settings.

REFERENCES

1. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research: principles and quantitative methods. Chichester: Wiley, 1991.
2. Jongsma HE, Turner C, Kirkbride JB et al. International incidence of psychotic disorders, 2002-17: a systematic review and meta-analysis. Lancet Public Health 2019;4:e229-44.
3. Bastien RJ, Ding T, Gonzalez-Valderrama A et al. The incidence of non-affective psychotic disorders in low and middle-income countries: a systematic review and meta-analysis. Soc Psychiatry Psychiatr Epidemiol 2023;58:523-36.
4. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858.
5. Fusar-Poli P, Estradé A, Stanghellini G et al. The lived experience of psychosis: a bottom-up review co-written by experts by experience and academics. World Psychiatry 2022;21:168-88.
6. Estradé A, Onwumere J, Venables J et al. The lived experiences of family members and carers of people with psychosis: a bottom-up review co-written by experts by experience and academics. Psychopathology 2023;56:371-82.
7. Chan JKN, Correll CU, Wong CSM et al. Life expectancy and years of potential life lost in people with mental disorders: a systematic review and meta-analysis. EClinicalMedicine 2023;65:102294.
8. Weye N, Santomauro DF, Agerbo E et al. Register-based metrics of years lived with disability associated with mental and substance use disorders: a register-based cohort study in Denmark. Lancet Psychiatry 2021;8:310-9.
9. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. Lancet Psychiatry 2016;3:171-8.
10. Fusar-Poli P, Estradé A, Esposito CM et al. The lived experience of mental disorders in adolescents: a bottom-up review co-designed, co-conducted and co-written by experts by experience and academics. World Psychiatry 2024;23:191-208.
11. Fusar-Poli P, McGorry PD, Kane JM. Improving outcomes of first-episode psychosis: an overview. World Psychiatry 2017;16:251-65.
12. McGorry PD, Hickie IB, Yung AR et al. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Aust N Z J Psychiatry 2006;40:616-22.
13. Benrimoh D, Dlugunovych V, Wright AC et al. On the proportion of patients who experience a prodrome prior to psychosis onset: a systematic review and meta-analysis. Mol Psychiatry 2024;29:1361-81.
14. Krebs MD, Themudo GE, Benros ME et al. Associations between patterns in comorbid diagnostic trajectories of individuals with schizophrenia and etiological factors. Nat Commun 2021;12:6617.
15. Lu C, Jin D, Palmer N et al. Large-scale real-world data analysis identifies comorbidity patterns in schizophrenia. Transl Psychiatry 2022;12:154.
16. Correll CU, Solmi M, Veronese N et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 2017;16:163-80.
17. Stubbs B, Koyanagi A, Veronese N et al. Physical multimorbidity and psychosis: comprehensive cross sectional analysis including 242,952 people across 48 low- and middle-income countries. BMC Med 2016;14:189.
18. Vancampfort D, Correll CU, Galling B et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry 2016;15:166-74.
19. Vancampfort D, Stubbs B, Mitchell AJ et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 2015;14:339-47.
20. Arango C, Dragioti E, Solmi M et al. Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas. World Psychiatry 2021;20:417-36.
21. Dragioti E, Radua J, Solmi M et al. Global population attributable fraction of potentially modifiable risk factors for mental disorders: a meta-umbrella systematic review. Mol Psychiatry 2022;27:3510-9.
22. Radua J, Ramella-Cravaro V, Ioannidis JPA et al. What causes psychosis? An umbrella review of risk and protective factors. World Psychiatry 2018;17:49-66.
23. Fusar-Poli P. Integrated mental health services for the developmental period (0 to 25 years): a critical review of the evidence. Front Psychiatry 2019;10:355.
24. Hansen HG, Speyer H, Starzer M et al. Clinical recovery among individuals with a first-episode schizophrenia an updated systematic review and meta-analysis. Schizophr Bull 2023;49:297-308.
25. Jääskeläinen E, Juola P, Hirvonen N et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull 2013;39:1296-306.
26. Solmi M, Cortese S, Vita G et al. An umbrella review of candidate predictors of response, remission, recovery, and relapse across mental disorders. Mol Psychiatry 2023;28:3671-87.
27. Dragioti E, Radua J, Solmi M et al. Impact of mental disorders on clinical outcomes of physical diseases: an umbrella review assessing population attributable fraction and generalized impact fraction. World Psychiatry 2023;22:86-104.
28. Solmi M, Fiedorowicz J, Poddighe L et al. Disparities in screening and treatment of cardiovascular diseases in patients with mental disorders across the world: systematic review and meta-analysis of 47 observational studies. Am J Psychiatry 2021;178:793-803.
29. Solmi M, Firth J, Miola A et al. Disparities in cancer screening in people with mental illness across the world versus the general population: prevalence and comparative meta-analysis including 4 717 839 people. Lancet Psychiatry 2020;7:52-63.
30. De Hert M, Correll CU, Bobes J et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry 2011;10:52-77.
31. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry 2014;13:153-60.
32. Huhn M, Nikolakopoulou A, Schneider-Thoma J et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 2019;394:939-51.
33. Ostuzzi G, Bertolini F, Tedeschi F et al. Oral and long-acting antipsychotics for relapse prevention in schizophrenia-spectrum disorders: a network meta-analysis of 92 randomized trials including 22,645 participants. World Psychiatry 2022;21:295-307.
34. Ostuzzi G, Vita G, Bertolini F et al. Continuing, reducing, switching, or stopping antipsychotics in individuals with schizophrenia-spectrum disorders who are clinically stable: a systematic review and network meta-analysis. Lancet Psychiatry 2022;9:614-24.
35. Vita G, Pollini D, Canozzi A et al. Efficacy and acceptability of long-acting antipsychotics in acutely ill individuals with schizophrenia-spectrum disorders: a systematic review and network meta-analysis. Psychiatry Res 2024;340:116124.
36. Bighelli I, Rodolico A, García-Mieres H et al. Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network meta-analysis. Lancet Psychiatry 2021;8:969-80.
37. Bighelli I, Wallis S, Reitmeir C et al. Effects of psychological treatments on functioning in people with schizophrenia: a systematic review and meta-analysis of randomized controlled trials. Eur Arch Psychiatry Clin Neurosci 2023;273:779-810.
38. Solmi M, Croatto G, Piva G et al. Efficacy and acceptability of psychosocial interventions in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. Mol Psychiatry 2023;28:354-68.
39. Firth J, Siddiqi N, Koyanagi A et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatry 2019;6:675-712.
40. Vancampfort D, Firth J, Correll CU et al. The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in

people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials. World Psychiatry 2019;18:53-66.
41. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. London: National Institute for Health and Care Excellence, 2014.
42. Keepers GA, Fochtmann LJ, Anzia JM et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 2020;177:868-72.
43. Hasan A, Falkai P, Lehmann I et al. Revised S3 guidelines on schizophrenia: developmental process and selected recommendations. Nervenarzt 2020;91:26-33.
44. Correll CU, Martin A, Patel C et al. Systematic literature review of schizophrenia clinical practice guidelines on acute and maintenance management with antipsychotics. Schizophrenia 2022;8:5.
45. Grover S, Chakrabarti S, Kulhara P et al. Clinical practice guidelines for management of schizophrenia. Indian J Psychiatry 2017;59:S19-33.
46. Republic of Uganda Ministry of Health. Uganda clinical guidelines 2023. Kampala: Republic of Uganda Ministry of Health, 2023.
47. Singh SP, Javed A, WPA Expert International Advisory Panel for Early Intervention in Psychosis. Early intervention in psychosis in low- and middle-income countries: a WPA initiative. World Psychiatry 2020;19:122.
48. Hunt X, Abdurahman H, Omobowale O et al. Interventions for adolescents and adults with psychosis in Africa: a systematic review and narrative synthesis. Glob Ment Health 2022;9:223-40.
49. Wakida EK, Obua C, Haberer JE et al. Enhancing the capacity of providers in mental health integration (ECaP-MHI) in rural Uganda: the adaptation process. J Multidiscip Healthc 2023;16:387-96.
50. Otieno E, Seeiso T, Businge J et al. Achieving universal health coverage in Sub-Saharan Africa through the reformation of mental health financing. Global Health Economics and Sustainability 2025;3:21-7.
51. Lora A, Kohn R, Levav I et al. Service availability and utilization and treatment gap for schizophrenic disorders: a survey in 50 low- and middle-income countries. Bull World Health Organ 2012;90:47-54.
52. Smartt C, Prince M, Frissa S et al. Homelessness and severe mental illness in low- and middle-income countries: scoping review. BJPsych Open 2019;5:e57.
53. United Nations Department of Economic and Social Affairs. World population projected to reach 9.8 billion in 2050, and 11.2 billion in 2100. New York: United Nations Department of Economic and Social Affairs, 2017.
54. Metreau E, Young KE, Eapen SG. World Bank country classifications by income level for 2024-2025. https://blogs.worldbank.org.
55. Saraceno B, van Ommeren M, Batniji R et al. Barriers to improvement of mental health services in low-income and middle-income countries. Lancet 2007;370:1164-74.
56. Selamu M, Asher L, Hanlon C et al. Beyond the biomedical: community resources for mental health care in rural Ethiopia. PLoS One 2015;10:e0126666.
57. United Nations. Convention on the rights of persons with disabilities. New York: United Nations, 2006.
58. Thornicroft G, Sunkel C, Alikhon Aliev A et al. The Lancet Commission on ending stigma and discrimination in mental health. Lancet 2022;400:1438-80.
59. Fusar-Poli P, Sunkel C, Larrauri CA et al. Violence and schizophrenia: the role of social determinants of health and the need for early intervention. World Psychiatry 2023;22:230-1.
60. Slade M, Amering M, Farkas M et al. Uses and abuses of recovery: implementing recovery-oriented practices in mental health systems. World Psychiatry 2014;13:12-20.
61. Asher L, Rapiya B, Repper J et al. Peer-led recovery groups for people with psychosis in South Africa (PRIZE): results of a randomized controlled feasibility trial. Epidemiol Psychiatr Sci 2024;33:e47.
62. Jester DJ, Thomas ML, Sturm ET et al. Review of major social determinants of health in schizophrenia-spectrum psychotic disorders: I. Clinical outcomes. Schizophr Bull 2023;49:837-50.
63. Maguire J, Sizer H, Mifsud N et al. Outcomes for migrants with a first episode of psychosis: a systematic review. Schizophr Res 2020;222:42-8.
64. Hanlon C, Smartt C, Mutiso VN et al. Improving outcomes for people who are homeless and have severe mental illness in Ethiopia, Ghana and Kenya: overview of the HOPE programme. Epidemiol Psychiatr Sci 2025;34:e26.
65. Sisodia S, Hammond Z, Leonardi-Bee J et al. Sexual and reproductive health needs of women with severe mental illness in low- and middle-income countries: a scoping review. PLoS One 2025;20:e0311554.
66. Papola D, Patel V. Towards person-centered care in global mental health: implications for meta-analyses and clinical trials. Epidemiol Psychiatr Sci 2025;34:e13.
67. Paksarian D, Mojtabai R, Kotov R et al. Perceived trauma during hospitalization and treatment participation among individuals with psychotic disorders. Psychiatr Serv 2014;65:266-9.
68. Mendon GB, Gurung D, Loganathan S et al. Establishing partnerships with people with lived experience of mental illness for stigma reduction in low- and middle-income settings. Glob Ment Health 2024;11:e70.
69. Fisher HL. The public mental health revolution must privilege lived experience voices and create alliances with affected communities. World Psychiatry 2024;23:2-3.
70. Fusar-Poli P, Correll CU, Arango C et al. Preventive psychiatry: a blueprint for improving the mental health of young people. World Psychiatry 2021;20:200-21.
71. Catalan A, Salazar de Pablo G, Vaquerizo Serrano J et al. Annual Research Review: Prevention of psychosis in adolescents – systematic review and meta-analysis of advances in detection, prognosis and intervention. J Child Psychol Psychiatry 2021;62:657-73.
72. Fusar-Poli P, Salazar de Pablo G, Correll CU et al. Prevention of psychosis: advances in detection, prognosis, and intervention. JAMA Psychiatry 2020;77:755-65.
73. Catalan A, Salazar de Pablo G, Aymerich C et al. Neurocognitive functioning in individuals at clinical high risk for psychosis: a systematic review and meta-analysis. JAMA Psychiatry 2021;78:859-67.
74. Solmi M, Soardo L, Kaur S et al. Meta-analytic prevalence of comorbid mental disorders in individuals at clinical high risk of psychosis: the case for transdiagnostic assessment. Mol Psychiatry 2023;28:2291-300.
75. Fusar-Poli P, Nelson B, Valmaggia L et al. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. Schizophr Bull 2014;40:120-31.
76. Carney R, Cotter J, Firth J et al. Cannabis use and symptom severity in individuals at ultra high risk for psychosis: a meta-analysis. Acta Psychiatr Scand 2017;136:5-15.
77. Ang SH, Venkateswaran S, Goda MB et al. Prevalence of suicidal behaviour in adolescents and youth at ultra high risk for psychosis: a systematic review and meta-analysis. Eur Psychiatry 2025;68:e56.
78. Salazar de Pablo G, Woods SW, Drymonitou G et al. Prevalence of individuals at clinical high-risk of psychosis in the general population and clinical samples: systematic review and meta-analysis. Brain Sci 2021;11:1544.
79. Fusar-Poli P, Spencer T, De Micheli A et al. Outreach and support in South-London (OASIS) 2001-2020: twenty years of early detection, prognosis and preventive care for young people at risk of psychosis. Eur Neuropsychopharmacol 2020;39:111-22.
80. Addington J, Addington D, Abidi S et al. Canadian treatment guidelines for individuals at clinical high risk of psychosis. Can J Psychiatry 2017;62:656-61.
81. Orygen. Australian clinical guidelines for early psychosis. Parkville: Orygen, 2016.
82. Schultze-Lutter F, Michel C, Schmidt SJ et al. EPA guidance on the early detection of clinical high risk states of psychoses. Eur Psychiatry 2015;30:405-16.
83. Kotlicka-Antczak M, Podgorski M, Oliver D et al. Worldwide implementation of clinical services for the prevention of psychosis: the IEPA early intervention in mental health survey. Early Interv Psychiatry 2020;14:741-50.
84. Fusar-Poli P, Bauer M, Borgwardt S et al. European College of Neuropsychopharmacology network on the prevention of mental disorders and mental health promotion (ECNP PMD-MHP). Eur Neuropsychopharmacol 2019;29:1301-11.
85. Salazar de Pablo G, Estradé A, Cutroni M et al. Establishing a clinical service to prevent psychosis: what, how and when? Systematic review. Transl Psychiatry 2021;11:43.
86. McGorry P, Trethowan J, Rickwood D. Creating headspace for integrated youth mental health care. World Psychiatry 2019;18:140-1.
87. Rickwood D, Paraskakis M, Quin D et al. Australia's innovation in youth mental health care: the headspace centre model. Early Interv Psychiatry 2019;13:159-66.
88. Filia K, Rickwood D, Menssink J et al. Clinical and functional characteristics of a subsample of young people presenting for primary mental healthcare at headspace services across Australia. Soc Psychiatry Psychiatr Epidemiol 2021;56:1311-23.
89. Rickwood D, McEachran J, Saw A et al. Sixteen years of innovation in youth mental healthcare: outcomes for young people attending Australia's headspace centre services. PLoS One 2023;18:e0282040.
90. Yung AR, Yuen HP, McGorry PD et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust N Z J Psychiatry 2005;39:964-71.
91. Woods SW, Walsh BC, Powers AR et al. Reliability, validity, epidemiology, and cultural variation of the Structured Interview for Psychosis-Risk Syndromes

(SIPS) and the Scale of Psychosis-Risk Symptoms (SOPS). In: Li H, Shapiro DI, Seidman LJ (eds). Handbook of attenuated psychosis syndrome across cultures: international perspectives on early identification and intervention. Cham: Springer, 2019:85-113.
92. Stefana A, Oliver D, Vaz A et al. The mini-CAARMS: development and validation of a short version of the Comprehensive Assessment of At-Risk Mental States to facilitate preventive psychiatry. Schizophr Bull 2025; doi: 10.1093/schbul/sbaf146.
93. World Health Organization. The ICD-10 classification of mental and behavioural disorders. Geneva: World Health Organization, 1993.
94. Reed V, Gander F, Pfister H et al. To what degree does the Composite International Diagnostic Interview (CIDI) correctly identify DSM-IV disorders? Testing validity issues in a clinical sample. Int J Methods Psychiatr Res 1998;7:142-55.
95. Wittchen HU. Reliability and validity studies of the WHO - Composite International Diagnostic Interview (CIDI): a critical review. J Psychiatr Res 1994;28:57-84.
96. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-76.
97. Kølbæk P, Dines D, Holm T et al. Clinical validation of ratings on the six-item Positive and Negative Syndrome Scale obtained via the Simplified Negative and Positive Symptoms Interview. J Psychopharmacol 2021;35:1081-90.
98. Nielsen CM, Kølbæk P, Dines D et al. Validation of ratings on the six-item Positive and Negative Syndrome Scale obtained via the Simplified Negative and Positive Symptoms Interview among outpatients with schizophrenia. J Psychopharmacol 2022;36:1208-17.
99. Taylor DM. The Maudsley prescribing guidelines. Hoboken: Wiley-Blackwell, 2025.
100. Taylor DM, Gaughran F, Pillinger T. The Maudsley practice guidelines for physical health conditions in psychiatry. Hoboken: Wiley-Blackwell, 2020.
101. Shah JL, Scott J, McGorry PD et al. Transdiagnostic clinical staging in youth mental health: a first international consensus statement. World Psychiatry 2020;19:233-42.
102. Uhlhaas PJ, Davey CG, Mehta UM et al. Towards a youth mental health paradigm: a perspective and roadmap. Mol Psychiatry 2023;28:3171-81.
103. Arango C, Díaz-Caneja CM, McGorry PD et al. Preventive strategies for mental health. Lancet Psychiatry 2018;5:591-604.
104. Behan C, Kennelly B, Roche E et al. Early intervention in psychosis: health economic evaluation using the net benefit approach in a real-world setting. Br J Psychiatry 2020;217:484-90.
105. Correll CU, Galling B, Pawar A et al. Comparison of early intervention services vs treatment as usual for early-phase psychosis. JAMA Psychiatry 2018;75:555-65.
106. Robinson DG, Schooler NR, Marcy P et al. Outcomes during and after early intervention services for first-episode psychosis: results over 5 years from the RAISE-ETP site-randomized trial. Schizophr Bull 2022;48:1021-31.
107. East London NHS Foundation Trust. Standards for antipsychotic treatment and monitoring 2.0. London: East London NHS Foundation Trust, 2021.
108. O'Connell N, O'Connor K, McGrath D et al. Early intervention in psychosis services: a systematic review and narrative synthesis of the barriers and facilitators to implementation. Eur Psychiatry 2021;65:e2.
109. Starzer M, Hansen HG, Hjorthoj C et al. 20-year trajectories of positive and negative symptoms after the first psychotic episode in patients with schizophrenia spectrum disorder: results from the OPUS study. World Psychiatry 2023;22:424-32.
110. Correll C, Agid O, Crespo-Facorro B et al. A guideline and checklist for initiating and managing clozapine treatment in patients with treatment-resistant schizophrenia. CNS Drugs 2022;36:659-79.
111. Valle R, Singh SP, Loch AA et al. How "global" is research in early intervention for psychosis? A bibliometric analysis. Asian J Psychiatr 2024;98:104128.
112. Farooq S, Fonseka N, Ali MW et al. Early intervention in psychosis and management of first episode psychosis in low- and lower-middle-income countries: a systematic review. Schizophr Bull 2024;50:521-32.
113. Mamah D, Mutiso VN, Ndetei DM. Longitudinal and cross-sectional validation of the WERCAP screen for assessing psychosis risk and conversion. Schizophr Res 2022;241:201-9.
114. Fekih-Romdhane F, Abassi B, Ghrissi F et al. Suicide risk among individuals at ultra-high risk (UHR) of psychosis in a developing North African country: a 12-month naturalistic prospective cohort study from the TRIP project. Psychiatry Res 2023;327:115409.
115. Fekih-Romdhane F, Ghrissi F, Abassi B et al. Impulsivity as a predictor of clinical and psychological outcomes in a naturalistic prospective cohort of subjects at ultra-high risk (UHR) for psychosis from Tunisia. Psychiatry Res 2024;340:116090.
116. Awhangansi S, Okewole A, Archard PJ et al. Perspective on clinical high-risk for psychosis in Africa. Front Psychiatry 2023;14:1226012.
117. Theodoridou A, Schultze-Lutter F, Ambarini TK. Implementing early intervention in psychosis in Indonesia: a scoping review. Asian J Psychiatr 2024;101:104189.
118. Yung AR, Wood SJ, Malla A et al. The reality of at risk mental state services: a response to recent criticisms. Psychol Med 2021;51:212-8.
119. McGorry PD, Mei C, Dalal N et al. The Lancet Psychiatry Commission on youth mental health. Lancet Psychiatry 2024;11:731-74.
120. Hetrick SE, Bailey AP, Smith KE et al. Integrated (one-stop shop) youth health care: best available evidence and future directions. Med J Australia 2017;207:S5-18.
121. Hegde PR, Nirisha LP, Basavarajappa C et al. Schizophrenia spectrum disorders in India: a population-based study. Indian J Psychiatry 2023;65:1223-9.
122. World Health Organization. mhGAP training manuals for the mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings. Geneva: World Health Organization, 2017.
123. Purgato M, Adams C, Barbui C. Schizophrenia trials conducted in African countries: a drop of evidence in the ocean of morbidity? Int J Ment Health Syst 2012;6:1-10.
124. Morgan C, Cohen A, Esponda GM et al. Epidemiology of untreated psychoses in 3 diverse settings in the Global South. JAMA Psychiatry 2022;80:40-8.
125. Mwesiga EK, Nakasujja N, Nakku J et al. One year prevalence of psychotic disorders among first treatment contact patients at the National Psychiatric Referral and Teaching Hospital in Uganda. PLoS One 2020;15:e0218843.
126. Mutamba BB, Twikirize G, Ssemalulu J et al. Diagnostic pattern of mental, neurological and substance use disorders at primary health care facilities in Uganda. Int J Ment Health Syst 2024;18:26.
127. Blanco C, Wall MM, Olfson M. Implications of telepsychiatry for cost, quality, and equity of mental health care. JAMA Psychiatry 2022;79:1147-8.
128. Asher L, Hanlon C, Birhane R et al. Community-based rehabilitation intervention for people with schizophrenia in Ethiopia (RISE): a 12 month mixed methods pilot study. BMC Psychiatry 2018;18:250.
129. Kaminga AC, Myaba J, Dai W et al. Association between referral source and duration of untreated psychosis in pathways to care among first episode psychosis patients in Northern Malawi. Early Interv Psychiatry 2020;14:594-605.
130. Gureje O, Ojagbemi A. Applicability and future status of schizophrenia as a construct in Africa. Schizophr Res 2022;242:52-5.
131. Davies T, Lund C. Integrating mental health care into primary care systems in low- and middle-income countries: lessons from PRIME and AFFIRM. Glob Ment Health 2017;4:e7.
132. Dijkstra LG, Weiss HA, Birhane R et al. Effects of community-based rehabilitation on caregivers of people with schizophrenia in Ethiopia in the RISE trial. BMC Psychiatry 2025;25:231.
133. Keynejad RC, Dua T, Barbui C et al. WHO Mental Health Gap Action Programme (mhGAP) Intervention Guide: a systematic review of evidence from low and middle-income countries. Evid Based Ment Health 2018;21:30-4.
134. Hanlon C, Medhin G, Dewey ME et al. Efficacy and cost-effectiveness of task-shared care for people with severe mental disorders in Ethiopia (TaSCS): a single-blind, randomised, controlled, phase 3 non-inferiority trial. Lancet Psychiatry 2022;9:59-71.
135. Appiah-Poku J, Bello T, Kola L et al. The effect of collaborative care between traditional/faith healers and primary health care workers to improve psychosis outcome in Nigeria and Ghana (COSIMPO) – a cluster randomized controlled trial. Lancet 2020;396:612-22.
136. Chatterjee S, Naik S, John S et al. Effectiveness of a community-based intervention for people with schizophrenia and their caregivers in India (COPSI): a randomised controlled trial. Lancet 2014;383:1385-94.
137. Omigbodun O, Ryan G, Fasoranti B et al. Reprioritising global mental health: psychoses in sub-Saharan Africa. Int J Ment Health Syst 2023;17:6.
138. Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz. Guía basada en la evidencia de la Asociación Psiquiátrica de América Latina y de la Asociación Psiquiátrica Mexicana para el tratamiento del paciente con esquizofrenia. Salud Mental 2014;37(Suppl. 1).
139. Fusar-Poli P, Bechdolf A, Taylor MJ et al. At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. Schizophr Bull 2013;39:923-32.
140. Salazar de Pablo G, Radua J, Pereira J et al. Probability of transition to psychosis in individuals at clinical high risk: an updated meta-analysis. JAMA Psychiatry 2021;78:970-8.
141. Fusar-Poli P, Cappucciati M, Borgwardt S et al. Heterogeneity of psychosis risk within individuals at clinical high risk: a meta-analytical stratification. JAMA

Psychiatry 2016;73:113-20.
142. Fusar-Poli P, Cappucciati M, Bonoldi I et al. Prognosis of brief psychotic episodes: a meta-analysis. JAMA Psychiatry 2016;73:211-20.
143. Fusar-Poli P, Cappucciati M, De Micheli A et al. Diagnostic and prognostic significance of brief limited intermittent psychotic symptoms (BLIPS) in individuals at ultra high risk. Schizophr Bull 2017;43:48-56.
144. Fusar-Poli P, De Micheli A, Chalambrides M et al. Unmet needs for treatment in 102 individuals with brief and limited intermittent psychotic symptoms (BLIPS): implications for current clinical recommendations. Epidemiol Psychiatr Sci 2019;29:e67.
145. Fusar-Poli P, Salazar de Pablo G, Rajkumar RP et al. Diagnosis, prognosis, and treatment of brief psychotic episodes: a review and research agenda. Lancet Psychiatry 2022;9:72-83.
146. Provenzani U, Salazar de Pablo G, Arribas M et al. Clinical outcomes in brief psychotic episodes: a systematic review and meta-analysis. Epidemiol Psychiatr Sci 2021;30:e71.
147. Kirkbride JB, Errazuriz A, Croudace TJ et al. Incidence of schizophrenia and other psychoses in England, 1950-2009: a systematic review and meta-analyses. PLoS One 2012;7:e31660.
148. Salazar de Pablo G, Besana F, Arienti V et al. Longitudinal outcome of attenuated positive symptoms, negative symptoms, functioning and remission in people at clinical high risk for psychosis: a meta-analysis. EClinicalMedicine 2021;36:100909.
149. Salazar de Pablo G, Soardo L, Cabras A et al. Clinical outcomes in individuals at clinical high risk of psychosis who do not transition to psychosis: a meta-analysis. Epidemiol Psychiatr Sci 2022;31:e9.
150. Fusar-Poli P, Rutigliano G, Stahl D et al. Long-term validity of the At Risk Mental State (ARMS) for predicting psychotic and non-psychotic mental disorders. Eur Psychiatry 2017;42:49-54.
151. Stefanelli R, Estrade A, Azis M et al. The semi-structured interview for bipolar at-risk states (SIBARS): psychometric properties and validation. J Affect Disord 2025;387:119529.
152. Fusar-Poli P, Salazar de Pablo G, Correll CU et al. Prevention of psychosis: advances in detection, prognosis, and intervention. JAMA Psychiatry 2020;77:755-65.
153. Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep 1962;10:799-812.
154. Leucht S, Kane JM. Measurement-based psychiatry: definitions of response, remission, stability, and relapse in schizophrenia. J Clin Psychiatry 2006;67:1813-4.
155. Østergaard SD, Lemming OM, Mors O et al. PANSS-6: a brief rating scale for the measurement of severity in schizophrenia. Acta Psychiatr Scand 2016;133:436-44.
156. Samara MT, Leucht C, Leeflang MM et al. Early improvement as a predictor of later response to antipsychotics in schizophrenia: a diagnostic test review. Am J Psychiatry 2015;172:617-29.
157. Rubio JM, Guinart D, Kane JM et al. Early non-response to antipsychotic treatment in schizophrenia: a systematic review and meta-analysis of evidence-based management options. CNS Drugs 2023;37:499-512.
158. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). Iowa City: University of Iowa, 1981.
159. Schmid P, Czekaj A, Frick J et al. The Screen for Cognitive Impairment in Psychiatry (SCIP) as a routinely applied screening tool: pathology of acute psychiatric inpatients and cluster analysis. BMC Psychiatry 2021;21:494.
160. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry 1993;163(Suppl. 22):39-44.
161. Hynes C, Keating D, McWilliams S et al. Glasgow Antipsychotic Side-effects Scale for Clozapine – Development and validation of a clozapine-specific side-effects scale. Schizophr Res 2015;168:505-13.
162. Schneider LC, Struening EL. SLOF: a behavioral rating scale for assessing the mentally ill. Soc Work Res Abstr 1983;19:9-21.
163. Heinrichs DW, Hanlon TE, Carpenter WT Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull 1984;10:388-98.
164. Auquier P, Simeoni MC, Sapin C et al. Development and validation of a patient-based health-related quality of life questionnaire in schizophrenia: the S-QoL. Schizophr Res 2003;63:137-49.
165. Wilkinson G, Hesdon B, Wild D et al. Self-report quality of life measure for people with schizophrenia: the SQLS. Br J Psychiatry 2000;177:42-6.
166. Palmier-Claus JE, Ainsworth J, Machin M et al. The feasibility and validity of ambulatory self-report of psychotic symptoms using a smartphone software application. BMC Psychiatry 2012;12:172.
167. Perry BI, Osimo EF, Upthegrove R et al. Development and external validation of the Psychosis Metabolic Risk Calculator (PsyMetRiC): a cardiometabolic risk prediction algorithm for young people with psychosis. Lancet Psychiatry 2021;8:589-98.
168. Pillinger T, Howes OD, Correll CU et al. Antidepressant and antipsychotic side-effects and personalised prescribing: a systematic review and digital tool development. Lancet Psychiatry 2023;10:860-76.
169. Dinakaran D, Sreeraj VS, Venkatasubramanian G. Measurement based care in schizophrenia – Feasibility in routine clinical practice. Asian J Psychiatr 2020;49:101954.
170. Thara R, Srinivasan T, John S et al. Design and clinical characteristics of a homogeneous schizophrenia pedigree sample from Tamil Nadu, India. Aust N Z J Psychiatry 2009;43:561-70.
171. Grover S, Avasthi A, Shah S et al. Indian Psychiatric Society multicentric study on assessment of health-care needs of patients with severe mental illnesses. Indian J Psychiatry 2015;57:43-50.
172. Chadda RK, Sood M, Chawla N et al. Protocol-based assessment and management of first episode psychosis: comparison of short and medium-term outcomes in psychopathology, quality of life, functioning and family burden across two sites in India. Asian J Psychiatr 2024;98:104103.
173. Thara R. Twenty-year course of schizophrenia: the Madras Longitudinal Study. Can J Psychiatry 2004;49:564-9.
174. Bressan RA, Chaves AC, Shirakawa I et al. Validity study of the Brazilian version of the Calgary Depression Scale for Schizophrenia. Schizophr Res 1998;32:31-9.
175. Husain MO, Chaudhry IB, Khan Z et al. Depression and suicidal ideation in schizophrenia spectrum disorder: a cross-sectional study from a lower middle-income country. Int J Psychiatry Clin Pract 2021;25:245-51.
176. Garland AF, Deyessa N, Desta M et al. Use of the WHO's Perceived Well-Being Index (WHO-5) as an efficient and potentially valid screen for depression in a low income country. Fam Syst Health 2018;36:148-58.
177. Pheko MM, Mhaka-Mutepfa M, Mfolwe LM et al. Psychometrics validation of the WHO-5 Wellbeing Index in Botswana, Zimbabwe, and Malaysia: coping with COVID-19 pandemic in the Global South Study. SAGE Open 2023;13:21582440231.
178. Larsen A, Agorinya J, Beaulieu A et al. Digital health for early psychosis in Ghana: patient and caregiver needs and preferences. Schizophrenia 2025;11:5.
179. Botha UA, Koen L, Joska JA et al. Assessing the efficacy of a modified assertive community-based treatment programme in a developing country. BMC Psychiatry 2010;10:73.
180. Chiliza B, Ojagbemi A, Esan O et al. Combining depot antipsychotic with an assertive monitoring programme for treating first-episode schizophrenia in a resource-constrained setting. Early Interv Psychiatry 2016;10:54-62.
181. Hanlon C. Next steps for meeting the needs of people with severe mental illness in low- and middle-income countries. Epidemiol Psychiatr Sci 2017;26:348-54.
182. Thomas IF, Lawani AO, James BO. Effect of short message service reminders on clinic attendance among outpatients with psychosis at a psychiatric hospital in Nigeria. Psychiatr Serv 2017;68:75-80.
183. Stauffer VL, Case M, Kinon BJ et al. Early response to antipsychotic therapy as a clinical marker of subsequent response in the treatment of patients with first-episode psychosis. Psychiatry Res 2011;187:42-8.
184. Zeng J, Raballo A, Gan R et al. Antipsychotic exposure in clinical high risk of psychosis: empirical insights from a large cohort study. J Clin Psychiatry 2022;83:21m14092.
185. Bhattacharyya S, Appiah-Kusi E, Wilson R et al. Effects of cannabidiol on symptoms in people at clinical high risk for psychosis. World Psychiatry 2024;23:451-2.
186. Raballo A, Poletti M, Preti A. Do antidepressants prevent transition to psychosis in individuals at clinical high-risk (CHR-P)? Systematic review and meta-analysis. Psychol Med 2023;53:4550-60.
187. McGorry PD, Mei C, Amminger GP et al. A sequential adaptive intervention strategy targeting remission and functional recovery in young people at ultra-high risk of psychosis: the Staged Treatment in Early Psychosis (STEP) sequential multiple assignment randomized trial. JAMA Psychiatry 2023;80:875-85.
188. Hojlund M, Stovring H, Andersen K et al. Impact of low-dose quetiapine-use on glycosylated hemoglobin, triglyceride and cholesterol levels. Acta Psychiatr Scand 2023;147:105-16.
189. Hojlund M, Andersen K, Ernst MT et al. Use of low-dose quetiapine increases the risk of major adverse cardiovascular events: results from a nationwide active comparator-controlled cohort study. World Psychiatry 2022;21:444-51.
190. Hojlund M, Wesselhoeft R, Heinrichsen M et al. Excess cardiometabolic risk in children and adolescents initiating antipsychotic treatment compared to young adults: results from a nationwide cohort study. World Psychiatry 2025;

24:103-12.
191. National Institute for Health and Care Excellence. Shared decision making. London: National Institute for Health and Care Excellence, 2021.
192. Hamann J, Leucht S, Kissling W. Shared decision making in psychiatry. Acta Psychiatr Scand 2003;107:403-9.
193. Taylor DM, Barnes TRE, Young AH. The Maudsley prescribing guidelines in psychiatry. Hoboken: Wiley-Blackwell, 2021.
194. Galletly C, Castle D, Dark F et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry 2016;50:410-72.
195. Hasan A, Falkai P, Wobrock T et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia – a short version for primary care. Int J Psychiatry Clin Pract 2017;21:82-90.
196. Brand BA, Haveman YRA, de Beer F et al. Antipsychotic medication for women with schizophrenia spectrum disorders. Psychol Med 2022;52:649-63.
197. Uchida H, Mamo DC, Mulsant BH et al. Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. J Clin Psychiatry 2009;70:397-405.
198. Battaglia J, Moss S, Rush J et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. Am J Emerg Med 1997;15:335-40.
199. Barbee JG, Mancuso DM, Freed CR et al. Alprazolam as a neuroleptic adjunct in the emergency treatment of schizophrenia. Am J Psychiatry 1992;149:506-10.
200. Garza-Treviño ES, Hollister LE, Overall JE et al. Efficacy of combinations of intramuscular antipsychotics and sedative-hypnotics for control of psychotic agitation. Am J Psychiatry 1989;146:1598-601.
201. Zaman H, Sampson SJ, Beck AL et al. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database Syst Rev 2017;12:CD003079.
202. Kishimoto T, Hagi K, Kurokawa S et al. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. Lancet Psychiatry 2021;8:387-404.
203. Correll CU, Solmi M, Croatto G et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry 2022;21:248-71.
204. Arango C, Fagiolini A, Gorwood P et al. Delphi panel to obtain clinical consensus about using long-acting injectable antipsychotics to treat first-episode and early-phase schizophrenia: treatment goals and approaches to functional recovery. BMC Psychiatry 2023;23:453.
205. Aymerich C, Salazar de Pablo G, Pacho M et al. All-cause mortality risk in long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis. Mol Psychiatry 2024;30:263-71.
206. Correll CU, Bitter I, Hoti F et al. Factors and their weight in reducing life expectancy in schizophrenia. Schizophr Res 2022;250:67-75.
207. Solmi M, Croatto G, Gupta A et al. Effects of antipsychotic treatment on cardiocerebrovascular related mortality in schizophrenia: a subanalysis of a systematic review and meta-analysis with meta-regression of moderators. Eur Neuropsychopharmacol 2024;88:6-20.
208. Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. World Psychiatry 2013;12:216-26.
209. McCutcheon R, Beck K, D'Ambrosio E et al. Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia. Acta Psychiatr Scand 2018;137:39-46.
210. El Alili M, Vrijens B, Demonceau J et al. A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. Br J Clin Pharmacol 2016;82:268-79.
211. Velligan DI, Wang M, Diamond P et al. Relationships among subjective and objective measures of adherence to oral antipsychotic medications. Psychiatr Serv 2007;58:1187-92.
212. Larsen KG, Areberg J, Åström DO. Are self-reported and self-monitored adherence good proxies for reaching relevant plasma concentrations?: Experiences from a study of anti-depressants in healthy volunteers. Clin Trials 2021;18:505-10.
213. Kristiansen O, Sverre E, Peersen K et al. The relationship between directly measured statin adherence, self-reported adherence measures and cholesterol levels in patients with coronary heart disease. Atherosclerosis 2021;336:23-9.
214. Schoretsanitis G, Kane JM, Correll CU et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie. J Clin Psychiatry 2020;81:19cs13169.
215. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. Eur Psychiatry 2010;25(Suppl. 2):S12-21.
216. Hojlund M, Correll CU. Switching to long-acting injectable antipsychotics: pharmacological considerations and practical approaches. Expert Opin Pharmacother 2023;24:1463-89.
217. Howes OD, McCutcheon R, Agid O et al. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group consensus guidelines on diagnosis and terminology. Am J Psychiatry 2017;174:216-29.
218. Dong S, Schneider-Thoma J, Bighelli I et al. A network meta-analysis of efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia. Eur Arch Psychiatry Clin Neurosci 2024;274:917-28.
219. Samara MT, Dold M, Gianatsi M et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. JAMA Psychiatry 2016;73:199-210.
220. Masuda T, Misawa F, Takase M et al. Association with hospitalization and all-cause discontinuation among patients with schizophrenia on clozapine vs other oral second-generation antipsychotics: a systematic review and meta-analysis of cohort studies. JAMA Psychiatry 2019;76:1052-62.
221. Vermeulen JM, van Rooijen G, van de Kerkhof MPJ et al. Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1.1-12.5 years. Schizophr Bull 2019;45:315-29.
222. Shah P, Iwata Y, Plitman E et al. The impact of delay in clozapine initiation on treatment outcomes in patients with treatment-resistant schizophrenia: a systematic review. Psychiatry Res 2018;268:114-22.
223. Galling B, Roldán A, Rietschel L et al. Safety and tolerability of antipsychotic co-treatment in patients with schizophrenia: results from a systematic review and meta-analysis of randomized controlled trials. Expert Opin Drug Saf 2016;15:591-612.
224. Galling B, Roldán A, Hagi K et al. Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. World Psychiatry 2017;16:77-89.
225. Højlund M, Köhler-Forsberg O, Gregersen AT et al. Prevalence, correlates, tolerability-related outcomes, and efficacy-related outcomes of antipsychotic polypharmacy: a systematic review and meta-analysis. Lancet Psychiatry 2024;11:975-89.
226. van Bennekom MWL, IntHout J, Gijsman HJ et al. Efficacy and tolerability of antipsychotic polypharmacy for schizophrenia spectrum disorders. A systematic review and meta-analysis of individual patient data. Schizophr Res 2024;272:1-11.
227. Correll CU, Rubio JM, Kane JM. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? World Psychiatry 2018;17:149-60.
228. Tiihonen J, Tanskanen A, Taipale H. 20-year nationwide follow-up study on discontinuation of antipsychotic treatment in first-episode schizophrenia. Am J Psychiatry 2018;175:765-73.
229. Gangadin SS, de Beer F, Wijnen B et al. Risk of relapse during tapering of antipsychotic medication after a first psychotic episode: association with D2 receptor affinity but not with tapering speed. World Psychiatry 2025;24:240-9.
230. Kishi T, Ikuta T, Matsui Y et al. Effect of discontinuation v. maintenance of antipsychotic medication on relapse rates in patients with remitted/stable first-episode psychosis: a meta-analysis. Psychol Med 2019;49:772-9.
231. Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. Neuropsychiatr Dis Treat 2020;16:519-34.
232. Giordano GM, Caporusso E, Pezzella P et al. Updated perspectives on the clinical significance of negative symptoms in patients with schizophrenia. Exp Rev Neurother 2022;22:541-55.
233. Millan MJ, Agid Y, Brüne M et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov 2012;11:141-68.
234. Vita A, Barlati S, Cavallaro R et al. Definition, assessment and treatment of cognitive impairment associated with schizophrenia: expert opinion and practical recommendations. Front Psychiatry 2024;15:1451832.
235. Carbon M, Correll CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. CNS Spectr 2014;19:35-53.
236. Sabe M, Zhao N, Crippa A et al. Antipsychotics for negative and positive symptoms of schizophrenia: dose-response meta-analysis of randomized controlled acute phase trials. NPJ Schizophr 2021;7:43.
237. Højlund M, Kemp AF, Haddad PM et al. Standard versus reduced dose of antipsychotics for relapse prevention in multi-episode schizophrenia: a systematic review and meta-analysis of randomised controlled trials. Lancet Psychiatry 2021;8:471-86.

238. Højlund M, Kemp AF, Haddad PM et al. Withdrawal-associated relapse is a potential source of bias – Authors' reply. Lancet Psychiatry 2021;8:748-9.
239. Moncrieff J, Crellin N, Stansfeld J et al. Antipsychotic dose reduction and discontinuation versus maintenance treatment in people with schizophrenia and other recurrent psychotic disorders in England (the RADAR trial): an open, parallel-group, randomised controlled trial. Lancet Psychiatry 2023;10:848-59.
240. Krause M, Zhu Y, Huhn M et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci 2018;268:625-39.
241. Németh G, Laszlovszky I, Czobor P et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. Lancet 2017;389: 1103-13.
242. Helfer B, Samara MT, Huhn M et al. Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a systematic review and meta-analysis. Am J Psychiatry 2016;173:876-86.
243. Chang JS, Ahn YM, Park HJ et al. Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2008;69:720-31.
244. Kaar SJ, Natesan S, McCutcheon R et al. Antipsychotics: mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. Neuropharmacology 2020;172:107704.
245. McCutcheon RA, Harrison PJ, Howes OD et al. Data-driven taxonomy for antipsychotic medication: a new classification system. Biol Psychiatry 2023; 94:561-8.
246. Fabiano N, Wong S, Zhou C et al. Efficacy, tolerability, and safety of xanomeline-trospium chloride for schizophrenia: a systematic review and meta-analysis. Eur Neuropsychopharmacol 2025;92:62-73.
247. Brannan SK, Sawchak S, Miller AC et al. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. N Engl J Med 2021;384:717-26.
248. Kaul I, Sawchak S, Correll CU et al. Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial. Lancet 2024;403:160-70.
249. McCutcheon RA, Weber LA, Nour MM et al. Psychosis as a disorder of muscarinic signalling: psychopathology and pharmacology. Lancet Psychiatry 2024;11:554-65.
250. Correll CU, Sliwa JK, Najarian DM et al. Practical considerations for managing breakthrough psychosis and symptomatic worsening in patients with schizophrenia on long-acting injectable antipsychotics. CNS Spectr 2019;24:354-70.
251. Haddad PM, Correll CU. Long-acting antipsychotics in the treatment of schizophrenia: opportunities and challenges. Exp Opin Pharmacother 2023;24:473-93.
252. McCutcheon RA, Keefe RSE, McGuire PK. Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. Mol Psychiatry 2023;28: 1902-18.
253. Correll CU, Solmi M, Cortese S et al. The future of psychopharmacology: a critical appraisal of ongoing phase 2/3 trials, and of some current trends aiming to de-risk trial programmes of novel agents. World Psychiatry 2023;22:48-74.
254. Feber L, Peter NL, Chiocchia V et al. Antipsychotic drugs and cognitive function: a systematic review and network meta-analysis. JAMA Psychiatry 2025;82: 47-56.
255. McCutcheon RA, Keefe RSE, McGuire PM et al. Deconstructing cognitive impairment in psychosis with a machine learning approach. JAMA Psychiatry 2024;82:57-65.
256. Mancini V, Latreche C, Fanshawe JB et al. Anticholinergic burden and cognitive function in psychosis: a systematic review and meta-analysis. Am J Psychiatry 2024;182:349-59.
257. Baldez DP, Biazus TB, Rabelo-da-Ponte FD et al. The effect of antipsychotics on the cognitive performance of individuals with psychotic disorders: network meta-analyses of randomized controlled trials. Neurosci Biobehav Rev 2021;126:265-75.
258. Bighelli I, Çıray O, Leucht S. Cognitive behavioural therapy without medication for schizophrenia. Cochrane Database Syst Rev 2024;2:CD015332.
259. Hagi K, Nosaka T, Dickinson D et al. Association between cardiovascular risk factors and cognitive impairment in people with schizophrenia: a systematic review and meta-analysis. JAMA Psychiatry 2021;78:510-8.
260. Maurus I, Wagner S, Spaeth J et al. EPA guidance on lifestyle interventions for adults with severe mental illness: a meta-review of the evidence. Eur Psychiatry 2024;67:e80.
261. Diniz E, Fonseca L, Rocha D et al. Treatment resistance in schizophrenia: a meta-analysis of prevalence and correlates. Braz J Psychiatry 2023;45:448-58.
262. Tiihonen J, Mittendorfer-Rutz E, Majak M et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. JAMA Psychiatry 2017;74:686-93.
263. Grover S, Naskar C. Patient and caregivers perspective about clozapine: a systematic review. Schizophr Res 2024;268:223-32.
264. Correll CU. Clozapine: past, present and future. World Psychiatry 2025;24:153-4.
265. De Leon J, Schoretsanitis G, Smith RL et al. An international adult guideline for making clozapine titration safer by using six ancestry-based personalized dosing titrations, CRP, and clozapine levels. Pharmacopsychiatry 2022;55:73-86.
266. Wagner E, Siskind D, Falkai P et al. Clozapine optimization: a Delphi consensus guideline from the Treatment Response and Resistance in Psychosis Working Group. Schizophr Bull 2023;49:962-72.
267. Northwood K, Pearson E, Arnautovska U et al. Optimising plasma clozapine levels to improve treatment response: an individual patient data meta-analysis and receiver operating characteristic curve analysis. Br J Psychiatry 2023;222:241-5.
268. Wagner E, Löhrs L, Siskind D et al. Clozapine augmentation strategies – a systematic meta-review of available evidence. Treatment options for clozapine resistance. J Psychopharmacol 2019;33:423-35.
269. Tiihonen J, Tanskanen A, Mittendorfer-Rutz E et al. Effectiveness of clozapine augmentation with specific doses of other antipsychotics in schizophrenia: a meta-analysis from two nationwide cohorts. World Psychiatry 2025;24:250-9.
270. Wang G, Zheng W, Li X-B et al. ECT augmentation of clozapine for clozapine-resistant schizophrenia: a meta-analysis of randomized controlled trials. J Psychiatr Res 2018;105:23-32.
271. Yeh T-C, Correll CU, Yang F-C et al. Pharmacological and nonpharmacological augmentation treatments for clozapine-resistant schizophrenia: a systematic review and network meta-analysis with normalized entropy assessment. Asian J Psychiatr 2023;79:103375.
272. Petrides G, Malur C, Braga RJ et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. Am J Psychiatry 2015;172:52-8.
273. Chidarikire S, Cross M, Skinner I et al. Treatments for people living with schizophrenia in Sub-Saharan Africa: an adapted realist review. Int Nursing Rev 2018;65:78-92.
274. Rukat A, Musisi S, Ströhle A et al. Prescription patterns of psychotropic medications for the treatment of psychotic disorders in the largest mental health institutions of Uganda. J Clin Psychopharmacol 2014;34:571-6.
275. Mwesiga EK, Nakasujja N, Nankaba L et al. Quality of individual and group level interventions for first-episode psychosis at the tertiary psychiatric hospital in Uganda. South Afr J Psychiatry 2021;27:1604.
276. Lubinga SJ, Mutamba BB, Nganizi A et al. A cost-effectiveness analysis of antipsychotics for treatment of schizophrenia in Uganda. Appl Health Econ Health Policy 2015;13:493-506.
277. Galvañ J, Nguepy-Keubo F. Second generation long-acting injectable antipsychotics in Africa: about a case. Eur Psychiatry 2023;19:S820.
278. Grover S, Nebhinani N, Chakrabarti S et al. Evaluation of psychotropic prescription patterns at the time of discharge from inpatient unit of a tertiary care general hospital psychiatric unit. J Ment Health Hum Behav 2016;21:48-54.
279. Ying J, Chew QH, Wang Y et al. Global neuropsychopharmacological prescription trends in individuals with schizophrenia, clinical correlates and implications for practice: a scoping review. Brain Sci 2024;14:6.
280. Joshi SS, Shetty YC, Karande S. Generic drugs – The Indian scenario. J Postgrad Med 2019;65:67-9.
281. Docrat S, Besada D, Cleary S et al. The impact of social, national and community-based health insurance on health care utilization for mental, neurological and substance-use disorders in low- and middle-income countries: a systematic review. Health Econ Rev 2020;10:1-23.
282. Murthy RS. National mental health survey of India 2015-2016. Indian J Psychiatry 2017;59:21-6.
283. Colgan S, Faasse K, Martin LR et al. Perceptions of generic medication in the general population, doctors and pharmacists: a systematic review. BMJ Open 2015;5:e008915.
284. Flood D, Mathieu I, Chary A et al. Perceptions and utilization of generic medicines in Guatemala: a mixed-methods study with physicians and pharmacy staff. BMC Health Serv Res 2017;17:1-11.
285. Patel A, Gauld R, Norris P et al. Quality of generic medicines in South Africa: perceptions versus reality – a qualitative study. BMC Health Serv Res 2012; 12:1-8.
286. Kumar S, Sudhakar S, Sajatovic M et al. Antipsychotic medication in sub-Saharan Africa: a systematic literature review. J Clin Psychopharmacol 2020;40: 541-52.
287. Shenoy SRA, Bhandary RP, Praharaj SK. Frequency, reasons, and factors as-

sociated with antipsychotic polypharmacy in schizophrenia: a retrospective chart review in a tertiary hospital in India. Asian J Psychiatr 2020;51:102022.
288. Ayenew W, Asmamaw G, Bitew T. Antipsychotic polypharmacy among patients with schizophrenia in Africa: a systematic review and meta-analysis. Int J Neuropsychopharmacol 2021;24:956-64.
289. Kukreja S, Kalra G, Shah N et al. Polypharmacy in psychiatry: a review. Mens Sana Monogr 2013;11:82-99.
290. Solmi M, Pigato G, Kane JM et al. Clinical risk factors for the development of tardive dyskinesia. J Neurol Sci 2018;389:21-7.
291. Tang CT, Chua EC, Chew QH et al. Patterns of long acting injectable antipsychotic use and associated clinical factors in schizophrenia among 15 Asian countries and region. Asia Pac Psychiatry 2020;12:e12393.
292. Mbwambo J, Kaaya S, Lema I et al. An interventional pilot of customized adherence enhancement combined with long-acting injectable antipsychotic medication (CAE-L) for poorly adherent patients with chronic psychotic disorder in Tanzania. BMC Psychiatry 2022;22:62.
293. Kane JM, Agid O, Baldwin ML et al. Clinical guidance on the identification and management of treatment-resistant schizophrenia. J Clin Psychiatry 2019; 80:18com12123.
294. Shrivastava A, Shah N. Prescribing practices of clozapine in India: results of a opinion survey of psychiatrists. Indian J Psychiatry 2009;51:225-6.
295. Daniels MV, Ramlall S. Clozapine monitoring at a specialised psychiatric hospital: a retrospective chart review. South Afr J Psychiatry 2023;29:2039.
296. Fusar-Poli P, Davies C, Solmi M et al. Preventive treatments for psychosis: umbrella review (just the evidence). Front Psychiatry 2019;10:764.
297. Bechdolf A, Wagner M, Ruhrmann S et al. Preventing progression to first-episode psychosis in early initial prodromal states. Br J Psychiatry 2012;200:22-9.
298. van der Gaag M, van den Berg D, Ising H. CBT in the prevention of psychosis and other severe mental disorders in patients with an at risk mental state: a review and proposed next steps. Schizophr Res 2019;203:88-93.
299. Stafford MR, Jackson H, Mayo-Wilson E et al. Early interventions to prevent psychosis: systematic review and meta-analysis. BMJ 2013;346:f185.
300. Davies C, Cipriani A, Ioannidis JPA et al. Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. World Psychiatry 2018;17:196-209.
301. Bosnjak Kuharic D, Kekin I, Hew J et al. Interventions for prodromal stage of psychosis. Cochrane Database Syst Rev 2019;11:CD012236.
302. Wykes T, Steel C, Everitt B et al. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. Schizophr Bull 2008;34: 523-37.
303. Berendsen S, Berendse S, van der Torren J et al. Cognitive behavioural therapy for the treatment of schizophrenia spectrum disorders: an umbrella review of meta-analyses of randomised controlled trials. EClinicalMedicine 2024;67:102392.
304. Wykes T, Huddy V, Cellard C et al. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am J Psychiatry 2011;168:472-85.
305. Vita A, Barlati S, Ceraso A et al. Durability of effects of cognitive remediation on cognition and psychosocial functioning in schizophrenia: a systematic review and meta-analysis of randomized clinical trials. Am J Psychiatry 2024;181:520-31.
306. Dark FL, Amado I, Erlich MD et al. International experience of implementing cognitive remediation for people with psychotic disorders. Schizophr Bull 2024;50:1017-27.
307. Bird VJ, Davis S, Jawed A et al. Implementing psychosocial interventions within low and middle-income countries to improve community-based care for people with psychosis – a situation analysis. Front Psychiatry 2022;13:807259.
308. Mascayano F, Toso-Salman J, Ho YCS et al. Including culture in programs to reduce stigma toward people with mental disorders in low- and middle-income countries. Transcult Psychiatry 2020;57:140-60.
309. Bolton P, West J, Whitney C et al. Expanding mental health services in low- and middle-income countries: a task-shifting framework for delivery of comprehensive, collaborative, and community-based care. Glob Mental Health 2023;10:e16.
310. Galvin M, Byansi W. A systematic review of task shifting for mental health in sub-Saharan Africa. Int J Ment Health 2020;49:336-60.
311. Lyles S, Khan Z, Qureshi O et al. A systematic review of the effectiveness and implementation readiness of psychosocial interventions for psychosis in South Asia. PLoS One 2023;18:e0283411.
312. Naeem F, Saeed S, Irfan M et al. Brief culturally adapted CBT for psychosis (CaCBTp): a randomized controlled trial from a low income country. Schizophr Res 2015;164:143-8.
313. Thara R, John S, Rao K. Telepsychiatry in Chennai, India: the SCARF experience. Behav Sci Law 2008;26:315-22.
314. Math SB, Manjunatha N, Kumar CN et al. Telepsychiatry operational guidelines – 2020. Bangalore: National Institute of Mental Health and Neuro Sciences, 2020.
315. Lad RA, Padroo BS. Advancements and challenges in digital health implementation in India: a comprehensive literature review. World J Biol Pharm Health Sci 2024;18:205-8.
316. Bighelli I, Salanti G, Huhn M et al. Psychological interventions to reduce positive symptoms in schizophrenia: systematic review and network meta-analysis. World Psychiatry 2018;17:316-29.
317. Burgess-Barr S, Nicholas E, Venus B et al. International rates of receipt of psychological therapy for psychosis and schizophrenia: systematic review and meta-analysis. Int J Ment Health Syst 2023;17:8.
318. Deste G, Kakli M, Barlati S et al. Application of cognitive remediation in the world: new experiences from two schizophrenia rehabilitation centers in Togo and Benin. Soc Psychiatry Psychiatr Epidemiol 2024;59:1775-83.
319. Kantipudi SJ, Venkatasubramanian P, Rattehalli R. Effectiveness of cognitive remediation interventions for schizophrenia in Asian population: a systematic review and meta-analysis of randomized controlled trials. J Psychiatr Spectr 2025;4:100-10.
320. Poletti M, Pelizza L, Preti A et al. Clinical high-risk for psychosis (CHR-P) circa 2024: synoptic analysis and synthesis of contemporary treatment guidelines. Asian J Psychiatr 2024;100:104142.
321. Herrera SN, Sarac C, Phili A et al. Psychoeducation for individuals at clinical high risk for psychosis: a scoping review. Schizophr Res 2023;252:148-58.
322. Xia J, Merinder LB, Belgamwar MR. Psychoeducation for schizophrenia. Schizophr Bull 2011;37:21-2.
323. Pharoah F, Mari J, Rathbone J et al. Family intervention for schizophrenia. Cochrane Database Syst Rev 2010;12:CD000088.
324. Henderson C, Kotera Y, Lloyd-Evans B et al. Social inclusion of people with severe mental illness: a review of current practices, evidence and unmet needs, and future directions. World Psychiatry 2026;25:56-82.
325. Brinchmann B, Widding-Havneraas T, Modini M et al. A meta-regression of the impact of policy on the efficacy of individual placement and support. Acta Psychiatr Scand 2020;141:206-20.
326. Rog DJ, Marshall T, Dougherty RH et al. Permanent supportive housing: assessing the evidence. Psychiatr Serv 2014;65:287-94.
327. McGorry PD, Hickie IB, Jorm AF et al. Early intervention in youth mental health. Med J Aust 2008;188:492-3.
328. Valencia M, Rascon ML, Juarez F et al. Application in Mexico of psychosocial rehabilitation with schizophrenia patients. Psychiatry 2010;73:248-63.
329. Valencia M, Rascon ML, Juarez F et al. A psychosocial skills training approach in Mexican out-patients with schizophrenia. Psychol Med 2007;37:1393-402.
330. Patel V. Universal health coverage for schizophrenia: a global mental health priority. Schizophr Bull 2016;42:885-90.
331. Asher L, Birhane R, Teferra S et al. "Like a doctor, like a brother": achieving competence amongst lay health workers delivering community-based rehabilitation for people with schizophrenia in Ethiopia. PLoS One 2021;16:e0246158.
332. Iyidobi TO, Onu JU, Iteke O et al. The effect of structured psychoeducation on caregiver burden in carers of patients with schizophrenia in Nigeria: a 12-week follow-up investigation. S Afr J Psychiatry 2022;28:1703.
333. Brooke-Sumner C, Petersen I, Asher L et al. Systematic review of feasibility and acceptability of psychosocial interventions for schizophrenia in low and middle income countries. BMC Psychiatry 2015;15:1-12.
334. Hanlon C, Medhin G, Selamu M et al. Impact of integrated district level mental health care on clinical and social outcomes of people with severe mental illness in rural Ethiopia: an intervention cohort study. Epidemiol Psychiatr Sci 2020;29:e45.
335. Asher L, Birhane R, Weiss HA et al. Community-based rehabilitation intervention for people with schizophrenia in Ethiopia (RISE): results of a 12-month cluster-randomised controlled trial. Lancet Glob Health 2022;10:e530-42.
336. Iyer SN, Malla A, Taksal A et al. Context and contact: a comparison of patient and family engagement with early intervention services for psychosis in India and Canada. Psychol Med 2022;52:1538-47.
337. Jagannathan A, Harish N, Venkatalakshmi C et al. Supported employment programme for persons with severe mental disorders in India: a feasibility study. Int J Soc Psychiatry 2020;66:607-13.
338. Annapally SR, Jagannathan A, Kishore T et al. Development of a supported education program for students with severe mental disorders in India. Indian J Psychol Med 2021;43:217-22.
339. Alomari E, Steinke C. Quality of life in assisted living facilities for seniors: a descriptive exploratory study. Nurs Open 2024;11:e2084.
340. Patel V, Thara R. Meeting the mental health needs of developing countries: NGO innovations in India. New Delhi: Sage, 2003.

341. Gong Y, Xu SQ. Implementation and challenge of supported employment for people with disabilities in China. Intellect Dev Disabil 2024;62:114-25.
342. Crump C, Winkleby MA, Sundquist K et al. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. Am J Psychiatry 2013;170:324-33.
343. Hoang U, Goldacre MJ, Stewart R. Avoidable mortality in people with schizophrenia or bipolar disorder in England. Acta Psychiatr Scand 2013;127:195-201.
344. Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. Annu Rev Clin Psychol 2014;10:425-48.
345. Brown S, Kim M, Mitchell C et al. Twenty-five year mortality of a community cohort with schizophrenia. Br J Psychiatry 2010;196:116-21.
346. McCreadie RG, Scottish Schizophrenia Lifestyle Group. Diet, smoking and cardiovascular risk in people with schizophrenia. Br J Psychiatry 2003;183:534-9.
347. Pillinger T, McCutcheon RA, Vano L et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 2020;7:64-77.
348. Pillinger T, McCutcheon RA, Howes OD. Variability of glucose, insulin, and lipid disturbances in first-episode psychosis: a meta-analysis. Psychol Med 2023;53:3150-6.
349. Mondelli V, Blackman G, Kempton MJ et al. Serum immune markers and transition to psychosis in individuals at clinical high risk. Brain Behav Immun 2023;110:290-6.
350. Pillinger T, D'Ambrosio E, McCutcheon R et al. Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. Mol Psychiatry 2019;24:776-94.
351. Pillinger T, Osimo EF, Brugger S et al. A meta-analysis of immune parameters, variability, and assessment of modal distribution in psychosis and test of the immune subgroup hypothesis. Schizophr Bull 2019;45:1120-33.
352. Holt RIG, Gossage-Worrall R, Hind D et al. Structured lifestyle education for people with schizophrenia, schizoaffective disorder and first-episode psychosis (STEPWISE): randomised controlled trial. Br J Psychiatry 2019;214:63-73.
353. Walburg FS, van Meijel B, Hoekstra T et al. Effectiveness of a lifestyle intervention for people with a severe mental illness in Dutch outpatient mental health care: a randomized clinical trial. JAMA Psychiatry 2023;80:886-94.
354. Yu O, Lu M, Lai TKY et al. Metformin co-commencement at time of antipsychotic initiation for attenuation of weight gain: a systematic review and meta-analysis. Ther Adv Psychopharmacol 2024;14:20451253241255476.
355. National Institute for Health and Care Excellence. Metformin in type 2 diabetes. London: National Institute for Health and Care Excellence, 2022.
356. Siskind D, Gallagher E, Winckel K et al. Does switching antipsychotics ameliorate weight gain in patients with severe mental illness? A systematic review and meta-analysis. Schizophr Bull 2021;47:948-58.
357. Marteene W, Winckel K, Hollingworth S et al. Strategies to counter antipsychotic-associated weight gain in patients with schizophrenia. Exp Opin Drug Saf 2019;18:1149-60.
358. Siskind D, Hahn M, Correll CU et al. Glucagon-like peptide-1 receptor agonists for antipsychotic-associated cardio-metabolic risk factors: systematic review and individual participant data meta-analysis. Diabetes Obes Metab 2019;21:293-302.
359. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017;357:j2099.
360. Cernea S, Dima L, Correll CU et al. Pharmacological management of glucose dysregulation in patients treated with second-generation antipsychotics. Drugs 2020;80:1763-81.
361. Buzea CA, Dima L, Correll CU et al. Drug-drug interactions involving antipsychotics and antihypertensives. Exp Opin Drug Metab Toxicol 2022;18:285-98.
362. Buzea CA, Manu P, Dima L et al. Drug-drug interactions involving combinations of antipsychotic agents with antidiabetic, lipid-lowering, and weight loss drugs. Exp Opin Drug Metab Toxicol 2022;18:729-44.
363. Kane JM, Durgam S, Satlin A et al. Safety and tolerability of lumateperone for the treatment of schizophrenia: a pooled analysis of late-phase placebo- and active-controlled clinical trials. Int Clin Psychopharmacol 2021;36:244-50.
364. Carbon M, Hsieh C-H, Kane JM et al. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. J Clin Psychiatry 2017;78:20738.
365. Carbon M, Kane JM, Leucht S et al. Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. World Psychiatry 2018;17:330-40.
366. Siafis S, Wu H, Wang D et al. Antipsychotic dose, dopamine D2 receptor occupancy and extrapyramidal side-effects: a systematic review and dose-response meta-analysis. Mol Psychiatry 2023;28:3267-77.
367. Wu H, Siafis S, Wang D et al. Antipsychotic-induced akathisia in adults with acute schizophrenia: a systematic review and dose-response meta-analysis. Eur Neuropsychopharmacol 2023;72:40-9.
368. Pringsheim T, Gardner D, Addington D et al. The assessment and treatment of antipsychotic-induced akathisia. Can J Psychiatry 2018;63:719-29.
369. Furukawa Y, Imai K, Takahashi Y et al. Comparative efficacy and acceptability of treatment strategies for antipsychotic-induced akathisia: a systematic review and network meta-analysis. Schizophr Bull Open 2024;5:sbae098.
370. Gerolymos C, Barazer R, Yon DK et al. Drug efficacy in the treatment of antipsychotic-induced akathisia: a systematic review and network meta-analysis. JAMA Netw Open 2024;7:e241527.
371. Solmi M, Pigato G, Kane JM et al. Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. Drug Des Devel Ther 2018;12:1215-38.
372. Solmi M, Fornaro M, Caiolo S et al. Efficacy and acceptability of pharmacological interventions for tardive dyskinesia in people with schizophrenia or mood disorders: a systematic review and network meta-analysis. Mol Psychiatry 2025;30:1207-22.
373. Montejo ÁL, Arango C, Bernardo M et al. Multidisciplinary consensus on the therapeutic recommendations for iatrogenic hyperprolactinemia secondary to antipsychotics. Front Neuroendocrinol 2017;45:25-34.
374. Holt RIG, Peveler RC. Antipsychotics and hyperprolactinaemia: mechanisms, consequences and management. Clin Endocrinol 2011;74:141-7.
375. Kinon BJ, Gilmore JA, Liu H et al. Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. Psychoneuroendocrinology 2003;28:55-68.
376. Montgomery J, Winterbottom E, Jessani M et al. Prevalence of hyperprolactinemia in schizophrenia: association with typical and atypical antipsychotic treatment. J Clin Psychiatry 2004;65:1491-8.
377. Chen J-X, Su Y-A, Bian Q-T et al. Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: a randomized, double-blind, placebo-controlled, dose-response study. Psychoneuroendocrinology 2015;58:130-40.
378. Solmi M, Lähteenvuo M, Tanskanen A et al. Antipsychotic use and risk of breast cancer in women with severe mental illness: replication of a nationwide nested case-control database study. Schizophr Bull 2024;50:1471-81.
379. Solmi M, Lähteenvuo M, Correll CU et al. Antipsychotic use and risk of low-energy fractures in people with schizophrenia: a nationwide nested case-control study in Finland. Schizophr Bull 2023;49:78-89.
380. Taipale H, Solmi M, Lähteenvuo M et al. Antipsychotic use and risk of breast cancer in women with schizophrenia: a nationwide nested case-control study in Finland. Lancet Psychiatry 2021;8:883-91.
381. Sugawara N, Maruo K, Sugai T et al. Prevalence of underweight in patients with schizophrenia: a meta-analysis. Schizophr Res 2018;195:67-73.
382. Paulson G. Closing the asylums: causes and consequences of the deinstitutionalization movement. Jefferson: McFarland, 2012.
383. Gowda GS, Isaac MK. Models of care of schizophrenia in the community – an international perspective. Curr Psychiatry Rep 2022;24:195-202.
384. Dixon L. Assertive community treatment: twenty-five years of gold. Psychiatr Serv 2000;51:759-65.
385. Maughan D, Molodynski A, Rugkåsa J et al. A systematic review of the effect of community treatment orders on service use. Soc Psychiatry Psychiatr Epidemiol 2014;49:651-63.
386. Kisely S, Yu D, Maehashi S et al. A systematic review and meta-analysis of predictors and outcomes of community treatment orders in Australia and New Zealand. Aust N Z J Psychiatry 2021;55:650-65.
387. Kane JM, Kishimoto T, Correll CU. Assessing the comparative effectiveness of long-acting injectable vs. oral antipsychotic medications in the prevention of relapse provides a case study in comparative effectiveness research in psychiatry. J Clin Epidemiol 2013;66:S37-41.
388. Murphy SM, Irving CB, Adams CE et al. Crisis intervention for people with severe mental illnesses. Cochrane Database Syst Rev 2015;12:CD001087.
389. Glover G, Arts G, Babu KS. Crisis resolution/home treatment teams and psychiatric admission rates in England. Br J Psychiatry 2006;189:441-5.
390. Soldini E, Alippi M, Zufferey MC et al. Effectiveness of crisis resolution home treatment for the management of acute psychiatric crises in Southern Switzerland: a natural experiment based on geography. BMC Psychiatry 2022;22:405.
391. Cornelis J, Barakat A, Blankers M et al. The effectiveness of intensive home treatment as a substitute for hospital admission in acute psychiatric crisis resolution in the Netherlands: a two-centre Zelen double-consent randomised

controlled trial. Lancet Psychiatry 2022;9:625-35.
392. Bechdolf A, Nikolaidis K, von Peter S et al. Utilization of psychiatric hospital services following intensive home treatment: a nonrandomized clinical trial. JAMA Netw Open 2024;7:e2445042.
393. Asher L, Patel V, De Silva MJ. Community-based psychosocial interventions for people with schizophrenia in low and middle-income countries: systematic review and meta-analysis. BMC Psychiatry 2017;17:355.
394. Mroueh L, Ekmekdjian D, Aghekyan E et al. Can a brief training intervention on schizophrenia and depression improve knowledge, attitudes and practices of primary healthcare workers? The experience in Armenia. Asian J Psychiatr 2021;66:102862.
395. Gureje O, Appiah-Poku J, Bello T et al. Effect of collaborative care between traditional and faith healers and primary health-care workers on psychosis outcomes in Nigeria and Ghana (COSIMPO): a cluster randomised controlled trial. Lancet 2020;396:612-22.
396. Thornicroft G, Alem A, Antunes Dos Santos R et al. WPA guidance on steps, obstacles and mistakes to avoid in the implementation of community mental health care. World Psychiatry 2010;9:67-77.
397. Thara R, Patel V. Role of non-governmental organizations in mental health in India. Indian J Psychiatry 2010;52:S389-95.
398. Fusar-Poli P. Extending the benefits of indicated prevention to improve outcomes of first-episode psychosis. JAMA Psychiatry 2017;74:667-8.
399. Johnson S, Dalton-Locke C, Baker J et al. Acute psychiatric care: approaches to increasing the range of services and improving access and quality of care. World Psychiatry 2022;21:220-36.
400. Asher L, Fekadu A, Teferra S et al. "I cry every day and night, I have my son tied in chains": physical restraint of people with schizophrenia in community settings in Ethiopia. Global Health 2017;13:47.
401. Hunt AJ, Guth RE, Setiyawati D. Evaluating the Indonesia Free Pasung Movement: understanding continuing use of restraint of the mentally ill in rural Java. Transcult Psychiatry 2023;60:552-65.
402. World Health Organization. World mental health report: transforming mental health for all. Geneva: World Health Organization, 2022.
403. Barnett BS, Kusunzi V, Magola L et al. Description of the inpatient population and care received at a psychiatric unit in Lilongwe, Malawi. Int J Cult Ment Health 2018;11:574-82.
404. Kwobah KE, Kiptoo SR, Jaguga F et al. Incidents related to safety in mental health facilities in Kenya. BMC Health Serv Res 2023;23:95.
405. Raja T, Tuomainen H, Madan J et al. Psychiatric hospital reform in low-income and middle-income countries Structured Individualised inTervention And Recovery (SITAR): a two-arm pragmatic randomised controlled trial study protocol. BMJ Open 2020;10:e035753.
406. Ma HJ, Zheng YC, Shao Y et al. Status and clinical influencing factors of involuntary admission in Chinese patients with schizophrenia. BMC Psychiatry 2022;22:818.
407. Thara R, Eaton WW. Outcome of schizophrenia: the Madras longitudinal study. Aust N Z J Psychiatry 1996;30:516-22.
408. Galderisi S, Appelbaum PS, Gill N et al. Ethical challenges in contemporary psychiatry: an overview and an appraisal of possible strategies and research needs. World Psychiatry 2024;23:364-86.
409. Funk M, Drew N. WHO QualityRights: transforming mental health services. Lancet Psychiatry 2017;4:826-7.
410. Chadda RK, Sood M. General hospital psychiatry in India: history, scope, and future. Indian J Psychiatry 2018;60:S258-63.
411. World Health Organization. Guidance and technical packages on community mental health services: promoting person-centred and rights-based approaches. Geneva: World Health Organization, 2021.
412. Fortuna KL, Solomon P, Rivera J. An update of peer support/peer provided services underlying processes, benefits, and critical ingredients. Psychiatr Q 2022;93:571-86.
413. Smit D, Miguel C, Vrijsen JN et al. The effectiveness of peer support for individuals with mental illness: systematic review and meta-analysis. Psychol Med 2023;53:5332-41.
414. Kruger E, Hall L, Martinez AP et al. Cognitive behavioral self-help interventions for individuals experiencing psychosis: a systematic review. Psychol Med 2024;54:1-11.
415. Scott AJ, Webb TL, Rowse G. Self-help interventions for psychosis: a meta-analysis. Clin Psychol Rev 2015;39:96-112.
416. Qin K, Yu Y, Cai H et al. Effectiveness of mindfulness-based intervention in schizophrenia: a meta-analysis of randomized controlled trials. Psychiatry Res 2024;334:115808.
417. Chen CR, Lee YW, Chen TT et al. The effects of mindful exercise on cognition in patients with schizophrenia: a systematic review and meta-analysis of randomized controlled trials. Schizophr Res 2024;271:237-45.
418. Sims S, Hepsipa Omega JS, Joseph J et al. Acceptability of peer support for people with schizophrenia in Chennai, India: a cross sectional study amongst people with lived experience, caregivers, and mental health professionals. Front Psychiatry 2022;13:797427.
419. Haun MH, Girit S, Goldfarb Y et al. Mental health workers' perspectives on the implementation of a peer support intervention in five countries: qualitative findings from the UPSIDES study. BMJ Open 2024;14:e081963.
420. Patel V, Chisholm D, Parikh R et al. Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd ed. Lancet 2016;387:1672-85.
421. Ong QS, Yang HZ, Kuek JHL et al. Implementation of peer-support services in Asia: a scoping review. J Psychiatr Ment Health Nurs 2023;30:309-25.
422. Asher L, Birhanu R, Baheretibeb Y et al. "Medical treatments are also part of God's gift": holy water attendants' perspectives on a collaboration between spiritual and psychiatric treatment for mental illness in Ethiopia. Transcult Psychiatry 2021;58:585-99.
423. Campion J, Bhugra D. Experiences of religious healing in psychiatric patients in south India. Soc Psychiatry Psychiatr Epidemiol 1997;32:215-21.
424. Sharma DB, Gupta V, Saxena K et al. Role of faith healers: a barrier or a support system to medical care – a cross sectional study. J Family Med Prim Care 2020;9:4298-304.
425. Kashyap K, Kashyap H. A review of traditional healing methods' efficacy in treating mental disorders. Int J Indian Psychol 2024;12:1060-78.
426. Shi XJ, Fan FC, Liu H et al. Traditional Chinese medicine decoction combined with antipsychotic for chronic schizophrenia treatment: a systematic review and meta-analysis. Front Pharmacol 2020;11:616088.
427. Gureje O, Nortje G, Makanjuola V et al. The role of global traditional and complementary systems of medicine in the treatment of mental health disorders. Lancet Psychiatry 2015;2:168-77.
428. Gyimah L, Ofori-Atta A, Asafo S et al. Seeking healing for a mental illness: understanding the care experiences of service users at a prayer camp in Ghana. J Religion Health 2023;62:1853-71.
429. Ofori-Atta A, Attafuah J, Jack H et al. Joining psychiatric care and faith healing in a prayer camp in Ghana: randomised trial. Br J Psychiatry 2018;212:34-41.
430. Nadine N, Olivier J. Providing mental healthcare through faith-based entities in Africa: a systematic review. Christ J Glob Health 2024;11:148-76.
431. van der Zeijst MCE, Veling W, Chiliza B et al. Traditional and faith-based healthcare in the management of psychotic disorders in Africa: in search for synergy. Curr Opin Psychiatry 2023;36:337-44.
432. Nortje G, Oladeji B, Gureje O et al. Effectiveness of traditional healers in treating mental disorders: a systematic review. Lancet Psychiatry 2016;3:154-70.
433. Morgan C, Thara R, Gureje O et al. Duration of untreated psychosis: a global perspective. World Psychiatry 2025;24:49-50.
434. Cappo D, Mutamba B, Ayesiga K et al. YouBelong Home: a Ugandan community mental health intervention. Community Ment Health J 2023;59:770-83.
435. Asher L, Fekadu A, Hanlon C. Global mental health and schizophrenia. Curr Opin Psychiatry 2018;31:193-9.
436. Brodeur S, Oliver D, Ahmed MS et al. Why we need to pursue both universal and targeted prevention to reduce the incidence of affective and psychotic disorders: systematic review and meta-analysis. Neurosci Biobehav Rev 2024;161:105669.
437. Perälä J, Suvisaari J, Saarni SI et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry 2007;64:19-28.
438. Hall W, Degenhardt L. Cannabis use and the risk of developing a psychotic disorder. World Psychiatry 2008;7:68-71.
439. Oliver D, Chesney E, Cullen AE et al. Exploring causal mechanisms of psychosis risk. Neurosci Biobehav Rev 2024;161:105699.
440. Davies C, Segre G, Estradé A et al. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. Lancet Psychiatry 2020;7:399-410.
441. Meyer U, Yee BK, Feldon J. The neurodevelopmental impact of prenatal infections at different times of pregnancy: the earlier the worse? Neuroscientist 2007;13:241-56.
442. Canetta S, Sourander A, Surcel H-M et al. Elevated maternal C-reactive protein and increased risk of schizophrenia in a national birth cohort. Am J Psychiatry 2014;171:960-8.
443. Cannon M, Clarke MC, Cotter DR. Priming the brain for psychosis: maternal inflammation during fetal development and the risk of later psychiatric disorder. Am J Psychiatry 2014;171:901-5.
444. van den Broek N. Keep it simple – Effective training in obstetrics for low- and middle-income countries. Best Pract Res Clin Obstet Gynaecol 2022;80:25-38.
445. Magro-Malosso ER, Saccone G, Di Tommaso M et al. Exercise during preg-

nancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. Acta Obstet Gynecol Scand 2017;96:921-31.
446. Thangaratinam S, Rogozińska E, Jolly K et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. BMJ 2012;344:e2088.
447. Davenport MH, Ruchat S-M, Poitras VJ et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. Br J Sports Med 2018;52:1367-75.
448. Chan WS, Koren G, Barrera M et al. Neurocognitive development of children following in-utero exposure to labetalol for maternal hypertension: a cohort study using a prospectively collected database. Hypertens Pregnancy 2010;29:271-83.
449. Kintiraki E, Goulis DG. Gestational diabetes mellitus: multi-disciplinary treatment approaches. Metabolism 2018;86:91-101.
450. Jiang L, Tang K, Magee LA et al. A global view of hypertensive disorders and diabetes mellitus during pregnancy. Nat Rev Endocrinol 2022;18:760-75.
451. Saraf R, Morton SM, Camargo CA Jr et al. Global summary of maternal and newborn vitamin D status – a systematic review. Matern Child Nutr 2016;12: 647-68.
452. Safiri S, Kolahi A-A, Noori M et al. Burden of anemia and its underlying causes in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. J Hematol Oncol 2021;14:185.
453. Wulifan JK, Brenner S, Jahn A et al. A scoping review on determinants of unmet need for family planning among women of reproductive age in low and middle income countries. BMC Women's Health 2015;16:1-15.
454. de Bruin O, Phijffer E, Ahmadizar F et al. Are maternal vaccines effective and safe for mothers and infants? A systematic review and meta-analysis of randomised controlled trials. BMJ Global Health 2023;8:e012376.
455. Etti M, Calvert A, Galiza E et al. Maternal vaccination: a review of current evidence and recommendations. Am J Obstet Gynecol 2022;226:459-74.
456. Branco MSS, Altafim ERP, Linhares MBM. Universal intervention to strengthen parenting and prevent child maltreatment: updated systematic review. Trauma Violence Abuse 2022;23:1658-76.
457. Sánchez-Cesáreo M, Sánchez-Cardona I, González-Jiménez C et al. Factores asociados al abuso de menores: resultados de una intervención para el fortalecimiento de prácticas de crianza. Revista Puertorriqueña de Psicología 2018; 29:16-35.
458. Bolhuis K, Koopman-Verhoeff ME, Blanken LME et al. Psychotic-like experiences in pre-adolescence: what precedes the antecedent symptoms of severe mental illness? Acta Psychiatr Scand 2018;138:15-25.
459. Wilkinson RG, Pickett KE. The enemy between us: the psychological and social costs of inequality. Eur J Soc Psychol 2017;47:11-24.
460. Tibber MS, Walji F, Kirkbride JB et al. The association between income inequality and adult mental health at the subnational level – a systematic review. Soc Psychiatry Psychiatr Epidemiol 2022;57:1-24.
461. Burns JK, Tomita A, Kapadia AS. Income inequality and schizophrenia: increased schizophrenia incidence in countries with high levels of income inequality. Int J Soc Psychiatry 2014;60:185-96.
462. Paul KI, Moser K. Unemployment impairs mental health: meta-analyses. J Vocat Behav 2009;74:264-82.
463. Simpson J, Albani V, Bell Z et al. Effects of social security policy reforms on mental health and inequalities: a systematic review of observational studies in high-income countries. Soc Sci Med 2021;272:113717.
464. Thomson RM, Igelström E, Purba AK et al. How do income changes impact on mental health and wellbeing for working-age adults? A systematic review and meta-analysis. Lancet Public Health 2022;7:e515-28.
465. Costello EJ, Compton SN, Keeler G et al. Relationships between poverty and psychopathology: a natural experiment. JAMA 2003;290:2023-9.
466. Hsueh Y-C, Batchelor R, Liebmann M et al. A systematic review of studies describing the effectiveness, acceptability, and potential harms of place-based interventions to address loneliness and mental health problems. Int J Environ Res Public Health 2022;19:4766.
467. South EC, Hohl BC, Kondo MC et al. Effect of greening vacant land on mental health of community-dwelling adults: a cluster randomized trial. JAMA Netw Open 2018;1:e180298.
468. Engemann K, Pedersen CB, Arge L et al. Childhood exposure to green space – A novel risk-decreasing mechanism for schizophrenia? Schizophr Res 2018; 199:142-8.
469. Ward S. How can Asset-Based Community Development (ABCD) contribute to community health and wellbeing? PhD Thesis, University of Glasgow, 2019.
470. Sandel M, Faugno E, Mingo A et al. Neighborhood-level interventions to improve childhood opportunity and lift children out of poverty. Acad Pediatr 2016; 16:S128-35.
471. Shah JL, Malla AK. Much ado about much: stress, dynamic biomarkers and HPA axis dysregulation along the trajectory to psychosis. Schizophr Res 2015; 162:253-60.
472. Petrilli K, Ofori S, Hines L et al. Association of cannabis potency with mental ill health and addiction: a systematic review. Lancet Psychiatry 2022;9:736-50.
473. Kiburi SK, Molebatsi K, Ntlantsana V et al. Cannabis use in adolescence and risk of psychosis: are there factors that moderate this relationship? A systematic review and meta-analysis. Subst Abus 2021;42:527-42.
474. Gruber SA, Sagar KA, Dahlgren MK et al. Age of onset of marijuana use and executive function. Psychol Addict Behav 2012;26:496.
475. Arseneault L, Cannon M, Poulton R et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 2002;325:1212-3.
476. Di Forti M, Quattrone D, Freeman TP et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry 2019;6:427-36.
477. Newton NC, Teesson M, Mather M et al. Universal cannabis outcomes from the Climate and Preventure (CAP) study: a cluster randomised controlled trial. Subst Abuse Treat Prev Policy 2018;13:1-13.
478. Newton NC, Chapman C, Slade T et al. A national effectiveness trial of an eHealth program to prevent alcohol and cannabis misuse: responding to the replication crisis. Psychol Med 2022;52:274-82.
479. Government of Canada. Cannabis regulations for licensed producers. www.canada.ca/en/health-canada.
480. Freeman TP, Lorenzetti V. 'Standard THC units': a proposal to standardize dose across all cannabis products and methods of administration. Addiction 2020;115:1207-16.
481. Fischer B, Russell C, Sabioni P et al. Lower-risk cannabis use guidelines: a comprehensive update of evidence and recommendations. Am J Public Health 2017; 107:e1-12.
482. Gerlinger G, Hauser M, De Hert M et al. Personal stigma in schizophrenia spectrum disorders: a systematic review of prevalence rates, correlates, impact and interventions. World Psychiatry 2013;12:155-64.
483. Gaebel W, Zäske H, Baumann A et al. Evaluation of the German WPA "Program against stigma and discrimination because of schizophrenia - Open the Doors": Results from representative telephone surveys before and after three years of antistigma interventions. Schizophr Res 2008;98:184-93.
484. González-Sanguino C, Potts LC, Milenova M et al. Time to Change's social marketing campaign for a new target population: results from 2017 to 2019. BMC Psychiatry 2019;19:417.
485. World Health Organization. Preventing suicide: a resource for media professionals. Geneva: World Health Organization, 2023.
486. Fusar-Poli P, Esposito CM, Estradé A et al. The lived experience of persons who attempt suicide: a bottom-up review co-designed, co-produced and co-written by experts by experience and academics. World Psychiatry 2024;22:352-65.
487. Fusar-Poli P, Sunkel C, Patel V. Associating violence with schizophrenia – risks and biases. JAMA Psychiatry 2022;79:738-9.
488. Nordt C, Rössler W, Lauber C. Attitudes of mental health professionals toward people with schizophrenia and major depression. Schizophr Bull 2006;32:709 - 14.
489. Islam Z, Rabiee F, Singh SP. Black and minority ethnic groups' perception and experience of early intervention in psychosis services in the United Kingdom. J Cross-Cult Psychol 2015;46:737-53.
490. Barnett P, Mackay E, Matthews H et al. Ethnic variations in compulsory detention under the Mental Health Act: a systematic review and meta-analysis of international data. Lancet Psychiatry 2019;6:305-17.
491. Mongelli F, Georgakopoulos P, Pato MT. Challenges and opportunities to meet the mental health needs of underserved and disenfranchised populations in the United States. Focus 2020;18:16-24.
492. Ballard T, Campinha-Bacote J. Cultural competemility training and use of a standardized assessment tool in reducing misdiagnosis of Black patients with schizophrenia spectrum disorders and psychotic disorders. J Am Psychiatr Nurses Assoc 2025;31:306-12.
493. Moe AM, Llamocca E, Wastler HM et al. Racial and ethnic disparities in the diagnosis and early treatment of first-episode psychosis. Schizophr Bull Open 2024;5:sgae019.
494. de Jong MH, Kamperman AM, Oorschot M et al. Interventions to reduce compulsory psychiatric admissions: a systematic review and meta-analysis. JAMA Psychiatry 2016;73:657-64.
495. Swartz MS, Swanson JW. Psychiatric advance directives: challenges emerging from implementation and possible steps forward. World Psychiatry 2026; 25:145-6.
496. Dalal M. Barriers to mental health care in Africa. www.afro.who.int.
497. James BO, Thomas FI, Seb-Akahomen OJ et al. Barriers to care among people

with schizophrenia attending a tertiary psychiatric hospital in Nigeria. S Afr J Psychiatry 2019;25:1392.
498. Voz Pro Salud Mental México. Solos somos invisibles, unidos somos invencibles. www.vozprosaludmental.org.mx.
499. Rodríguez MS, Saracco RA. El complejo estigma-discriminación en psiquiatría: una visión desde la clínica Latinoamericana. México: Asociación Mexicana de Médicos Psiquiatras, 2024.
500. Hailemariam M, Fekadu A, Prince M et al. Engaging and staying engaged: a phenomenological study of barriers to equitable access to mental healthcare for people with severe mental disorders in a rural African setting. Int J Equity Health 2017;16:156.
501. Asher L, Fekadu A, Hanlon C et al. Development of a community-based rehabilitation intervention for people with schizophrenia in Ethiopia. PLoS One 2015;10:e0143572.
502. Hailemariam M, Ghebrehiwet S, Baul T et al. "He can send her to her parents": the interaction between marriageability, gender and serious mental illness in rural Ethiopia. BMC Psychiatry 2019;19:315.
503. Naamara W, Twesigye J, Mutamba BB et al. Family caregivers' perceptions of schizophrenia and community members' attitudes toward patients and their family caregivers. Soc Work Public Health 2025;40:102-18.
504. Kihumuro RB, Kaggwa MM, Kintu TM et al. Knowledge, attitude and perceptions of medical students towards mental health in a university in Uganda. BMC Med Educ 2022;22:730.
505. Fekih-Romdhane F, Fayhaa H, Haitham J et al. Attitudes toward schizophrenia among Tunisian family medicine residents and non-medical students. Psychosis 2023;15:168-80.
506. Kohrt BA, Jordans MJD, Turner EL et al. Collaboration with people with lived experience of mental illness to reduce stigma and improve primary care services: a pilot cluster randomized clinical trial. JAMA Netw Open 2021;4:e2131475.
507. Fadele K, Ayuba D, Igwe S et al. Addressing mental health in Africa: integrating mental health first aid. Authorea, November 21, 2024.
508. Chisholm D, Docrat S, Abdulmalik J et al. Mental health financing challenges, opportunities and strategies in low- and middle-income countries: findings from the Emerald project. BJPsych Open 2019;5:e68.
509. Abayneh S, Lempp H, Rai S et al. Empowerment training to support service user involvement in mental health system strengthening in rural Ethiopia: a mixed-methods pilot study. BMC Health Serv Res 2022;22:880.
510. World Health Organization. The World Health Organization Assessment Instrument for Mental Health Systems (WHO-AIMS). Geneva: World Health Organization, 2005.
511. Lund C, Orkin K, Witte M et al. The effects of mental health interventions on labor market outcomes in low- and middle-income countries. Cambridge: National Bureau of Economic Research, 2024.
512. Burns JK, Tomita A. Traditional and religious healers in the pathway to care for people with mental disorders in Africa: a systematic review and meta-analysis. Soc Psychiatry Psychiatr Epidemiol 2015;50:867-77.
513. Kaggwa MM, Harms S, Mamun MA. Mental health care in Uganda. Lancet Psychiatry 2022;9:766-7.
514. Chibanda D, Abas M, Musesengwa R et al. Mental health research capacity building in sub-Saharan Africa: the African Mental Health Research Initiative. Glob Ment Health 2020;7:e8.
515. Mamah D, Mutiso V, Musyimi C et al. Kenya Psychosis-Risk Outcomes Study (KePROS): development of an Accelerated Medicine Partnership Schizophrenia-aligned project in Africa. Schizophr Bull Open 2024;5:sgae009.
516. Bhogal J, Singh SP, Chadda R et al. An analysis of financial hardship faced by patients with first episode psychosis, and their families, in an Indian setting. Asian J Psychiatr 2024;97:104066.
517. Malinowski F, Noto C, Cavalcante D et al. Urban distance to mental healthcare units and public transport increases duration of untreated psychosis in first-episode patients. Int J Soc Psychiatry 2023;69:1938-48.
518. Wootton O, King A, Moy K et al. Disability benefits protect against lost income for South Africans living with schizophrenia. Soc Psychiatry Psychiatr Epidemiol 2024;59:1279-83.

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What does it take to make real-world changes in schizophrenia care?

Fusar-Poli et al[1] present a thorough and compelling review of evidence for high-quality treatment of schizophrenia across stages and care settings. The paper makes a strong case for early, continuous and integrated approaches to care and, importantly, addresses low- and middle-income as well as high-income countries. The review synthesizes decades of research into a coherent model of comprehensive care, emphasizing early intervention, continuity between inpatient and community services, multidisciplinary teamwork, and active family involvement, with recovery as the ultimate goal.

Psychiatry has an abundance of evidence, although the vast majority stems from research in high-income countries. High-quality randomized controlled trials, systematic reviews and meta-analyses consistently show the benefits of coordinated specialty care, individual placement and support, assertive community treatment, antipsychotic medication, and family psychoeducation. Early intervention for psychosis has one of the strongest evidence bases of all psychiatric interventions[2]. Cost-effectiveness studies indicate that these services are not only clinically beneficial, but financially justifiable[3]. Yet, service coverage remains far below need. In many high-income countries, only a minority of people with first-episode psychosis can access specialized services. In low- and middle-income countries, the treatment gap is even more profound, compounded by a severe shortage of psychiatrists, psychologists and other trained professionals.

The problem of insufficient workforce capacity should not be underestimated. Scaling up services requires both increasing the number of skilled staff and ensuring the availability of essential antipsychotic medication. In low-resource countries, task-sharing has been promoted as one of the possibilities to use to remediate lack of specialized staff.

Fusar-Poli et al's paper consolidates that quality of schizophrenia care can be improved when provided early, consistently and collaboratively. Some of these recommendations already appear in national and international guidelines. Yet, the gap between what we know and what we deliver is striking. In fact, the World Health Organization estimates that around 90% of patients with schizophrenia in low-resource countries receive no treatment at all[4]. In high-income countries, the question is no longer what works. It is how to make it work in practice. What does it take to move from persuasive publications to genuine, large-scale changes in real-world care?

Evidence alone does not drive implementation. The psychiatric field sometimes assumes that robust trials and meta-analyses will automatically lead to system change, but the reality is more complex. Evidence is necessary, but insufficient. We already have valuable tools that can support the translation of evidence into practice. Clinical guidelines, together with health economic analyses, provide legitimacy and a shared framework for service development. Fidelity measures and quality indicators help ensure that interventions are delivered as intended, creating benchmarks for policy makers and funders. Epidemiological studies highlight the scale of the problem and clarify the long-term consequences of untreated psychosis for individuals and families. These resources are important. They strengthen the case for investment. But, despite them, large-scale change remains elusive.

If evidence and guidelines are not enough, what more is needed? One essential element is reducing stigma. Schizophrenia remains one of the most misunderstood and stigmatized health conditions. As long as it is associated primarily with danger, chronic disability, or hopelessness, mental health services will struggle to attract sustained funding and political commitment. Tackling stigma is therefore not only an ethical obligation, but also a practical prerequisite for service development. This requires changing public narratives. Numbers and cost-effectiveness arguments are not sufficient; personal stories are needed to shift opinion. When patients and families speak openly about their experiences, about both the hardships and the possibilities of recovery, they humanize the condition and change the terms of debate. Visibility is political. Only if schizophrenia is seen as a treatable condition with potential for recovery, it will compete successfully for public attention and resources.

Another challenge lies in overlooked risk groups. Substance-induced psychosis is often neglected in service planning, yet it has the highest transition rate to schizophrenia among all identified risk states[5]. Among substances, cannabis deserves particular attention: it is now well established as a significant risk factor for schizophrenia[6], especially in young people[7]. Addressing these risk factors must become part of public health and prevention strategies, complementing efforts to expand early intervention services.

Real-world change also requires building coalitions. Change does not occur through the efforts of clinicians or researchers alone. It requires alliances between patients, families, non-governmental organizations (NGOs), professional organizations, and policy makers. NGOs can mobilize awareness campaigns and hold governments accountable. Professional associations can develop training programs and practical implementation tools. Academic institutions can generate real-world evidence and ensure that the next generation of mental health professionals are trained in recovery-oriented models of care. Most importantly, patients and families must become active partners in shaping services rather than passive recipients. Power-sharing in service design and decision-making is crucial for legitimacy and sustainability.

Political leadership is another decisive factor. Evidence-based services do not arise spontaneously; they require prioritization. Governments must commit to allocating resources, developing workforce capacity, and building infrastructure[8]. National early intervention programs in Australia, UK and Denmark show what is possible when political will is present[9]. In low- and middle-income countries, innovative strategies such as task-shifting, use of community health workers, and digital technologies can expand access to care despite scarce resources. These examples demonstrate that, while one universal model may not exist, principles of effective care can be adapted to different contexts. What matters most is the

commitment to make it happen.

Even with these elements in place, change is rarely straightforward. Services require persistence and resilience to be sustained. Early intervention programs, once established, must guard against erosion of fidelity, workforce shortages, and funding cuts. Implementation is an ongoing process rather than a one-off achievement. Every year without adequate services means more young people developing psychosis without timely support, more families facing crises alone, and more lives limited by preventable disability.

If we believe, as the evidence shows, that schizophrenia is treatable and outcomes can be transformed, then failure to act is not just a missed opportunity, but a social and moral failure. Fatigue is a risk, but persistence is an obligation. The review by Fusar-Poli et al offers us a map. But a map only becomes useful when someone builds the road. That responsibility lies with all of us: clinicians, researchers, policy makers, patients, and communities. Real-world change in schizophrenia care will never come from evidence alone. It requires visibility, public engagement, leadership, sustained investment, and above all, collective will.

What it takes to make real-world change is not only good science but determination, shared across disciplines and stakeholders, to ensure that the interventions we know to be effective become available to all who need them. The work ahead is difficult, but not impossible. The next step is to make sure that the roadmap laid out in this important review does not remain on paper, but becomes a living guide to action in health systems worldwide.

Merete Nordentoft
Copenhagen Research Center for Mental Health, Copenhagen University Hospital, Copenhagen, Denmark

1. Fusar-Poli P, Pillinger T, McCutcheon RA et al. World Psychiatry 2026;25:231-64.
2. Correll CU, Galling B, Pawar A et al. JAMA Psychiatry 2018;75:555-65.
3. Hastrup LH, Kronborg C, Bertelsen M et al. Br J Psychiatry 2013;202:35-41.
4. Lora A, Kohn R, Levav I et al. Bull World Health Organ 2012;90:47-54B.
5. Starzer MSK, Nordentoft M, Hjorthøj C. Am J Psychiatry 2018;175:343-50.
6. Hjorthøj C, Posselt CM, Nordentoft M. JAMA Psychiatry 2021;78:1013-9.
7. McDonald AJ, Kurdyak P, Rehm J et al. Psychol Med 2024;54:2926-36.
8. Nordentoft M, Rasmussen M, Høgh L et al. Eur Psychiatry 2023;66:e68.
9. Nordentoft M, Melau M, Iversen T et al. Early Interv Psychiatry 2015;9:156-62.

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An excitement building in the development of psychological treatments for schizophrenia

Evidence-based care is a wise recommendation by Fusar-Poli et al[1]. In the case of psychological therapies for schizophrenia, the evidence base is evolving rapidly – and in a highly promising fashion. Recent years have brought a transformation in the psychological understanding of psychosis. New mechanisms to target in treatment have been identified. An impressive range of psychological techniques focusing on those mechanisms has been – and continues to be – tested. In addition, key insights from the successful treatment of other mental health conditions are being adapted and applied.

Amid such diverse activity, the scholarly task is to avoid homogenizing psychological interventions that target different factors in psychosis (and in different ways). Instead, we need to find the true signals in the noise. Those signals are auspicious. We now have at our disposal a number of psychological therapies that produce larger benefits than the pioneering first-generation approaches. We are discovering how to help many more patients with schizophrenia.

Recent theory-driven psychological therapies have shown very large treatment effects. Critically, their mechanistic targets are tractable, and sufficiently important for meaningful change in psychosis to result. A key example is the Feeling Safe programme, whose clinical focus is the most common psychotic experience: persecutory delusions. Underpinning this treatment are three theoretical insights[2]. First, persecutory delusions are inaccurate threat beliefs. Second, their impact can be diminished by developing a counterweight belief that the person is safe now. The new belief is generated through direct experience of situations that the person finds difficult. Third, establishing such a safety belief is easier if one first tackles any blocking problems (e.g., worry, negative self-beliefs, sleep disruption). Patients are then in a psychological position to discover that they are safe enough to do the things that they want to do. This approach recognizes that directly challenging delusions is rarely successful. Instead, change happens when a counterweight belief is embedded. Initially, the new belief coexists with the delusion. Over time, however, the scales can tip decisively in favour of the counterweight. The effects of the Feeling Safe programme are very large[3], with half of patients recovering from persistent delusions. The effect sizes are considerable even above the provision of alternative psychological therapy.

Psychological theorists have long highlighted the role that trauma, especially via post-traumatic stress disorder (PTSD), can play in psychosis. Most obviously, if others have treated you badly, the self may seem vulnerable and others potentially hostile. Intrusive memories may keep a sense of threat alive, which then contributes to the occurrence of persecutory ideas. This insight from psychological theories of PTSD is increasingly being applied to schizophrenia treatment. Evidence-based therapies for PTSD (prolonged exposure, eye movement desensitization and reprocessing, trauma-focused cognitive behavior therapy) have been shown to work well with patients with schizophrenia[4,5]. Their PTSD is substantially reduced – a significant benefit in and of itself. But we also see moderate reductions in persecutory delusions.

Intriguing new psychological methods are also being trialled. Emerging from the hearing voices movement, Talking with Voices[6] highlights the role of trauma in both causing and influencing the

content of voices. Voices are seen as meaningful products of unresolved distress. In this 26-session intervention, therapist and patient work to understand the voices, especially the challenges they embody, and directly engage with them to develop a more peaceful relationship (of course, patients must be willing and able to dialogue with their voices). The primary clinical target is improving personal recovery. A successful pilot trial has led to a new multicentre randomized controlled trial (ISRCTN15897915) with three hundred patients.

Many other psychological treatments targeting single causes of psychotic experiences are currently being evaluated. These include treatments for sleep and circadian rhythm difficulties, reasoning biases, negative self-beliefs, and negative imagery.

Then there is the host of new digital psychological approaches being developed and trialled. Most of them exploit the advantages of particular technologies to maximize clinical efficacy and accessibility (while mitigating potential disadvantages). For example, Feeling Safer is a highly promising supported six-month online programme that expands the content and accessibility of face-to-face psychological therapy for persecutory delusions[7]. It is available on all screen sizes, from desktops to mobile phones.

SloMo is a digitally supported cognitive behavioral intervention that targets reasoning biases in eight individual, face-to-face sessions. It has shown small to moderate effects in reducing paranoia [8]. In avatar therapy, patients practise responding to a computer-generated representation of their voices in order to build feelings of power and control. Trials of various avatar therapies, delivered over six or twelve sessions, show small to moderate benefits in reducing distress caused by voices.

The list of digital therapies does not end there. Many virtual reality-based treatments for psychosis consistently deliver encouraging results. The range of their targets is wide, including paranoia, hallucinations, agoraphobic avoidance, and psychological wellbeing. Digital innovations, including the use of artificial intelligence, will undoubtedly form a larger part of the evidence base in coming years.

Fusar-Poli et al are right to highlight the importance of measurement-based monitoring. Provided the information collected is meaningful for patient and clinician, measurement-based care can drive real improvement in service provision. With regular review of the data, we can monitor the success of an intervention and judge whether changes are needed. Analysis at aggregate service level can show how outcomes compare both to benchmarks and similar psychosis services.

Measurement is an integral feature of the best psychological treatments, with information collected at every session and reviewed during weekly supervision. We have also used session-by-session data to map the typical trajectories of patients with psychosis receiving specialist psychological therapy, and understand who may benefit most (or least) from a particular treatment[9]. Such work also provides a reminder that the average effects of treatments reported in clinical trials often obscure the variation in individual responses.

Schizophrenia's presentations, causes and treatment are complex. Understanding this complexity, and applying it to the evidence base, is key to ensuring that the recommended psychological interventions are also the most efficacious. First, the umbrella diagnosis of schizophrenia encompasses many independent psychotic experiences, plus of course a range of emotional, occupational and social outcomes. This means that multiple treatment targets are in play, with much variation between individuals. We must read the evidence base with this in mind, being sensitive to specific outcome targets.

Second, causation is clearly multi-factorial and will vary to a degree by outcome target. Psychological treatments differ in the causal mechanisms they target. We must bring this insight to bear when examining the evidence base, and understand the wider literature on the importance of a mechanistic target. It can also be illuminating to consider mediation tests within clinical evaluations. Did the intervention affect the targeted mechanism? Was this associated with a changed outcome? If so, to what extent? Given the complexity of causation, treatments that target a single mechanism are unlikely to be sufficient. But they may be immensely helpful as part of a more comprehensive approach.

Third, psychological treatments can vary enormously in terms of factors such as length, intensity, staff type and training, adherence and competence, degree of personalization and patient choice, and the stage in the patient journey at which they are offered. This variation must be taken into account when evaluating interventions. Offering the right treatment, in the right way, at the right time for a patient can make a huge difference in efficacy.

The development of psychological treatments for psychosis is not static. On the contrary, things are continually evolving – and in ways that provide real grounds for optimism. Making sense of the evidence demands that we are alert to its contexts: the variety and complexity of patient presentations, theoretical models, and treatment methods. But there is no doubt that, in regard to psychological interventions for patients diagnosed with schizophrenia, there is much to be excited about.

Daniel Freeman
Department of Experimental Psychology, University of Oxford, Oxford, UK

1. Fusar-Poli P, Pillinger T, McCutcheon RA et al. World Psychiatry 2026;25:231-64.
2. Freeman D, Isham L, Waite F. Psychol Med 2025;55:e141.
3. Freeman D, Emsley R, Diamond R et al. Lancet Psychiatry 2021;8:696-707.
4. De Bont PAJM, Van Den Berg DPG, Van Der Vleugel BM et al. Psychol Med 2016;46:2411-21.
5. Peters E, Hardy A, Dudley R et al. Trials 2022;23:429.
6. Longden E, Corstens D, Bowe S et al. Schizophr Res 2022;250:172-9.
7. Freeman D, Isham L, Freeman J et al. Psychol Med 2025;55:e179.
8. Hardy A, Taylor KM, Grant A et al. Schizophr Res 2024;274:526-34.
9. Jenner L, Payne M, Waite F et al. Psychol Med 2024;54:4173-81.

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Moving on from the illusion of prevention towards effective prevention of psychosis

As one would expect from the first author, there is much to admire about the introductory paper of this Forum[1]. P. Fusar-Poli has assembled an impressive panel of co-authors to review the treatment of schizophrenia-like psychosis. The authors emphasize their commitment to evidence-based approaches to treatment, and to fostering hope with a recovery-based approach rather than the pessimistic Kraepelinian notion that schizophrenia is a progressive disease[2]. If the recommendations of this paper were implemented, then the lives of many psychotic patients and their relatives would be improved, particularly in low- and middle-income countries.

The only problem with this paper lies in its advocacy of services for patients at "clinical high risk for psychosis" (CHR-P), which the authors consider an early stage of schizophrenia. Yet, as the paper indicates, people attending specialized CHR-P services have only about a 20% chance of developing psychosis in the subsequent two years. Furthermore, the North American Prodrome Longitudinal Study (NAPLS) Consortium – which recently reported the largest follow-up of patients with CHR-P – showed that, among the minority who developed psychosis, 56% were diagnosed as having an affective psychosis and only 32% schizophrenia. It was concluded that "although it is tempting to model CHR-P as on a continuum with schizophrenia, a better conceptualization is to perhaps view this population as pluripotent and at risk for mental health problems in general"[3]. Thus, the CHR-P state cannot be regarded as an early stage of schizophrenia.

Furthermore, in considering the care of people with CHR-P, the authors seem to forget their commitment to recommend only treatments of proven value. In fact, as they point out, a Cochrane review[4] reported that no intervention for individuals with CHR-P has been shown to be effective in preventing transition to psychosis. In addition, studies examining the functioning of two of the best established prodromal clinics have shown that only a tiny proportion of patients who develop a first onset of psychosis have ever presented with the "at risk mental state" to the local prodromal clinic (4% in South London[5] and 7% in Melbourne[6]). In short, the CHR-P approach is ineffective and reaches only a minority of its target population. There is no economic argument supporting the investment of extra resources for specific CHR-P services, or indeed the transfer of scarce resources from treating patients with chronic psychosis to attempting to prevent the development of frank psychosis in CHR-P cases.

Cardiologists have long realized that the most effective way to prevent coronary artery disease is to move upstream to detect individuals with predisposing conditions (e.g., hypertension, diabetes mellitus, high cholesterol) or unhealthy lifestyles (e.g., smoking tobacco, eating junk food, or taking insufficient exercise). We need to follow the cardiologists' lead and identify candidates for selected prevention in childhood or adolescence, such as individuals with subclinical psychotic experiences, developmental delays, psychological and behavioral problems, or family history of mental illness. We need large-scale trials to assess the value of intervening in children with a combination of these risk factors. In the meantime, pioneering work has shown that children who are referred to child psychiatry departments have a much increased risk of later psychosis, and thus should be carefully followed up and monitored for early signs of psychosis[7].

Fusar-Poli et al outline the potential of population-level prevention by avoiding exposure to factors known to increase risk of psychosis. They point out that raising the standard of pre-and perinatal care will in the long-run reduce the number of individuals neurodevelopmentally impaired as a result of early hazards such as prematurity or perinatal hypoxia/infection. In the shorter term, it would pay dividends to ensure that mothers with established psychosis get effective care in pregnancy and labour, to avoid subtle damage to the brains of babies already carrying significant genetic risk.

The paper also raises the possibility of decreasing exposure to child abuse and to inequality and discrimination, factors known to increase risk of psychosis. In a previous visionary paper in this journal, Fusar-Poli et al[8] discussed the possibility of addressing the psychotogenic environment to which many children are exposed, and outlined "public health approaches targeting school climate or social determinants (demographic, economic, neighborhood, environmental, social/cultural) of mental disorders". These are admirable long-term goals to which we should strive. Sadly, supporting positive parenting, and reducing poverty and income inequality, or even re-engineering our cities to be less toxic to the developing mind, is currently beyond the reach of those of us concerned with psychoses.

Fusar-Poli et al consider but do not stress the most pressing issue in the prevention of psychosis, which is the urgent need to address the increasing recreational use of psychotogenic drugs. For psychosis, the most important are methamphetamine and cannabis. Methamphetamine psychosis has spread sequentially from Japan, Taiwan and the Pacific countries to Australia, South Africa, and then across North America from West to East. In some of these settings, it is a plague responsible for 25% of all cases of psychosis. Sadly, it now also being seen in Europe and the Middle East.

The more widespread rise in schizophrenia-like psychosis induced by heavy cannabis use has been facilitated by the worldwide trend towards normalizing cannabis use[9]. The incidence of psychosis across Europe is strongly correlated with the prevalence of use of high-potency cannabis in the local communities. Overall, 12% of new cases of psychosis would be prevented if no one smoked high-potency cannabis (>10% tetrahydrocannabinol, THC), and this proportion reaches 30% and 50% in London and Amsterdam, respectively. Similar findings have been reported from the Global South: the incidence of psychosis is low in rural India and in Nigeria, but much higher in Trinidad, where the use of highly potent cannabis (25% THC) is legal and endemic. As the use of cannabis

and its potency rises, so does the incidence of schizophrenia. This has been particularly demonstrated in Denmark, with its high-quality national registers, and in Canada, where cannabis-induced psychosis has trebled since so-called medicinal cannabis (often recreational use in disguise) was legalized in 2001[9].

Fusar-Poli et al point to the inadequacy of funds for the optimal care of psychotic people, particularly in low- and middle-income countries, and propose some innovative strategies for persuading reluctant governments to allocate additional funds for the treatment of individuals with psychosis. They make a very good case for such spending through their wide-ranging and sensible recommendations regarding the care of patients who have developed psychosis. Regarding prevention, they need to take their own advice and present universal population approaches to governments and other funders[8].

In conclusion, there is a widespread concern about the rising mental health problems in young people, with many factors – from social media to climate change – being blamed. However, unless we can reverse the worldwide increase in use of psychotogenic drugs, we are likely to see further increase in schizophrenia-like psychoses in the young. It is time for psychiatrists to speak up about the risks to mental health of heavy use of cannabis and other psychotogenic drugs. Public health campaigns about these risks will provide an avenue towards stemming the rise and enabling mental health services to provide better care for the remainder of patients with psychosis.

Robin M. Murray
Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

1. Fusar-Poli P, Pillinger T, McCutcheon RA et al. World Psychiatry 2026;25:231-64.
2. Murray RM, Bora E, Modinos G et al. Schizophr Res 2022;243:181-6.
3. Cadenhead KS, Kennedy H, Mirzakhanian et al. Schizophr Bull 2025; doi: 10.1093/schbul/sbaf133.
4. Bosnjak Kuharic D, Kekin I, Hew J et al. Cochrane Database Syst Rev 2019;11:CD012236.
5. Ajnakina O, Morgan C, Gayer-Anderson C et al. BMC Psychiatry 2017;17:308.
6. Burke T, Thompson A, Mifsud N et al. Schizophr Res 2022;241:94-101.
7. Leppanen J, Kieseppa V, Eskelinen S et al. Psychiatry Res 2025;351:116606.
8. Fusar Poli P, Correll C, Arango C et al. World Psychiatry 2021;20:200-21.
9. Murray RM, Paparelli A, Di Forti M et al. Neuropsychiatr 2025; doi: 10.1007/s40211-025-00541-7.

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Comprehensive care for schizophrenia: smart choices by clinicians can make a huge difference, even when resources are limited

The recommendations by Fusar-Poli et al[1] for a global approach to treating schizophrenia represent a comprehensive, pragmatic and – as far as the evidence allows – well-founded framework for improving outcomes across diverse clinical settings. The need for such recommendations is compelling. Despite considerable advances in our understanding and treatment of schizophrenia over the past several decades, the translation of these advances into tangible improvements in clinical care has consistently lagged behind scientific progress[2].

Even in well-resourced settings, treatment outcomes often fall short of their potential, due to inconsistent application of best practices, inadequate service integration, and persistent system-level inefficiencies. There remains a large and preventable gap between what is known to be effective and what is actually implemented in routine care[3]. More could be achieved by applying available interventions more judiciously, using resources efficiently, and ensuring that clinicians are well trained and supported to deliver evidence-based care.

The challenge is greater in settings where resources are limited. Regrettably, this applies to the majority of people with schizophrenia, who live in low- and middle-income countries, where health care services are sub-optimal and, in extreme cases, the treatment gap may be as high as 90%[4]. Most of these people do not have access to expensive, novel pharmacological agents or to individualized psychosocial interventions delivered by highly specialized clinicians[5]. Yet, schizophrenia can be effectively treated in most contexts – even in poorly resourced communities – if the available resources are used strategically, services are organized around patient needs, and families and communities are engaged as partners in care.

In contrast to certain medical specialties where access to recent treatment developments dramatically alters prognosis – oncology being a prime example, with immunotherapy and targeted therapies transforming survival in some cancers – the advances in schizophrenia treatment have been incremental rather than revolutionary[6]. Despite initial optimism, the introduction of new-generation antipsychotics has not met expectations. While they have offered improvements in side effect profiles, their overall efficacy remains broadly similar to that of first-generation drugs[7]. In low- and middle-income settings, available antipsychotic treatment is often limited to the older, inexpensive agents. Nevertheless, some of these are relatively well tolerated, and prescribing them at the lowest effective dose helps to mitigate side effects. Also, optimizing medication adherence is critically important: treatments are only effective when taken as intended.

Among modifiable determinants of outcome, treatment adherence is the most important. Non-adherence is strongly associated with relapse, suicide risk, and functional decline. Long-acting injectable (LAI) formulations are particularly useful in this context, as they ensure medication delivery and facilitate regular clinical contact. The ongoing under-utilization of these formulations is puzzling, and frequently stems from misperceptions held by both service users and providers.

The benefits of LAIs are best seen when used in early illness – when non-adherence is especially common, the illness is most aggressive, and the risk of severe relapses is greatest. Relapse prevention in the early years of illness should be prioritized by clinicians. The psychosocial consequences of illness recurrence in young people recovering from a first episode of schizophrenia cannot be overstated. The negative impact on aspects of daily living such as interrupted education, broken relationships and loss of personal autonomy may be devastating. In addition, relapses have been associated with illness progression in the form of accruing morbidity and emergent treatment failure[8].

While LAIs on their own do not ensure treatment adherence, their great advantage is that they provide transparency: when an individual misses an injection, non-adherence is immediately apparent, enabling clinicians to respond quickly with supportive interventions before relapse occurs. This highlights the importance of well-organized community services to provide continuity of care and proactive follow-up. Comprehensive, multidisciplinary services are desirable, but they are not always affordable. Nonetheless, even modestly resourced services – when combined with strategic use of LAIs and a system of monitoring and outreach led by trained nurses or community health workers – can make an enormous difference. Such an approach, as demonstrated in an African setting, has been shown to be a cost-efficient method of reducing relapse and rehospitalization rates and enabling sustained remission in first-episode schizophrenia[9].

While antipsychotic medication represents the cornerstone of treatment for schizophrenia, psychosocial interventions are a necessary component of comprehensive, patient-centred care. Although resource-intensive in their most developed forms, elements of these approaches can often be adapted to low-resource settings. For example, structured family education delivered by trained lay workers, peer-led recovery groups, and community-based rehabilitation programmes have been successfully implemented in low- and middle-income countries at relatively low cost. Engaging caregivers not only improves treatment outcomes, but also reduces their burden and stigma, thereby strengthening the social support system that is critical for recovery.

Stigma remains a formidable barrier to care worldwide. In many communities, schizophrenia is poorly understood, associated with shame, and surrounded by misconceptions that discourage help-seeking. Clinicians, therefore, have a duty not only to treat but also to educate. The provision of psychoeducation to patients, families and communities can have transformative effects, fostering earlier help-seeking and better engagement with care. Partnerships with schools, workplaces, and faith-based organizations can extend the reach of such interventions, promoting inclusion and reducing discrimination.

While focusing on improvement of clinical care in daily practice is a priority, psychiatry should also play a broader role. One of the most fundamental systemic challenges highlighted by Fusar-Poli et al is the chronic underfunding of mental health services. Globally, mental health accounts for less than 2% of government health budgets on average, despite mental disorders contributing to 14% of the global burden of disease[5]. In low-income countries, the proportion is often far smaller. The consequences of this funding gap are stark: limited service coverage, inadequate staffing, poor access to essential medicines, and near-total absence of structured psychosocial rehabilitation programmes. Scaling up investment in mental health is not only an ethical imperative, but also a cost-effective endeavour. Evidence suggests that investment in early detection, community-based care, and adherence support would yield substantial long-term savings, by reducing hospitalizations and improving functional recovery.

In addition to lobbying for more equitable budgetary allocations to mental health, psychiatry should play a prominent role in addressing the broader structural inequities that shape general health outcomes. The global disparities in access to psychiatric care, housing, education, and social inclusion mirror wider injustices in general health care and human rights. If we are to play a role as guardians of the humane aspects of medicine, we should be at the forefront of advocating for equitable health care. This involves engaging with policy, partnering with communities, and working across sectors to tackle the social determinants of mental and general health. It also requires embedding the voices of people with lived experience in every stage of service design, implementation and evaluation.

Fusar-Poli et al's recommendations offer a global blueprint for comprehensive care in schizophrenia. Their pragmatic orientation – grounded in evidence but attentive to real-world constraints – makes them particularly relevant for resource-constrained settings, where the majority of people with schizophrenia live and where the treatment gap remains largest. Once again, the challenge will be to translate these recommendations into practice, ensuring that evidence is not confined to academic journals, but is implemented in real world clinical care.

Robin Emsley
Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

1. Fusar-Poli P, Pillinger T, McCutcheon RA et al. World Psychiatry 2026;25:231-64.
2. Patel V, Saxena S, Lund C et al. Lancet 2018;392:1553-98.
3. Khorikian-Ghazari N, Lorenz C, Güler D et al. Eur Arch Psychiatry Clin Neurosci 2023;273:1587.
4. Charlson FJ, Ferrari AJ, Santomauro DF et al. Schizophr Bull 2018;44:1195-203.
5. World Health Organization. Schizophrenia. www.who.int.
6. Stein DJ, Shoptaw SJ, Vigo DV et al. World Psychiatry 2022;21:393-414.
7. Huhn M, Nikolakopoulou A, Schneider-Thoma J et al. Lancet 2019;394:939-51.
8. Emsley R, Chiliza B, Asmal L et al. BMC Psychiatry 2013;13:50.
9. Chiliza B, Ojagbemi A, Esan O et al. Early Interv Psychiatry 2016;10:54-62.

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Taking care of psychotic disorders globally, beyond clinical management

Fusar-Poli et al[1] provide recommendations for management of different phases of schizophrenia in a global context, based on accumulated evidence and experience. This is indeed timely, especially when contextualized to local economic, cultural and social circumstances. Here I will highlight a few key issues, particularly in the context of low- and middle- vs. high-income environments, and offer some additional recommendations.

Management of schizophrenia, as the authors point out, must involve more than symptom control and be focused on recovery. Even for symptom outcomes, pharmacotherapy – while invariably essential – achieves its maximum impact when combined with psychological and psychosocial interventions.

Within the broader array of therapeutic resources, the impact of family intervention needs to be highlighted and not simply described as "family support" activities. Despite a large number of controlled trials having demonstrated the significant impact that family intervention has on clinical outcomes in schizophrenia[2], including the first episode[3], only a minority of patients and their families receive this intervention, even in high-income environments.

Well-designed family intervention has a significant impact on clinical outcomes irrespective of the social, cultural and economic context, as demonstrated in low- and middle-income countries (LMICs)[4]. Families are a natural asset that a person with schizophrenia brings to the treatment process in all contexts. Family acquires an even greater importance in the context of LMICs, where financial resources are limited, and families burdened with care of the person with psychosis may resort to negative activities, such as coercion.

It is likely that the greater and more frequent involvement of families as partners in care explains the better outcomes of psychosis in LMIC contexts, when such differences are reported in comparison to high-income country (HIC) settings[5]. However, the content of family intervention, as well as the process of its delivery in LMICs, needs to be not just adapted to culturally and economically different environments, but designed to specifically address local demands and needs. There is little evidence of this having been achieved in any substantial way.

While management of schizophrenia must address outcomes that go beyond the clinical domain, the importance, desirability and relevance of such outcomes, and even the meaning of recovery, are likely to vary across jurisdictions[6], and so must the interventions to achieve such outcomes. In HICs, desirable outcomes are often focused on the individual with psychosis, while in societies where the individual exists more as part of a family or community, the preferred focus often incorporates these other components. Desirable outcomes in such settings may include ability to make contributions to family and community, in tasks ranging from day-to-day household chores to those generating income.

While the effectiveness of interventions does not vary much across phases of schizophrenia, their dose, intensity and length do. For individuals at clinical high risk for psychosis (CHR-P), the interventions are likely to be different, since the risk in the CHR-P is not specifically for psychosis but for a range of mental disorders. Additionally, few CHR-P programs are incorporated in service settings and systems. These programs should be aligned with other youth mental health services, given the pluripotential outcomes of CHR-P[7]. Integration of CHR-P within service systems needs further study.

For the LMICs, the limited resources available are best used for improving access to and providing early treatment of psychosis at its onset, prevention of relapses and disabilities in humane and respectful community treatment environments, and focusing on interventions to promote community and social integration of individuals with psychosis and their families. Key elements of care in these settings are: use of primary health and social/community resources for early case identification; access to free medications; judicious use of precious specialist workforce; use of non-mental health community and lay workers in the provision of specific interventions; homegrown family, psychological and other reintegrative interventions; advocacy for improving resources; and legal protection of people with psychotic disorders.

Focus on family for the overall care, in addition to providing contextually relevant family intervention, should be designed also to prevent and correct coercive activities towards the person with psychosis. In addition, interventions to reduce stigma and discrimination, as well as economic interventions to promote self-sufficiency, reduction of poverty, and promotion of social inclusion, are particularly relevant for low-resource environments.

Women with psychosis have needs that are different from those of men across all jurisdictions. These include impact of medication side effects on pre-menopausal women, perinatal and postnatal care needs, and women's primary responsibility for child and household care. In LMIC settings, women with psychosis face additional challenges that reflect their already low social status, stigma associated with potential loss of marriageability, poor economic opportunities, and family and gender violence[8]. Any recommendations for management of schizophrenia must include a special focus on women across different social, cultural and economic circumstances.

Last, but not least, in order to improve meaningful outcomes for schizophrenia, commitment for improved funding for mental health services must be directed specifically to care of people with severe mental illness. Interventions that are likely to reduce the apparently increasing rates of schizophrenia, especially in urban environments of LMICs, will require massive changes in the policy directions of powerful state actors globally. These include halting environmental degradation; reducing poverty and extreme inequality; eliminating risk of war and destruction of civilian life and infra-

structures; and much more.

Given the current global political environment, this is unlikely to happen in the near future. In addition, public discourse about mental health in all jurisdictions needs to be more explicit around mental *disorders* than the current promotion of an increasingly amorphous concept of "mental health/mental wellness", as this may take focus away from mental illness such as psychosis[9], especially in low-resourced settings.

Jurisdictions where the state strongly supports publicly funded comprehensive management of schizophrenia and provides adequate housing, income supports, employment and educational opportunities are likely to see significant improvement in the lives of people with psychoses. In this regard, recommendations contained in Fusar-Poli et al's paper should go a long way to guide clinical care. Hopefully, interventions that improve other aspects of lives of people with psychosis and their families will be equally well encouraged through large-scale policy changes.

Ashok Malla
Department of Psychiatry, McGill University, Montreal, QBC, Canada

1. Fusar-Poli P, Pillinger T, McCutcheon RA et al. World Psychiatry 2026;25:231-64.
2. Rodolico A, Bighelli I, Avanzato C et al. Lancet Psychiatry 2022;9:211-21.
3. Camacho-Gomez M, Castellvi P. Schizophr Bull 2020;46:98-109.
4. Morillo H, Lowry S, Henderson C. Soc Psychiatry Psychiatr Epidemiol 2022;57:1749-69.
5. Iyer S, Malla A, Taksal A et al. Psychol Med 2022;52:1538-47.
6. Gamieldien F, Galvaan R, Myers B et al. BMJ Open 2021;11:e045005.
7. Shah JL, Scott J, McGorry PD et al. World Psychiatry 2020;19:233-42.
8. Barber S, Mulushoa A, Hanlon C et al. Can J Psychiatry 2025;70:154-9.
9. Malla A, Gold I. J Psychiatry Neurosci 2024;49:E126-31.

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Implementing precision psychiatry in psychosis

Fusar-Poli et al[1] are to be congratulated for providing an excellent summary of current best practice in the clinical management of psychosis.

A key theme in the paper is the importance of adopting a person-centred approach. At present, clinical services for psychosis are configured to provide care that is broadly similar for all patients. However, psychosis is a heterogenous condition, comprising subtypes with different clinical outcomes that are likely to reflect distinct underlying pathophysiologies. Stratifying patients into subgroups with different clinical needs, described as precision psychiatry, provides a framework that is explicitly designed to support the delivery of more personalized care[2].

A precision psychiatry approach is already being implemented in the early detection of psychosis. Initially, this entails the stratification of young people with a variety of mental health problems into subgroups at clinical high risk for psychosis (CHR-P), with other mental health conditions, or with symptoms below the threshold for a mental health condition. The CHR-P individuals are offered care from an early detection service; those with other conditions are directed to other mental health services; and the third subgroup is advised that clinical care is not indicated.

The CHR-P population is itself heterogenous: over the next 2-3 years, a minority (15-20%) will develop a first episode of psychosis, but the remainder will not[3]. These two subgroups are difficult to distinguish on the basis of their presenting clinical features, and this has driven a global research effort to identify cognitive, neuroimaging and blood measures that may predict the later onset of psychosis[4]. Once biomarkers robust enough for individual prediction in a clinical setting become available, preventive interventions can be offered to those most likely to progress to illness, while care in those for whom this is unlikely could focus on resolving the presenting problems. A range of candidate preventive interventions for psychosis have been evaluated, and large-scale clinical trials are currently ongoing[5].

If a precision psychiatry approach was to be extended to people with a psychotic disorder, the optimal stage at which to do this would be at the beginning of their care. Subtypes of patients with distinct clinical needs could then be offered different forms of treatment as early as possible. As pointed out by Fusar-Poli et al, a major recent development in the care of psychosis has been the widespread implementation of early intervention services. These services could provide an ideal infrastructure for patient stratification.

It has long been known that, in a minority of patients, psychosis has an "organic" basis. However, recent research indicates that the size of this subgroup is larger than previously thought: around 10% of cases may be "secondary" to an underlying physical condition, or to substance use[6]. Distinguishing these patients from the majority with a "primary" psychosis is critical, as they often require care that is medical or surgical rather than psychiatric, and delaying access to alternative treatment can have serious consequences.

The population of patients with a primary psychosis is also heterogenous, particularly in terms of the response to treatment with antipsychotic medications. These drugs are effective in most patients, but around 25% do not benefit, and are described as showing "treatment resistance"[7]. At present, there is usually a long delay before treatment resistance is recognized and patients are offered alternative treatment. This reflects the challenges associated with determining treatment resistance in real-world clinical settings, which requires the careful evaluation of at least two courses of treatment, a process often complicated by poor adherence and concurrent substance use.

Early intervention services are effective at ameliorating the acute presenting symptoms of first episode psychosis, but were not designed to manage the needs of patients with either a secondary psychosis, or a primary psychosis that is treatment resistant. Modifying the remit of these services to include patient stratification could extend the benefits of early intervention to all types of patients with psychosis.

An initial stratification step would aim to identify the subgroup with a secondary psychosis through a comprehensive baseline

assessment, including physical examination, urinalysis for substances of abuse, structural neuroimaging, and blood testing (e.g., for central nervous system auto-antibodies)[6]. The results would indicate the nature of the underlying cause and the appropriate form of treatment. The remaining patients with a primary psychosis could then be stratified according to the effectiveness of antipsychotic medications.

Although promising candidate clinical, genetic and neuroimaging predictors for treatment resistance have been developed[7], these are not yet ready for clinical use. Treatment resistance would thus have to be determined through clinical evaluation of the antipsychotic response. However, this process could be completed more quickly if started when treatment is first initiated, and conducted in early intervention services, which typically have more time and resources to assess therapeutic responses than general teams.

Moreover, the speed and accuracy of the evaluation can be enhanced by conducting more frequent symptom assessments using standardized instruments, and the objective monitoring of treatment adherence and substance use through blood and urine testing[8]. Patients who respond to the first course of treatment would continue with the same medication. In those who do not, the process would then be repeated with a different antipsychotic. Patients not responding to this second course would represent the subgroup with treatment resistance, who could then have access to clozapine while still in the early phase of the disorder.

Implementing patient stratification in clinical care requires additional resources to support a greater volume of assessments and investigations, and the changes to practice have to be feasible in real-world settings, and acceptable to both patients and clinicians. These represent significant challenges, especially in health care systems where resources are scarce and some types of investigation (e.g., magnetic resonance imaging) may not be accessible. However, these issues can be mitigated by employing stratification measures that are more widely available and relatively inexpensive. For example, the automated analysis of routinely collected clinical data in electronic health records can be used to facilitate the identification of CHR-P individuals[9].

In conclusion, extending the precision psychiatry approach beyond early detection to the first episode stage could provide a way of delivering more personalized care for people with psychosis.

Philip McGuire
Department of Psychiatry, University of Oxford, Warneford Hospital, and NIHR Oxford Health Biomedical Research Centre, Oxford, UK

1. Fusar-Poli P, Pillinger T, McCutcheon RA et al. World Psychiatry 2026;25:231-64.
2. Coutts F, Koutsouleris N, McGuire P. Nature Rev Neurol 2023;19:221-34.
3. Fusar-Poli P, Bonoldi I, Yung A et al. Arch Gen Psychiatry 2012;69:220-9.
4. Dickens A, Sen P, Kempton M et al. Biol Psychiatry 2021;89:288-97.
5. Webster P, Healey N. Nat Med 2024;30:3384-8.
6. Blackman G, Byrne R, Gill N et al. World Psychiatry 2025;24:145-6.
7. McCutcheon R, McGuire P, Upthegrove R et al. World Psychiatry 2026;25:50-1.
8. Atkins M, Taylor D, Catalan A et al. Br J Psychiatry 2023;223:389-93.
9. Oliver D, Arribas M, Perry B et al. Biol Psychiatry 2024;96:532-42.

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Towards an integrative and personalized care across the stages of schizophrenia spectrum disorders

Fusar-Poli et al's paper[1] provides a comprehensive synthesis of the best practices for optimal and integrative care to individuals with psychosis in settings with variable levels of resources. While the recommendations are stratified according to the different disease stages, from clinical at-risk states to non-remitting schizophrenia, some cross-cutting issues can be further underlined.

It is now well demonstrated that early developmental disruptions linked to genetics and/or environmental insults are at the core of vulnerability to schizophrenia spectrum disorders. Considering neurodevelopmental burden is also an important dimension to personalize care across the different stages of these disorders. Indeed, this burden is not only a risk factor, but also predicts response to treatment in established psychosis[2]. While in high-income countries a comprehensive exploration may include genetic testing and brain imaging, neurodevelopmental burden can also be assessed by simple questions regarding developmental trajectories and disease history, possibly with the help of digital tools, and by a physical examination accessible everywhere.

The identification of rare genetic variants with major impact and the recent large genome-wide association studies open new avenues for therapeutic approaches, departing from dopaminergic dysregulation, taking into account that many patients are resistant to anti-dopaminergic medications. Indeed, glutamatergic systems and synaptic functioning are identified as key players in neurodevelopmental disorders, including schizophrenia, underlining the role of neuroplasticity in disease processes.

For instance, there is compelling evidence that omega 3 depletion or abnormalities in one-carbon metabolism (particularly involving folate[3]) are frequent in persons with schizophrenia spectrum disorders, even at early stages. These deficits impact many critical processes, including neurotransmitter synthesis and release, redox regulation, epigenetic mechanisms, and resilience to inflammation[4]. Interestingly, boosting the biological processes underlying neuroplasticity and resilience is attainable also without complex interventions. Supplementation and nutritional approaches are safe and cost-effective, and directly accessible across all stages of the schizophrenia spectrum[5].

Psychosocial and psychotherapeutic interventions also promote brain plasticity and resilience. Stress is a recognized precipitating factor for psychosis, impacting the amygdala-hippocampus-prefrontal circuits[6]. Cognitive behavioral therapy has a documented efficacy in stress-related disorders as well as acting on brain

connectivity[7]. Similarly, cognitive remediation has shown its efficacy and its positive impact on brain connectivity[8]. Thus, evidence-based effective psychological interventions in schizophrenia seem to act at the core of the pathophysiology of the disorder and should be deployed worldwide as disease-modifying strategies, with cultural and contextual adaptations.

The distribution and organization of mental health care resources have a major influence on the modalities and quality of care for patients with schizophrenia. The organization based on catchment areas/sectors implemented in some high-income countries has similarities with the picture described for several middle-income countries, where the community has a central role in delivering support and psychosocial interventions. The initiatives developed to cope with scarce resources provide inspiring perspectives to offer and sustain integrative care at the different stages of psychosis.

The development of the task-sharing model not only partly responds to the lack of specialized clinicians, but is also a natural way to involve users, caregivers, parents, peers, and non-specialized first-line professionals (e.g., counselors, job coaches) into integrative personalized care programs. The condition to ensure that appropriate care is delivered is nevertheless to extensively provide reliable training to all actors and sensibilization to the community, with relevant materials to be adapted to the cultural context. In addition, a critical issue in this type of organization is to maintain the access to physical care and emergency medical services, a critical need for severe forms of the illness and for those with somatic comorbidities.

As underlined in Fusar-Poli et al's paper, reducing the delay to care has a major impact on the outcome and the economic burden of schizophrenia. It is thus crucial to deploy sensibilization campaigns and ensure that first-line actors can appropriately decide what to do, since not all young people with emerging mental health difficulties require highly specialized care. Questionnaires, including self-rated questionnaires, can optimize the referral of persons with early symptoms of psychosis with no delay. This is also a way to destigmatize psychotic disorders, since it familiarizes non-professionals with the early symptoms experienced by patients, and helps patients to put words on their inner unusual perceptions[9].

Several of these interventions can rely on digital tools, which provide a true opportunity to reduce inequalities across countries or regions. Adapted to the cultural context, they enable remote dissemination of psychosocial care to patients and families, including cognitive remediation, psychoeducation and cognitive behavioral therapy, as well as sensibilization and training of professional and non-professional actors. Furthermore, questionnaires accessible online and/or on smartphones are valuable and transposable tools to facilitate access to care and optimize the use of specialized resources, especially useful in conditions of economic constraints.

Fusar-Poli et al's review brings solid bricks to build an integrative and personalized approach to schizophrenia spectrum disorders across stages and countries, worldwide. It opens an inspiring crosstalk between the different fields and settings, from the more clinical to the more community-based. This will improve the dissemination of new insights in the dynamics of the pathophysiology of these disorders and hopefully lead to better global care for all patients with these eventually disabling conditions.

Marie-Odile Krebs
Institute of Psychiatry and Neuroscience of Paris, Université Paris Cité, INSERM U1266, and GHU Paris Psychiatrie et Neurosciences, Paris, France

1. Fusar-Poli P, Pillinger T, McCutcheon RA et al. World Psychiatry 2026;25:231-64.
2. Iftimovici A, Krebs E, Dalfin W et al. Psychol Med 2024;54:1-12.
3. Frajerman A, Urban M, Rivollier F et al. Front Psychiatry 2023;14:1128890.
4. Cuenod M, Steullet P, Cabungcal JH et al. Mol Psychiatry 2022;4:1886-97.
5. Yoo S, Montazeri A, McNulty H et al. Schizophr Res 2025;280:39-47.
6. Godsil BP, Kiss JP, Spedding M et al. Eur Neuropsychopharmacol 2013;23:1165-8.
7. Mason L, Peters ER, Dima D et al. Schizophr Bull 2016;42:684-92.
8. Matsuda Y, Makinodan M, Morimoto T et al. Psychiatry Clin Neurosci 2019;73:676-84.
9. Krebs MO, Mathevet L, Lucarini V et al. Submitted for publication.

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The problem of recognition of clinical high-risk states is hampering the prevention of schizophrenia

Fusar-Poli et al[1] are to be congratulated on their landmark, authoritative review. Particularly welcome is the emphasis on recommendations for middle- and low-income countries, along with the comprehensive referencing of schizophrenia spectrum research emerging from these countries. The authors rightly include the clinical high-risk syndrome for psychosis (CHR-P) in their review. Here we extend some of their recommendations for this condition.

The recommendation for CHR-P detection in high-income countries can be extended by suggesting further research into task-sharing models. As noted in the review, CHR-P is common in high-income countries among adolescent and young adult clinical samples when ascertained in epidemiologic studies, but the CHR-P state may go unrecognized by many clinical providers. Moreover, several years after the establishment of a comprehensive CHR-P service in a high-income country, only 5% of emerging first episode psychosis cases in the same community had been previously detected as at CHR-P by the service[2]. In addition, a recent analysis in two CHR-P observational cohorts from high-income settings raised the possibility that clinicians had under-recognized the attenuated positive symptoms characteristic of the condition[3]. Lastly, even in high-income settings, it may be challenging to create and staff a sufficient number of CHR-P specialty clinics to meet the goal of preventing schizophrenia.

If supported by further research, task-sharing models could potentially enhance the recognition and detection of CHR-P in high-income settings as well as in middle/low-income ones. CHR-P spe-

cialty clinics could, for example, provide education, consultation and digital resources to practitioners in general youth mental health services. Ultimately, the best way for the CHR-P paradigm to realize its promise to prevent schizophrenia may be for every clinician to possess basic skills in recognizing and treating CHR-P. Such a development would be consistent with the trajectory of other specialty clinics in psychiatry (e.g., lithium clinics, tardive dyskinesia clinics, clozapine clinics).

However, our field must provide better reasons for clinicians to invest their time to learn about detection of CHR-P. For example, identification of a patient as at CHR-P does not help a busy clinician to determine which, if any, medication to recommend when psychological or psychosocial therapies are ineffective or unavailable, since no medications for CHR-P are approved by regulatory authorities in any country. In the past, the first approval of a medication for a new indication has dramatically increased recognition of previously neglected conditions (e.g., panic disorder).

The goal of the Accelerating Medicines Partnership® Schizophrenia (AMP® SCZ) programme – a partnership between the US National Institutes of Health, the US Food and Drug Administration, the European Medicines Agency, and other organizations – is to provide sufficient information about the heterogeneity of CHR-P and its determinants to encourage pharmaceutical investment in the condition. The AMP® SCZ Observational Study[4] has recently met its recruitment goal of >2,000 CHR-P participants at 43 sites in 13 countries.

In addition to potentially remediating under-recognition and under-detection of CHR-P, regulatory approval of a medication with a novel mechanism would help address reliance on traditional dopamine D2-blocking antipsychotics by offering an effective and safer alternative. The AMP® SCZ Proof of Principle Studies first project is investigating the effects of nicotinic mechanisms on cognition in CHR-P.

CHR-P may also be detected by clinical evaluations of referrals from realms beyond individual clinicians, such as schools, social media, health-care system databases, and Internet/social media. A recent report from two CHR-P observational cohorts demonstrates the impact of referral source on CHR-P sample demographic and severity features[5]. More research focus on the effects of referral source would shed more light on where CHR-P should be detected. Standardization of methods for capturing referral source would facilitate those efforts and the comparison of effects across cohorts.

Recommended interview detection of CHR-P should be extended to include – in addition to the tools mentioned by Fusar-Poli et al – the Positive SYmptoms and diagnostic criteria for the CAARMS Harmonized with the SIPS (PSYCHS) semi-structured interview[6] and the Abbreviated Structured Interview for Psychosis-Risk Syndromes (Mini-SIPS)[7]. The PSYCHS ascertains both Structured Interview for Psychosis–Risk Syndromes (SIPS) and Comprehensive Assessment of At-Risk Mental States (CAARMS) CHR-P diagnostic criteria. The Mini-SIPS ascertains SIPS CHR-P diagnostic criteria in 30 min. Training and certification are conducted fully online and are freely accessible.

As noted above, pharmaceutical company investment would likely substantially increase recognition and detection of CHR-P. Such investment in CHR-P, and consequently the public health benefit that comes with an approved treatment, has been hindered up to now by a lack of international agreement on CHR-P diagnostic criteria. Although the PSYCHS succeeded in fully harmonizing attenuated positive symptom assessment[6], CAARMS and SIPS diagnostic criteria for CHR-P remain discordant. A recent Schizophrenia International Research Society award is aiming to promote diagnostic criteria harmonization.

The methods of CHR-P detection mentioned by Fusar-Poli et al are all interview-based. Recently, progress has been made in designing and testing behavioral task batteries that can be self-administered online[8]. Sensitivity to the CHR-P diagnosis was excellent, suggesting that such methods can be employed for screening purposes; however, specificity was low, indicating that so far they are not yet ready for independent diagnostic use. In the future, similar digital innovations may be able to improve CHR-P detection in both high-resource and middle/low-resource settings.

Suicide is well-known as a tragic outcome of schizophrenia spectrum disorders, and patients are at higher risk earlier in the course of illness. A recent study reported that persistence of the attenuated positive symptoms characteristic of CHR-P was significantly associated with persistence of suicidal ideation, even when controlling for depressive symptoms[9]. These findings suggest that development of accessible, safe and effective treatments for CHR-P could have the benefit of reducing the risk for suicide.

Finally, although it has been argued that at-risk labelling may cause stigmatization, it is a fact that CHR-P individuals often already suffer from stigma related to their behaviors and symptoms, so that the timely identification and management of the at-risk condition may actually have a positive impact on stigma, including self-stigmatizing attitudes.

Scott W. Woods
PRIME Clinic, Yale University School of Medicine Department of Psychiatry and Connecticut Mental Health Center, New Haven, CT, USA

1. Fusar-Poli P, Pillinger T, McCutcheon RA et al. World Psychiatry 2026;25:231-64.
2. Fusar-Poli P, Rutigliano G, Stahl D et al. JAMA Psychiatry 2017;74:493-500.
3. Mukhtar H, Zhou D, Farina EA et al. Psychol Med 2025;55:e241.
4. Wannan CMJ, Nelson B, Addington J et al. Schizophr Bull 2024;50:496-512.
5. Farina EA, Mourgues-Codern C, Stimler K et al. Schizophrenia 2025;11:123.
6. Woods SW, Parker S, Kerr MJ et al. Early Interv Psychiatry 2024;18:255-72.
7. Woods SW, Lympus C, McGlashan TH et al. BMC Psychiatry 2022;22:84.
8. Williams TF, Gold JM, Waltz JA et al. Transl Psychiatry 2025;15:311.
9. Deng W, MacNutt C, Addington J et al. J Affect Disord 2025;384:208-13.

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Interventions in schizophrenia should be transdiagnostic, biologically informed, individualized, and disease modifying

Fusar-Poli et al[1] provide a compelling, globally relevant roadmap for stage- and setting-stratified care in schizophrenia. They advocate for early detection, integrated pharmacological and psychosocial treatment, and rights-based, person-centered care. Their recommendations – from task-sharing and digital augmentation in low-resource settings to sustained early intervention services in high-income countries – are laudable, and seek to reduce the current stark global disparities, where up to 90% of individuals with schizophrenia in low-income countries receive no evidence-based care.

However, it is also important to keep in mind that, at this time, few pharmacological and psychosocial interventions in schizophrenia are disease-modifying, differently from several chronic diseases in the rest of medicine, such as some cancers and autoimmune diseases[2]. A disease-modifying approach is one that favorably alters the trajectory of illness – halting, slowing or reversing progression – rather than simply alleviating symptoms. In schizophrenia, this means mitigating the etiopathological substrate related to psychosis, preventing relapses, and restoring long-term functioning.

Only some of the current prevention and early intervention efforts get close to addressing these disease modification goals – e.g., minimizing treatment delay, coordinated specialty care (CSC), relapse prevention with early use of long-acting injectables (LAIs), and addressing treatment resistance with early introduction of clozapine. Here I outline three key considerations toward these goals, which may extend and complement Fusar-Poli et al's vision.

First, Fusar-Poli et al's paper understandably focuses on schizophrenia, the most serious of psychotic disorders. However, it is important to keep in mind that current diagnostic systems define behavioral syndromes that lack biological specificity. Increasing evidence points to substantial overlaps in phenotypic signatures, neurobiological features, etiology and treatment response between schizophrenia and affective psychotic disorders[3]. The symptomatic overlap across disorders has produced categories with limited validity and utility, leading to frequent comorbidity labels and "not otherwise specified" diagnoses.

These neurobiological and etiological overlaps have led to delays in discoveries of targeted interventions, and lack of ability to predict outcome and treatment response. Diagnostic instability, particularly in early illness stages, further challenges the utility of rigid categorical diagnoses. A transdiagnostic stage-based approach may therefore better guide treatment planning, predict outcomes, and inform etiological research. Fusar-Poli et al rightly emphasize staging models, but these models are themselves heterogeneous, with variable long-term transition risks[3]. A transdiagnostic staging model enables clinicians to deliver interventions proportionate to illness stage, while preserving diagnostic fluidity in early and complex cases.

Second, the authors' call for measurement-based care invites expansion into biologically informed stratification. Traditional scales, while clinically useful, may insufficiently capture the underlying heterogeneity. Characterizing individuals with psychosis by biomarkers based on neurocognitive and electrophysiological dimensions may allow categorization of these disorders into biologically homogeneous subgroups (biotypes) which have better predictive value and are more useful for treatment selection.

Recently, scalable biologically grounded tools have been developed to guide treatment. The ADEPT (Algorithmic Diagnostics for Efficient Prescription of Treatments) utilizes low-cost clinical and cognitive metrics to derive neurobiological subtypes and predict treatment response[4]. As an example, consider a 22-year-old man who presents with psychosis, cognitive impairment, and catatonia. Based on cognitive and electroencephalographic (EEG) testing, ADEPT may diagnose him with psychosis spectrum disorder, biotype 2 (a transdiagnostic, brain informed diagnosis), leading to prescription of antipsychotics and early cognitive remediation.

Digital markers, such as automated speech and language features, which can be assessed with smartphones, are also promising as scalable, objective markers of psychosis severity in low-resource settings[5]. Complementary tools – e.g., point-of-care inflammatory assays, smartphone-based cognitive tasks, and passive monitoring apps – may support continuous, precision-informed care.

However, without global validation and local adaptation, biomarker technologies risk widening the equity gaps they seek to close[6]. A concerted effort is needed to develop and implement culturally appropriate, low-cost biomarkers that are scalable and feasible in low-resource settings.

Third, biomarker-informed care needs to be individualized. We have argued previously that person-centered care needs to be tailored to the individual's biology[7]. Personalized medicine, also called precision medicine, refers to providing the right treatments for the right patients at the right time, an approach which contrasts with a "one-size-fits-all" strategy, in which treatments are for the average person with a given diagnosis, with less consideration for individual differences. Treating all newly diagnosed patients who have clinically defined psychosis with antipsychotic medications is like treating all people who have headache with an analgesic. Biomarkers, a step toward precision psychiatry, can make an individualized approach realistic for psychoses, though implementation challenges need to be overcome.

The other aspect of individualizing care is person-centered medicine, which seeks to know the patient as a person and emphasizes sociocultural determinants of his/her care as critical ingredients of shared decision making. As an example, consider a 36-year-old cancer survivor with psychosis. A new seizure and labile blood pressure lead to further laboratory tests, and search for cerebrospinal fluid (CSF) and serum antibodies. A diagnosis of N-methyl-D-aspartate (NMDA) receptor encephalitis is made (precision psychiatry). However, the patient – being a Jehovah's Witness – declines intravenous immunoglobulin and plasma exchange, due to religious beliefs pro-

hibiting blood product use. She is then successfully treated with a non-blood-based second-line agent such as rituximab and high-dose corticosteroid (person-centered psychiatry).

Disease modification in schizophrenia requires combining today's best relapse-prevention care with tomorrow's precision tools. We already have a practicable path to limit progression: CSC for first-episode psychosis, continuous maintenance treatment (preferably with earlier use of LAIs), and systematic psychosocial supports – steps that shorten the duration of untreated psychosis, prevent relapse, and reduce cumulative morbidity, even if they are not curative[2]. However, benefits of CSC often wane over time, with long-term follow-up showing attenuation of functional gains[8]. Cognitive impairments, a core and persistent feature of schizophrenia, are strong predictors of functional outcomes[8]. Emerging evidence supports early cognitive remediation as a scalable, evidence-based intervention, adaptable even in resource-constrained settings[9]. Cognitive remediation in early-stage care, guided by staging and biotyping, may convert early symptomatic improvements into long-term functional recovery.

Moving beyond categorical syndromes toward a transdiagnostic, stage-based framework is critical for true disease modification: clinical staging must be paired with biologically informed stratification (e.g., biotypes/ADEPT) and person-centered tailoring, so that "the right treatment at the right time" becomes routine rather than rhetorical. However, the real problem is under-implementation, not lack of know-how. Precision, low-cost biomarkers such as EEG, culturally adapted language and digital markers, and scalable cognitive remediation should be embedded early to convert symptomatic gains into durable functional recovery, without widening equity gaps in low-resource settings.

In short, disease modification is both a current achievable goal (implement CSC + LAIs + continuous maintenance treatment) and an aspirational future direction (build transdiagnostic, biomarker-guided, individualized care at scale). To realize this vision, psychiatry needs to prioritize implementing CSC and LAIs, while simultaneously investing in low-cost biomarkers and scalable cognitive interventions.

Individualized, biologically informed, and transdiagnostic disease-modifying care should underpin the global effort to advance equity in schizophrenia treatment. By integrating flexible staging frameworks, pragmatic biomarker tools, and sustained cognitive interventions, the field can move beyond symptom stabilization toward disease modification and durable recovery across contexts and continents.

Matcheri S. Keshavan
Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

1. Fusar-Poli P, Pillinger T, McCutcheon RA et al. World Psychiatry 2026;25:231-64.
2. Lieberman JA, Mendelsohn A, Goldberg TE et al. J Psychiatr Res 2025;181:716-27.
3. Tandon R, Nasrallah HA, Akbarian S et al. Schizophr Res 2024;264:1-28.
4. Clementz BA, Chattopadhyay I, Kristian Hill S et al. Biomark Neuropsychiatry 2025;12:100117.
5. Tang SX, Spilka MJ, John M et al. NPP Digit Psychiatry Neurosci 2025;3:13.
6. Larsen SA, Klok L, Lehn-Schiøler W et al. Epileptic Disord 2024;26:694-700.
7. Keshavan MS, Clementz BA. Nat Rev Neurol 2023;19:193-4.
8. Hansen HG, Starzer M, Nilsson SF et al. JAMA Psychiatry 2023;80:371-9.
9. Keshavan MS, Eack SM. World Psychiatry 2023;22:326-7.

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The typology of common psychiatric disorders as depicted by genetic maps: a study based on Swedish population-based registers

Kenneth S. Kendler[1,2], Henrik Ohlsson[3], Ananda B. Amstadter[1,2], Jan Sundquist[3], Kristina Sundquist[3]

[1]Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA; [2]Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA; [3]Center for Primary Health Care Research, Lund University, Malmö, Sweden

We sought to clarify the inter-relationships among a range of psychiatric and substance use disorders by employing two-dimensional genetic maps, with axes defined by family genetic risk for major depression (MD) and drug use disorder (DUD). Using comprehensive Swedish national register data, we located cases of 12 disorders within this space and examined how their genetic risk profiles varied as a function of sex, age at onset, and level of recurrence. Disorders segregated robustly into two clusters. Internalizing disorders were characterized by moderate genetic liability for MD and low liability for DUD, while externalizing disorders displayed substantial risk for both genetic dimensions. These patterns were replicated across regions of Sweden. Post-traumatic stress disorder (PTSD) grouped with the internalizing cluster, whereas borderline personality disorder aligned with the externalizing group. Sex differences in genetic liability were common and frequently involved both axes: typically, the sex with the lower disorder prevalence carried higher genetic risk, with the most striking contrasts observed for alcohol use disorder (AUD) and DUD. Across most disorders, earlier age at onset was associated with elevated genetic liability, with particularly strong effects for AUD, MD and PTSD. Similarly, high level of recurrence consistently indexed increased genetic risk, often spanning both axes, with notable prominence for AUD, DUD, MD and PTSD. Taken together, these findings suggest that the genetic liabilities underlying psychiatric and substance use disorders are not fixed entities but vary systematically with key clinical features. Considering multiple genetic risks simultaneously provides an informative framework for understanding cross-disorder relationships between psychiatric disorders.

Key words: Common psychiatric disorders, substance use disorders, genetic maps, family genetic risk, national register data, age at onset, level of recurrence, cross-disorder relationships

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From the beginnings of modern psychiatric nosology, familial-genetic methods have been utilized to validate proposed categories and characterize the inter-relationships across disorders[1-6]. From such approaches examining one or two disorders, factor and structural equation modeling (SEM) began being applied to a larger number of disorders, first to phenotypic data[7] and then, using the twin methods, to model latent genetic relationships[8-11].

For example, a multivariate twin study of personally interviewed twins from the Norwegian register identified internalizing and externalizing factors[8]. The disorders with the strongest loadings on the internalizing factor included major depression (MD), panic disorder (PD), phobias, and generalized anxiety disorder (GAD). The externalizing factor loaded more prominently on drug use disorder (DUD), alcohol use disorder (AUD), conduct disorder (CD), and antisocial personality disorder.

With the development of polygenic risk scores from molecular genetic studies, similar SEMs have been applied in the attempt to clarify inter-relationships across larger numbers of conditions[12-15]. For example, Grotzinger et al[14], examining 11 psychiatric disorders, fit multivariate structural models to polygenic risk scores across these disorders. This study identified four genetic factors, including "internalizing disorders" which loaded substantially on MD, anxiety disorders and post-traumatic stress disorder (PTSD).

In this paper, we use a complementary method – "genetic maps" – to visualize genetic relationship across disorders. This requires defining two "foundational disorders" whose genetic risks constitute the x and y axes. A range of disorders are situated in this two-dimensional space, clearly displaying patterns that are more difficult to visualize with prior approaches. This method can be expanded to look at divisions within the disorders by clinical features, such as age at onset, which can clearly display the impact of such "sub-phenotypes" on patterns of genetic risks.

We apply this approach utilizing national data obtained from Swedish registers and the family genetic risk scores (FGRSs) generated from extended pedigrees[16-20]. We define our map by FGRS for a classical internalizing disorder (MD) and a classical externalizing disorder (DUD)[8,21-23]. On this map, we then place 12 relatively common psychiatric and substance use disorders and describe the observed pattern. Next, we subdivide each disorder as a function of sex, age at onset, and level of recurrence. Finally, we place on this map a set of six major psychiatric disorders not commonly considered as part of the internalizing or externalizing spectra, to evaluate how they relate, in their patterns of genetic risk, to the prior 12 internalizing/externalizing disorders.

METHODS

This study leveraged Swedish population-based registers with national coverage, linking individuals through unique personal identification numbers, which were pseudonymized using serial numbers to ensure confidentiality. Ethical approval was granted by the Regional Ethical Review Board in Lund, and participant consent was not required.

The study database included all individuals born in Sweden between 1960 and 2000 to Swedish-born parents. The analysis focused on 18 disorders (summarized in Table 1, with sample sizes ranging from 4,900 to 588,927), identified using ICD-8, ICD-9 or ICD-10 codes obtained from primary care data and specialist care and hospital registers (see supplementary information for details on data, registers and definitions). Criminal register data were also utilized for the diagnosis of AUD and DUD.

Table 1 Descriptive statistics for the psychiatric disorders considered in the study

	N	Population prevalence	% females	Median age at registration (years)	N. registrations, median (range)
Major depression (MD)	577,492	16.1%	63.3%	31.5	2 (1-13)
Drug use disorder (DUD)	172,999	4.9%	31.1%	23.1	2 (1-43)
Alcohol use disorder (AUD)	155,931	4.4%	31.4%	26.5	2 (1-44)
Attention-deficit/hyperactivity disorder (ADHD)	102,913	2.9%	42.8%	22.1	3 (1-30)
Conduct disorder (CD)	4,900	0.14%	39.2%	15.5	1 (1-14)
Obsessive-compulsive disorder (OCD)	35,950	1.0%	60.0%	26.1	2 (1-30)
Phobic anxiety disorders (PAD)	67,185	1.9%	59.2%	28.0	1 (1-29)
Other anxiety disorders (OAD)	588,927	16.5%	63.6%	30.3	2 (1-34)
Panic disorder (PD)	136,745	3.8%	63.6%	30.5	1 (1-30)
Generalized anxiety disorder (GAD)	80,628	2.3%	66.1%	32.7	1 (1-25)
Post-traumatic stress disorder (PTSD)	184,074	5.2%	69.8%	35.9	1 (1-27)
Borderline personality disorder (BPD)	17,581	0.49%	85.7%	26.5	1 (1-30)
Anorexia nervosa (AN)	13,495	0.38%	94.4%	18.1	1 (1-30)
Bulimia nervosa (BN)	7,626	0.21%	96.5%	24.3	1 (1-23)
Bipolar disorder (BD)	45,579	1.3%	63.5%	30.9	3 (1-42)
Other non-affective psychoses (ONAP)	31,983	0.89%	43.6%	29.0	2 (1-57)
Schizophrenia (SZ)	11,053	0.31%	36.0%	29.5	5 (1-45)
Autism spectrum disorder (ASD)	45,443	1.3%	37.2%	20.4	3 (1-30)

The study incorporated FGRSs for MD and DUD. These scores were calculated based on morbidity risks observed in first- through fifth-degree relatives, accounting for cohabitation effects separately for parent-offspring and sib-sib relationships.

Unlike molecular genetic data, FGRSs reflect familial phenotypes. The FGRS analyses control for the sex, age and geographical location of each relative, and their impact is weighted by their degree of genetic relatedness to the proband. After summing across all relatives, the score is standardized to a mean of zero and a standard deviation of unity (see also supplementary information).

We computed the mean FGRS for MD and DUD (respectively, $FGRS_{MD}$ and $FGRS_{DUD}$) in 12 classic internalizing or externalizing disorders – i.e., MD, DUD, AUD, attention-deficit/hyperactivity disorder (ADHD), CD, obsessive-compulsive disorder (OCD), phobic anxiety disorders (PAD), other anxiety disorders (OAD, ICD-10: F41), PD, GAD, PTSD, and borderline personality disorder (BPD) – and six disorders that are not typically associated with the internalizing/externalizing classification, i.e., anorexia nervosa (AN), bulimia nervosa (BN), bipolar disorder (BD), other non-affective psychoses (ONAP), schizophrenia (SZ), and autism spectrum disorder (ASD) (see Table 1).

Further subgroup analyses were performed by sex; early versus late age at onset (i.e., an age at onset lower or higher than the median); and level of recurrence, measured as low or high registration frequency (i.e., a registration number of 1 or higher than 1). Registrations that occurred within 90 days of a previous registration were not counted in the total calculations. Statistical analyses were conducted using SAS 9.4[24].

RESULTS

Table 1 depicts the sample sizes for the 18 disorders (12 internalizing or externalizing, six not typically associated with the internalizing/externalizing classification) considered in our analyses, along with their population prevalence. We also present, for each disorder, the proportion of our sample who are female, the median age at onset, and the median level of recurrence.

Figure 1 and Table 2 present the results of our primary analysis of the main 12 disorders, where the x and y axes represent, respectively, the $FGRS_{MD}$ and the $FGRS_{DUD}$ for all individuals diagnosed with each disorder.

We find five externalizing disorders in the upper right corner of the figure (AUD, DUD, CD, ADHD and BPD), all of which have a $FGRS_{DUD}$ ranging from +0.50 to +0.70, and a $FGRS_{MD}$ between +0.25 and +0.50 (see also Table 2). We see one "line" of disorders (DUD and CD) which have a very similar $FGRS_{DUD}$, with the latter having a considerably higher $FGRS_{MD}$.

We find seven disorders in a relatively small internalizing "box", all of which have a lower $FGRS_{DUD}$ than the externalizing disorders, ranging from +0.15 to +0.27, and a $FGRS_{MD}$ between +0.27 and +0.35 (see also Table 2). We see an upper "line" of disorders which are – left to right (i.e., from lower to higher $FGRS_{MD}$) – PTSD, PD, PAD and GAD. The middle line, with slightly lower $FGRS_{DUD}$, includes OAD and MD. The third line includes OCD, which has the lowest $FGRS_{DUD}$ (see also Table 2).

In Figure 2, we present the same disorders showing results separately for males and females (significant sex differences are high-

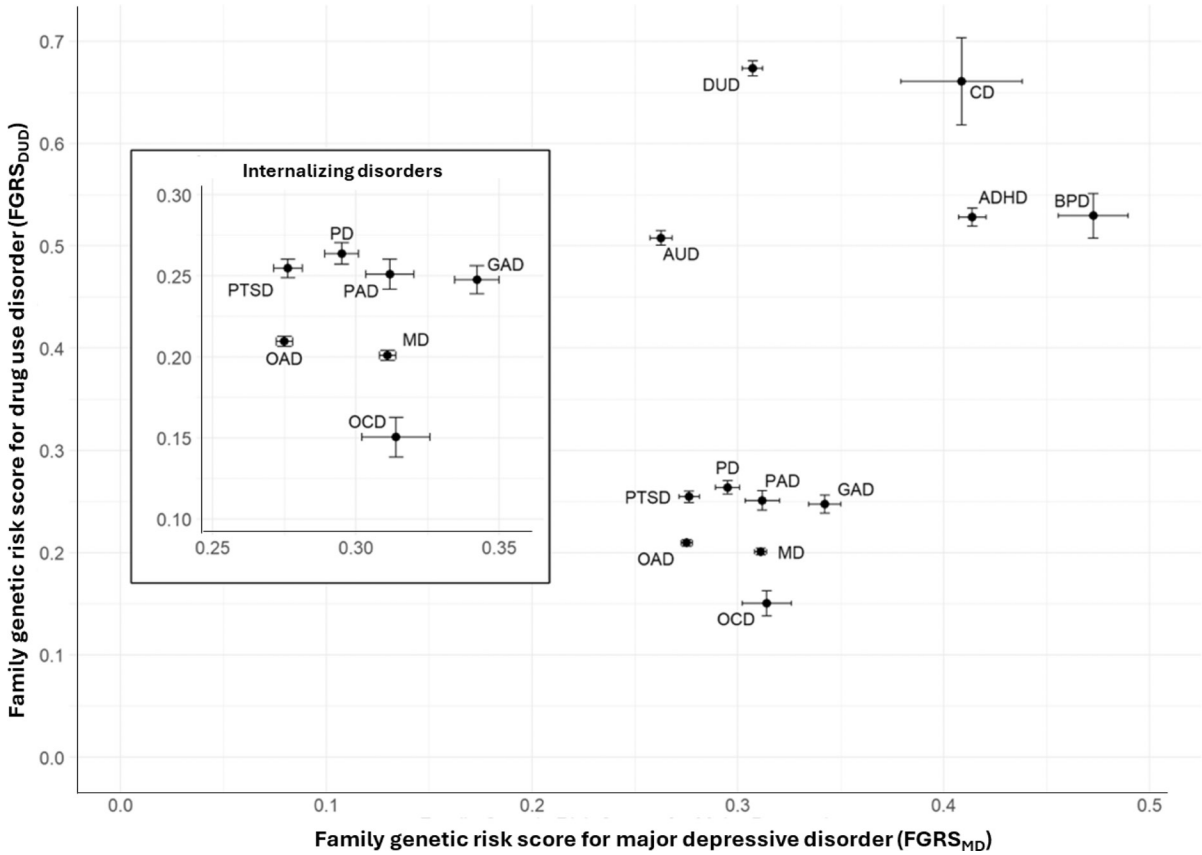

Figure 1 Genetic map containing the locations (± 95% CI) of 12 psychiatric disorders as a function of their family genetic risk score (FGRS) for drug use disorder (DUD) on the y-axis and major depression (MD) on the x-axis. ADHD – attention-deficit/hyperactivity disorder, AUD – alcohol use disorder, BPD – borderline personality disorder, CD – conduct disorder, GAD – generalized anxiety disorder, OAD – other anxiety disorders, OCD – obsessive-compulsive disorder, PAD – phobic anxiety disorders, PD – panic disorder, PTSD – post-traumatic stress disorder. The insert in the left part of the figure is an enlargement of the section of the main figure depicting the locations of internalizing disorders.

lighted in Table 3). Among the externalizing disorders, for AUD and DUD, females are shifted significantly both upward (i.e., higher $FGRS_{DUD}$) and to the right (higher $FGRS_{MD}$) compared to males. For ADHD, females have a significantly higher $FGRS_{MD}$ than males. By contrast, for BPD, males have a higher $FGRS_{DUD}$ than females, but this difference is only nominally significant (see Table 3). Looking at the internalizing disorders, we see significant sex differences for MD ($FGRS_{MD}$ and $FGRS_{DUD}$ higher in males), and for OAD and GAD ($FGRS_{MD}$ higher in males).

In Figure 3, we present the same disorders showing results separately for those with an early or late age at onset (significant differences are highlighted in Table 3). Among the externalizing disorders, we see significant differences in one or both genetic risks for all conditions but BPD. For AUD and DUD, the main effect is a substantially lower $FGRS_{DUD}$ in the late onset group. For CD, the levels of both $FGRS_{DUD}$ and $FGRS_{MD}$ are considerably higher in early-onset cases, whereas for ADHD the levels of $FGRS_{DUD}$ are surprisingly higher in late-onset cases. In the internalizing disorders, only age at onset of GAD is unrelated to the two genetic risks. For four of these disorders (PTSD, PD, OAD and MD), later-onset cases are significantly shifted down (reduced $FGRS_{DUD}$) and to the left (reduced $FGRS_{MD}$). For two disorders (PAD and OCD), significant shifts are only seen for $FGRS_{MD}$.

In Figure 4, we divided our 12 disorders in those with a low versus high frequency of registrations (significant differences are highlighted in Table 3). Among the externalizing disorders, significant differences in genetic risks were seen for AUD, DUD and ADHD. For all these disorders, the high recurrence subgroup had elevations of both $FGRS_{DUD}$ and $FGRS_{MD}$. All the internalizing disorders had significant differences between the two groups, which included increases in both genetic risks in the high recurrence subgroup, with the largest effects seen for PTSD, MD and PD. Highly recurrent MD stood out as having the highest $FGRS_{MD}$.

In Figure 5 (and Table 2), we compare our primary map of the 12 internalizing and externalizing disorders with six additional disorders that are not typically associated with the internalizing/externalizing classification. The two eating disorders – AN and BN – occupy a unique area in the map, with quite low levels of $FGRS_{DUD}$ and relatively low levels of $FGRS_{MD}$. At the other extreme, BD occupies a unique space, with a much higher $FGRS_{MD}$ and a higher $FGRS_{DUD}$ than any of the internalizing disorders. SZ is also uniquely positioned to the left of the internalizing disorders and relatively distinct from ONAP, which have higher levels of both $FGRS_{MD}$ and $FGRS_{DUD}$. Finally, ASD has a profile surprisingly similar to that of anx-

Table 2 Mean genetic risk (± 95% CI) for drug use disorder ($FGRS_{DUD}$) and major depression ($FGRS_{MD}$) in the psychiatric disorders considered in the study

	$FGRS_{DUD}$	$FGRS_{MD}$
Major depression (MD)	0.20 (0.20-0.20)	0.31 (0.31-0.31)
Drug use disorder (DUD)	0.67 (0.67-0.68)	0.31 (0.30-0.31)
Alcohol use disorder (AUD)	0.51 (0.50-0.51)	0.26 (0.26-0.27)
Attention-deficit/hyperactivity disorder (ADHD)	0.53 (0.52-0.54)	0.41 (0.41-0.42)
Conduct disorder (CD)	0.66 (0.62-0.70)	0.41 (0.38-0.44)
Obsessive-compulsive disorder (OCD)	0.15 (0.14-0.16)	0.31 (0.30-0.33)
Phobic anxiety disorders (PAD)	0.25 (0.24-0.26)	0.31 (0.30-0.32)
Other anxiety disorders (OAD)	0.21 (0.21-0.21)	0.28 (0.27-0.28)
Panic disorder (PD)	0.26 (0.26-0.27)	0.30 (0.29-0.30)
Generalized anxiety disorder (GAD)	0.25 (0.24-0.26)	0.34 (0.33-0.35)
Post-traumatic stress disorder (PTSD)	0.25 (0.25-0.26)	0.28 (0.27-0.28)
Borderline personality disorder (BPD)	0.53 (0.51-0.55)	0.47 (0.46-0.49)
Anorexia nervosa (AN)	0.03 (0.01-0.05)	0.19 (0.17-0.21)
Bulimia nervosa (BN)	0.09 (0.07-0.12)	0.21 (0.19-0.24)
Bipolar disorder (BD)	0.35 (0.34-0.36)	0.45 (0.44-0.46)
Other non-affective psychoses (ONAP)	0.34 (0.32-0.35)	0.25 (0.24-0.26)
Schizophrenia (SZ)	0.24 (0.21-0.26)	0.16 (0.14-0.18)
Autism spectrum disorder (ASD)	0.26 (0.25-0.27)	0.38 (0.37-0.39)

iety disorders within the internalizing "box", deviating from them only by a modestly elevated $FGRS_{MD}$.

DISCUSSION

In this study, we sought to clarify the nosological and etiological relationships among common psychiatric disorders, using national data obtained from Swedish registers and the FGRSs generated from extended pedigrees. From the many themes of potential interest, we emphasize six.

First, consistent with prior genetically informed analyses using different methods, we saw a sorting of disorders into distinct internalizing and externalizing groups[8-11,14]. Given the method differences, this convergence is an example of triangulation, which provides greater support for the validity of that classification than just replication[25].

One finding which emerged clearly using our method is not well captured in previous reports: all externalizing disorders have a high genetic risk for MD. Indeed, many of these disorders have a higher $FGRS_{MD}$ than internalizing disorders. We found no common psychiatric disorders in the upper left quadrant of our map (i.e., with high $FGRS_{DUD}$ and low $FGRS_{MD}$). Furthermore, two of our primary disorders – PTSD and BPD – have not been often studied in genetically informed multivariate analyses. It is therefore of interest that, in our analyses, PTSD clearly belongs among the internalizing disorders and BPD within the externalizing disorders.

Second, within internalizing and externalizing groups, each disorder had a unique place, with no evidence of overlapping confidence intervals. Some of this "sub-structure" is noteworthy. For internalizing disorders, we found three rows defined by the level of $FGRS_{DUD}$ and, within the rows, distinguished by the $FGRS_{MD}$. The first row included PTSD and the three anxiety disorders, suggesting that PTSD – originally conceptualized as an anxiety disorder – may be more closely related to anxiety disorders than MD. This finding is notable, as the best powered genetic correlation findings suggest a higher correlation between PTSD and MD than between PTSD and anxiety disorders[26]. Also, we found no evidence of an appreciable genetic link between PTSD and externalizing disorders, despite what would have been predicted by twin[27] and GWAS[26] findings. However, our PTSD findings are in line with the Hierarchical Taxonomy of Psychopathology (HiTOP) empirical and conceptual work, situating PTSD within the internalizing spectrum, marked by fear and distress[28]. Our results are also consistent with two prior multivariate twin studies which found a distinct genetic factor for GAD and classical phobias[29], as well as evidence that, while correlated, MD genetic risk could be partly separated from that of anxiety disorders[30]. Finally, OCD, consistent with prior family study data[31], had the lowest genetic risk for DUD of any of the internalizing cluster of disorders.

The externalizing disorders were differentiated by both $FGRS_{DUD}$ and $FGRS_{MD}$, with DUD and BPD at the two extremes. That is, DUD had the highest $FGRS_{DUD}$ and a relatively low $FGRS_{MD}$, and BPD the lowest $FGRS_{DUD}$ and the highest $FGRS_{MD}$. This latter result is congruent with a prior Norwegian study of BPD in twins[32], that showed – at both the diagnostic and criteria level – a substantial association with internalizing/mood symptoms. The evidence of high levels of $FGRS_{MD}$ in ADHD cases is consistent with prior results of familial genetic sharing with MD in family and twin studies[33].

Third, several different etiological models have been proposed to predict sex differences in prevalence for psychiatric and substance use disorders[34]. Key early work[35] proposed a multiple threshold multifactorial liability model, according to which the sex with the lower prevalence would have a higher genetic risk. We were able to test this prediction. Four disorders, when examined by sex, differed significantly in their $FGRS_{MD}$. Consistent with the model, males had a higher genetic risk in cases of MD (a female preponderant disorder), while females had a higher genetic risk in cases of AUD, DUD and ADHD (all male preponderant disorders).

Five disorders had sex differences in their $FGRS_{DUD}$. Again, consistent with the above theory, for OAD, MD and GAD, disorders with higher prevalences in females than males, $FGRS_{DUD}$ was significantly higher in males. For DUD and AUD, which have higher prevalences in males, $FGRS_{DUD}$ was significantly higher in females.

One finding that further complicates the sex differences in genetic risk is that prior approaches have solely looked at the genetic risk for the disorder under consideration – e.g., genetic risk for AUD in AUD male and female cases[34]. But our results show that the sex effects are more complex. Compared to male AUD cases, females (where the disorder is rarer) have significantly higher levels of *both* $FGRS_{DUD}$ and $FGRS_{MD}$. Compared to female MD cases, males

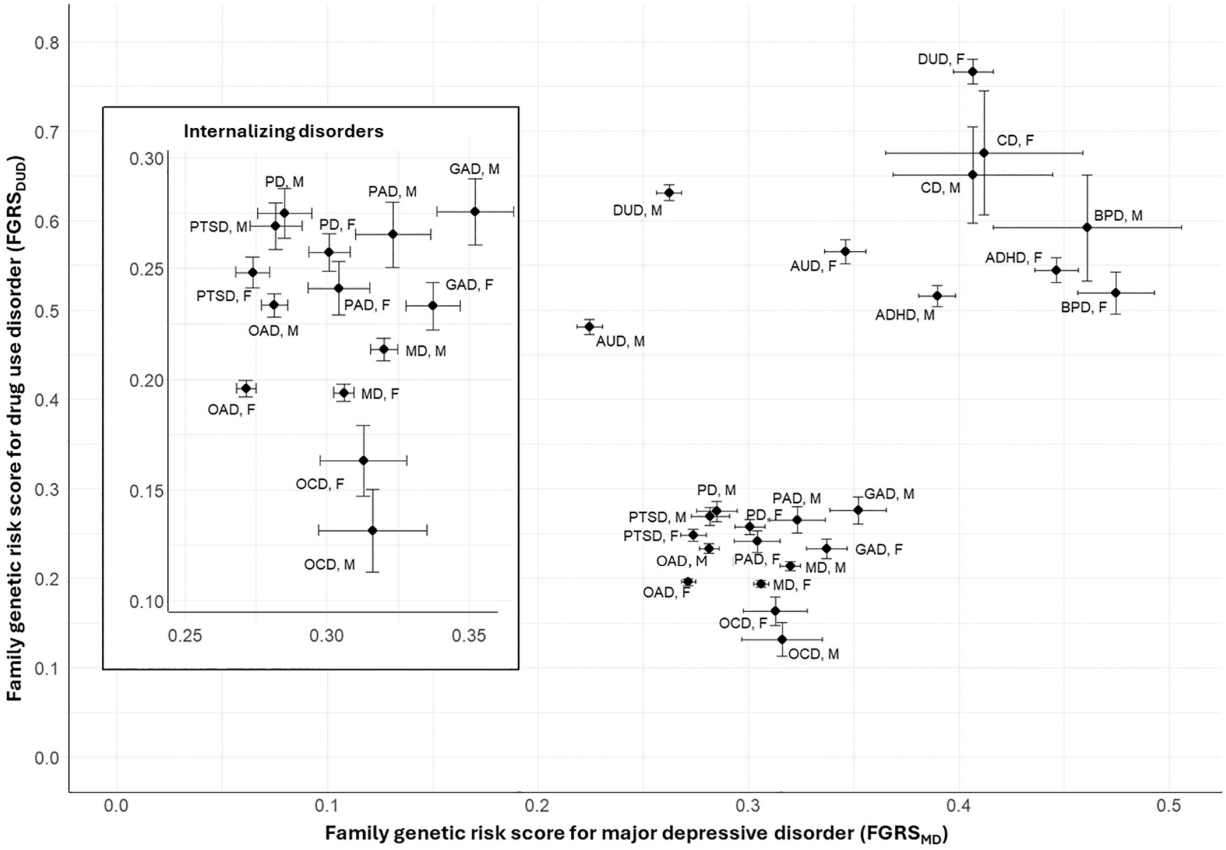

Figure 2 Genetic map containing the locations (± 95% CI) of 12 psychiatric disorders as a function of their family genetic risk score (FGRS) for drug use disorder (DUD) on the y-axis and major depression (MD) on the x-axis, divided into males (M) and females (F). ADHD – attention-deficit/hyperactivity disorder, AUD – alcohol use disorder, BPD – borderline personality disorder, CD – conduct disorder, GAD – generalized anxiety disorder, OAD – other anxiety disorders, OCD – obsessive-compulsive disorder, PAD – phobic anxiety disorders, PD – panic disorder, PTSD – post-traumatic stress disorder. The insert in the left part of the figure is an enlargement of the section of the main figure depicting the locations of internalizing disorders.

(where the disorder is rarer) have higher levels of *both* $FGRS_{MD}$ and $FGRS_{DUD}$.

Fourth, substantial evidence concerning both psychiatric and biomedical multifactorial disorders suggests that early onset is often an index of high familial/genetic risk[36-40]. We have been able to advance these findings by showing that the higher genetic risk associated with early age at onset is not always restricted to the disorder of interest. Indeed, in half of our 12 disorders, early onset forms were associated with significantly higher genetic risks for *both* DUD and MD. Furthermore, our results demonstrate how variable the magnitude of the genetic risk related to age at onset can be, with much larger effects seen for CD, AUD and MD, compared to small significant effects for PD and non-significant effects for GAD and BPD. Further research will be needed to explain the reverse effects seen for ADHD, with higher $FGRS_{DUD}$ in late- versus early-onset cases.

Fifth, we also saw a diversity of effects on genetic risk patterns when we divided our 12 disorders on level of recurrence: nine disorders differed on both $FGRS_{MD}$ and $FGRS_{DUD}$ in the expected direction. Some effects were very large – as for AUD, DUD and PTSD – and involved substantial changes in both genetic risks. Others were smaller, and some non-significant (BPD, CD). Together with our findings for age at onset, these results strongly suggest that genetic liabilities for psychiatric disorders do far more than predispose to the disorder. Rather, the genetic risk manifests in key clinical features.

Finally, we examined the position in our genetic map of psychotic, neurodevelopmental, eating and bipolar disorders. While each of these disorders is largely defined by unique genetic risk factors, it is noteworthy that none of them fell within the confines of the classical internalizing and externalizing disorders, and all of them – with the exception of BD – was closer to the internalizing than the externalizing space. This suggests, consistent with recent evidence[15], that the internalizing disorder group may come closer than other disorder groups in indexing a broad genetic vulnerability to all mental health conditions. That BD is the only disorder closer to the externalizing than to the internalizing cluster on our map is not surprising, since manic episodes are characterized by disinhibited and impulsive behaviors.

These results should be considered in the context of six potentially important limitations. First, the validity of our findings is dependent upon the quality of the diagnoses in the Swedish registers. These diagnoses are not research-based, but rather represent an av-

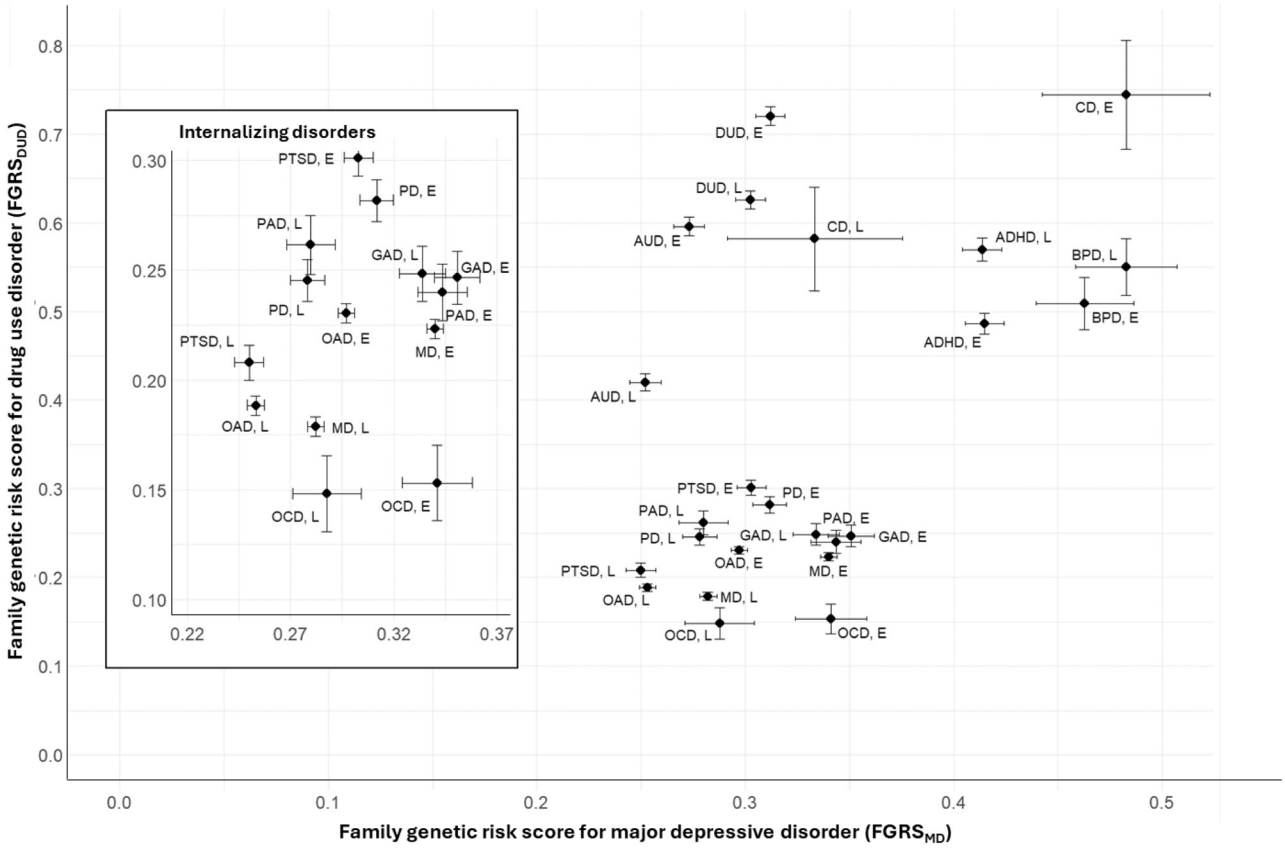

Figure 3 Genetic map containing the locations (± 95% CI) of 12 psychiatric disorders as a function of their family genetic risk score (FGRS) for drug use disorder (DUD) on the y-axis and major depression (MD) on the x-axis, divided into individuals with an early (E) or a late (L) age at onset. ADHD – attention-deficit/hyperactivity disorder, AUD – alcohol use disorder, BPD – borderline personality disorder, CD – conduct disorder, GAD – generalized anxiety disorder, OAD – other anxiety disorders, OCD – obsessive-compulsive disorder, PAD – phobic anxiety disorders, PD – panic disorder, PTSD – post-traumatic stress disorder. The insert in the left part of the figure is an enlargement of the section of the main figure depicting the locations of internalizing disorders.

Table 3 P-values for test of equality between groups according to sex, age at onset, and frequency of registrations for the level of mean genetic risk for drug use disorder ($FGRS_{DUD}$) and major depression ($FGRS_{MD}$)

	$FGRS_{DUD}$			$FGRS_{MD}$		
	Sex	**Age at registration**	**Number of registrations**	**Sex**	**Age at registration**	**Number of registrations**
Major depression (MD)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Alcohol use disorder (AUD)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Drug use disorder (DUD)	<0.0001	<0.0001	<0.0001	<0.0001	0.0682	<0.0001
Attention-deficit/hyperactivity disorder (ADHD)	0.002	<0.0001	<0.0001	<0.0001	0.8473	<0.0001
Conduct disorder (CD)	0.582	0.0002	0.8544	0.860	<0.0001	0.2964
Obsessive-compulsive disorder (OCD)	0.013	0.6867	0.0480	0.789	<0.0001	<0.0001
Phobic anxiety disorders (PAD)	0.0139	0.0232	<0.0001	0.0322	<0.0001	<0.0001
Other anxiety disorders (OAD)	<0.0001	<0.0001	<0.0001	0.0010	<0.0001	<0.0001
Panic disorder (PD)	0.0131	<0.0001	<0.0001	0.0102	<0.0001	<0.0001
Generalized anxiety disorder (GAD)	<0.0001	0.8348	<0.0001	0.0807	0.0346	<0.0001
Post-traumatic stress disorder (PTSD)	0.0010	<0.0001	<0.0001	0.1514	<0.0001	<0.0001
Borderline personality disorder (BPD)	0.0222	0.0637	0.6839	0.5757	0.2491	0.0348

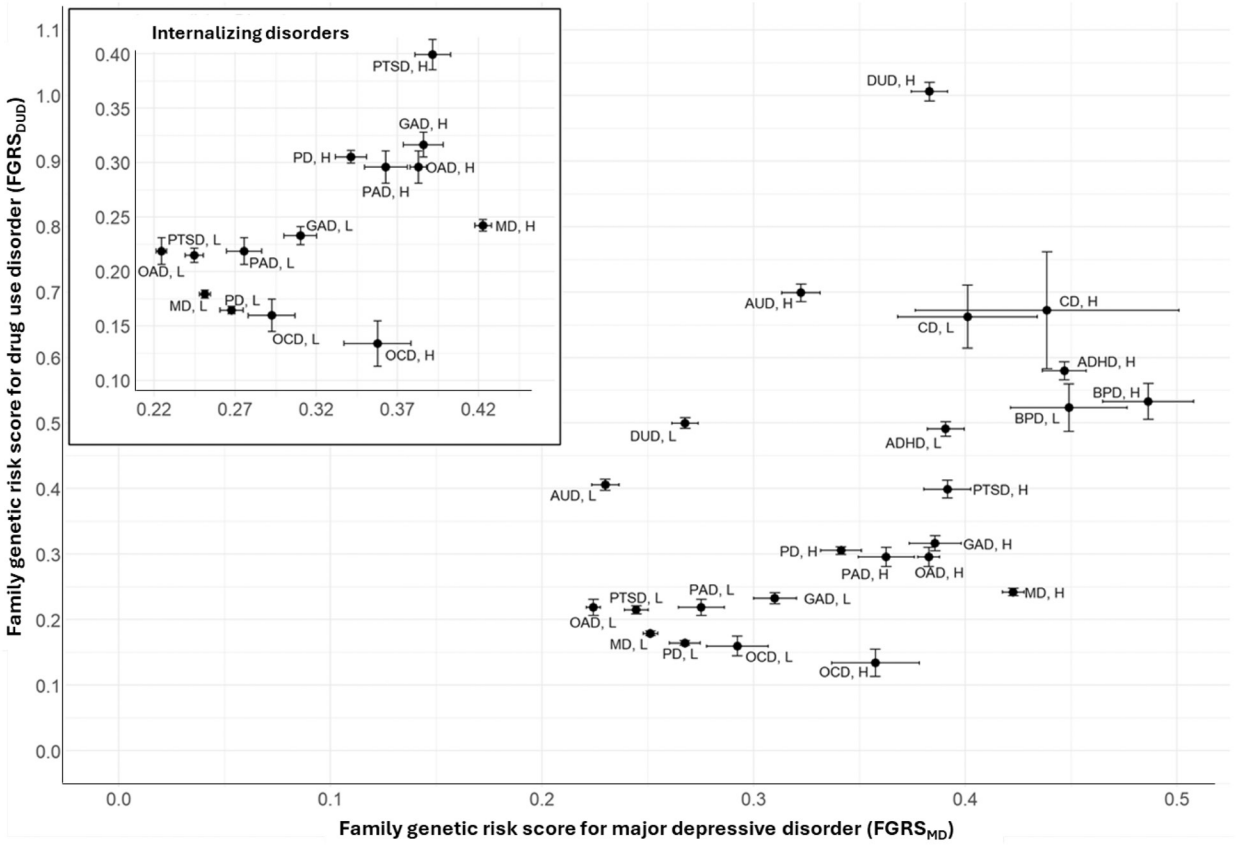

Figure 4 Genetic map containing the locations (± 95% CI) of 12 psychiatric disorders as a function of their family genetic risk score (FGRS) for drug use disorder (DUD) on the y-axis and major depression (MD) on the x-axis, divided into individuals with low (L) or high (H) level of recurrence. ADHD – attention-deficit/hyperactivity disorder, AUD – alcohol use disorder, BPD – borderline personality disorder, CD – conduct disorder, GAD – generalized anxiety disorder, OAD – other anxiety disorders, OCD – obsessive-compulsive disorder, PAD – phobic anxiety disorders, PD – panic disorder, PTSD – post-traumatic stress disorder. The insert in the left part of the figure is an enlargement of the section of the main figure depicting the locations of internalizing disorders.

eraging of the diagnostic approach of Swedish psychiatric clinicians over a number of decades. As is true of other Scandinavian countries, Sweden has had a long tradition of careful and conservative psychiatric diagnoses. The validity of Swedish hospital diagnoses of SZ and BD is well supported[41-43], as is the validity of the diagnoses of MD and anxiety disorders based on their prevalence, sex ratio, sibling and twin correlations, and associations with psychosocial risk factors[44]. The validity of AUD and DUD diagnoses is supported by the high rates of concordance across ascertainment methods[45,46], and the patterns of resemblance in relatives similar to those found in personally interviewed samples[47,48]. The diagnosis of ADHD in Sweden is validated by its close relationship with the receipt of stimulant medication[49]. We are not aware of a specific validation of Swedish register diagnoses of AN and BN, although they have been used in a number of prior research studies[50-52].

Second, we examined maps defined by the genetic risk for two disorders which, we judged, typified internalizing and externalizing disorders (MD and DUD). How much would our results differ if we used different disorders? We present in the supplementary information our key results for two additional pairs of disorders. While there were some modest individual differences across these analyses, the major pattern of results was stable.

Third, the sample sizes for our disorders varied widely. Thus, some of the differences in results across disorders could depend upon the associated differences in statistical power.

Fourth, FGRSs derive from diagnoses in extended pedigrees. We correct for shared environmental effects (specifically, for both parent-offspring and sibling relationships), with the validity of this method supported by simulations[53]. We have formally compared, both empirically and via simulations, the FGRSs and polygenic risk scores[20,54], showing that both scores behave (i.e., predict outcomes and intercorrelate) as measures of additive genetic liability consistent with expected levels of measurement error.

Fifth, we adopted a naturalistic approach to diagnoses in this report and did not attempt the difficult task of "correcting" for comorbidity, as it is not clear, given our research goals, that such corrections would produce more valid results. However, we have developed such a method based on the number of registrations for a comorbid disorder, which permits us to extrapolate the expected FGRS assuming no such diagnoses. Using this method, we observed a greater separation between AUD and DUD and between MD and anxiety disorders than in our main analysis (see supplementary information).

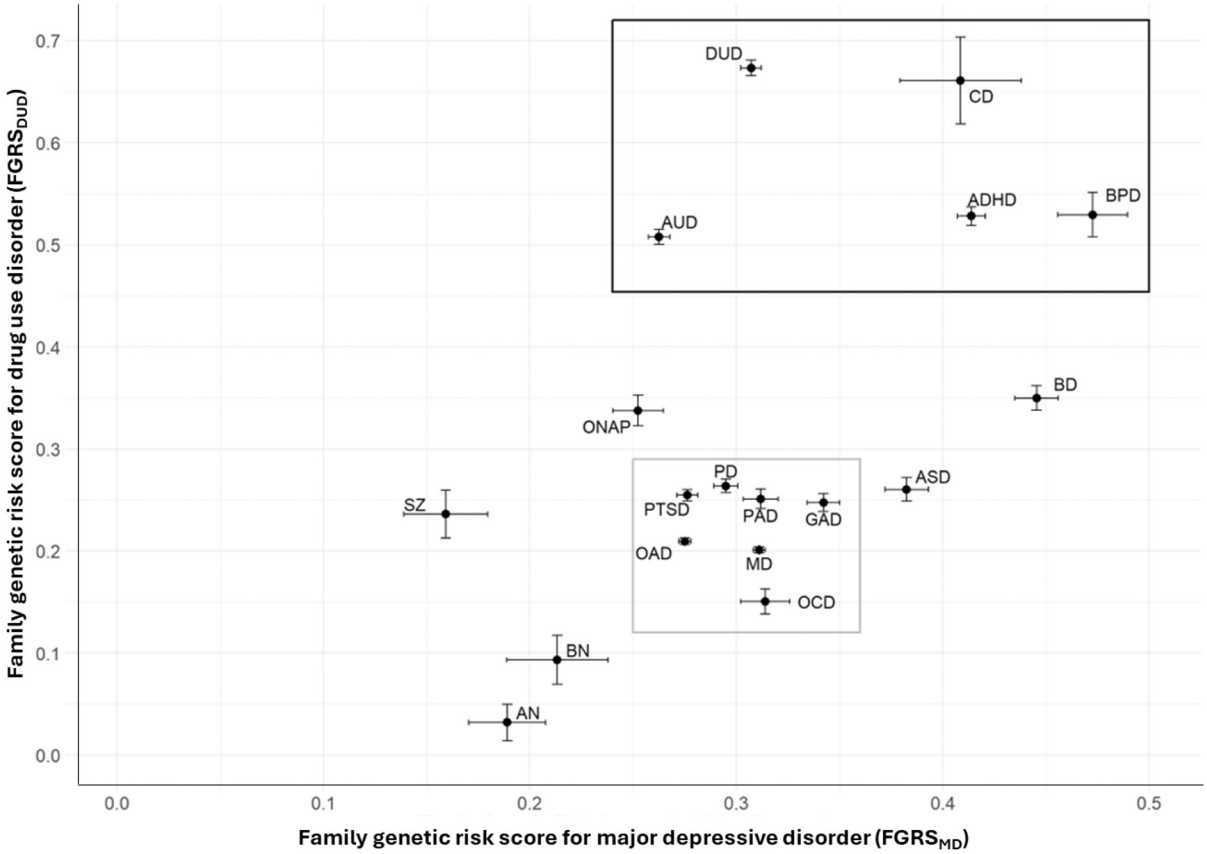

Figure 5 Genetic map containing the locations (± 95% CI) of 18 psychiatric disorders as a function of their family genetic risk score (FGRS) for drug use disorder (DUD) on the y-axis and major depression (MD) on the x-axis, with boxes for internalizing disorders (lower center of the figure) and externalizing disorders (upper right of the figure). ADHD – attention-deficit/hyperactivity disorder, AN – anorexia nervosa, ASD – autism spectrum disorder, AUD – alcohol use disorder, BD – bipolar disorder, BN – bulimia nervosa, BPD – borderline personality disorder, CD – conduct disorder, GAD – generalized anxiety disorder, OAD – other anxiety disorders, OCD – obsessive-compulsive disorder, ONAP – other non-affective psychoses, PAD – phobic anxiety disorders, PD – panic disorder, PTSD – post-traumatic stress disorder, SZ – schizophrenia.

Sixth, since we utilized register resources unique to Sweden, especially the primary care diagnoses[55], external replication of our findings was infeasible. Therefore, to test stability of our findings, we turned to an internal replication in the three traditional geographical regions of Sweden: Southern or Götaland (48% of the population), Central or Svealand (41%) and Northern or Norrland (11%). As reported in the supplementary information, the overall pattern of findings was very similar across the three populations.

In conclusion, our study produced a number of informative and potentially novel findings. Overall, we suggest two major conclusions from our efforts. First, examining multiple genetic risks together can refine our understanding of the genetic inter-relationships between psychiatric disorders. Second, sub-phenotypes of disorders – including sex, age at onset, and level of recurrence – can provide important further insights into the impact of genetic risk factors on disease risk and its clinical manifestation.

ACKNOWLEDGEMENTS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the 1975 Helsinki Declaration, as revised in 2008. We secured ethical approval for this study from the Regional Ethical Review Board in Lund (no. 2008/409). This project was supported in part by the US National Institutes of Health (grants nos. R01DA030005, R01AA023534 and 5U01MH126798) and the Swedish Research Council (grants nos. 2020-01175, 2021-06467, 2024-02796). The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication. Supplementary information on this study is available at https://doi.org/10.5281/zenodo.17297516.

REFERENCES

1. Kendler KS. Wilhelm Mayer's follow-up study of Kraepelin's cases of paraphrenia: diagnostic validity in 1921. Mol Psychiatry 2023;28:236-41.
2. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970;126:983-7.
3. Boven W. Similarité et Mendélisme dans l'hérédité de la démence précoce et de la folie maniaque-depressive. Châtel-St-Denis: Säuberlin & Pfeiffer, 1915.
4. Kendler KS, Justis V. William Boven's 1915 thesis "Similarity and Mendelism in the heredity of dementia praecox and manic-depressive insanity". Am J Med Genet B Neuropsychiatr Genet 2024;195:e32961.
5. Kendler KS, Klee A. The examination of Kraepelin's diagnoses of dementia praecox and manic-depressive insanity in pedigrees: studies of Schuppius in 1912 and Wittermann in 1913. Am J Med Genet B Neuropsychiatr Genet 2023;192:113-23.
6. Kraepelin E. Psychiatrie: Ein Lehrbuch fur Studirende und Aerzte, 6th ed. Leipzig: Barth, 1899.
7. Krueger RF. The structure of common mental disorders. Arch Gen Psychiatry 1999; 56:921-6.

8. Kendler KS, Aggen SH, Knudsen GP et al. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV Axis I and all Axis II disorders. Am J Psychiatry 2011;168:29-39.
9. Kendler KS, Prescott CA, Myers J et al. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch Gen Psychiatry 2003;60:929-37.
10. Cosgrove VE, Rhee SH, Gelhorn HL et al. Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. J Abnorm Child Psychol 2011;39:109-23.
11. Gustavson DE, Franz CE, Panizzon MS et al. Internalizing and externalizing psychopathology in middle age: genetic and environmental architecture and stability of symptoms over 15 to 20 years. Psychol Med 2020;50:1530-8.
12. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell 2019;179:1469-82.e11.
13. Waldman ID, Poore HE, Luningham JM et al. Testing structural models of psychopathology at the genomic level. World Psychiatry 2020;19:350-9.
14. Grotzinger AD, Mallard TT, Akingbuwa WA et al. Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic and molecular genetic levels of analysis. Nat Genet 2022;54:548-59.
15. Grotzinger AD, Werme J, Peyrot WJ et al. The landscape of shared and divergent genetic influences across 14 psychiatric disorders. medRxiv 2025; 2025. 2001.2014.25320574.
16. Kendler KS, Ohlsson H, Sundquist J et al. Family genetic risk scores and the genetic architecture of major affective and psychotic disorders in a Swedish national sample. JAMA Psychiatry 2021;78:735-43.
17. Kendler KS, Ohlsson H, Sundquist J et al. Impact of comorbidity on family genetic risk profiles for psychiatric and substance use disorders: a descriptive analysis. Psychol Med 2023;53:2389-8.
18. Kendler KS, Ohlsson H, Sundquist J et al. The patterns of family genetic risk scores for eleven major psychiatric and substance use disorders in a Swedish national sample. Transl Psychiatry 2021;11:326.
19. Kendler KS, Ohlsson H, Sundquist J et al. Relationship of family genetic risk score with diagnostic trajectory in a Swedish national sample of incident cases of major depression, bipolar disorder, other nonaffective psychosis, and schizophrenia. JAMA Psychiatry 2023;80:241-9.
20. Krebs MD, Hellberg K-L G, Lundberg M et al. Genetic liability estimated from large-scale family data improves genetic prediction, risk score profiling, and gene-mapping for major depression. Am J Hum Genet 2024;111:2494-509.
21. Kendler KS, Myers J. The boundaries of the internalizing and externalizing genetic spectra in men and women. Psychol Med 2014;44:647-55.
22. Kendler KS, Lonn SL, Maes HH et al. A Swedish population-based multivariate twin study of externalizing disorders. Behav Genet 2016;46:183-92.
23. Hicks BM, Krueger RF, Iacono WG et al. Family transmission and heritability of externalizing disorders: a twin-family study. Arch Gen Psychiatry 2004;61:922-8.
24. SAS Institute. SAS/STAT user's guide, version 9.4. New York: STATS Publishing Inc., 2012.
25. Munafo MR, Davey-Smith G. Robust research needs many lines of evidence. Nature 2018;553:399-401.
26. Nievergelt CM, Maihofer AX, Atkinson EG et al. Genome-wide association analyses identify 95 risk loci and provide insights into the neurobiology of post-traumatic stress disorder. Nat Genet 2024;56:792-808.
27. Wolf EJ, Miller MW, Krueger RF et al. Posttraumatic stress disorder and the genetic structure of comorbidity. J Abnorm Psychol 2010;119:320-30.
28. Kotov R, Krueger RF, Watson D et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): a quantitative nosology based on consensus of evidence. Annu Rev Clin Psychol 2021;17:83-108.
29. Hettema JM, Prescott CA, Myers JM et al. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Arch Gen Psychiatry 2005;62:182-9.
30. Hettema JM, Neale MC, Myers J et al. A population-based twin study of the relationship between neuroticism and internalizing disorders. Am J Psychiatry 2006; 163:857-64.
31. Bienvenu OJ, Samuels JF, Wuyek LA et al. Is obsessive-compulsive disorder an anxiety disorder, and what, if any, are spectrum conditions? A family study perspective. Psychol Med 2012;42:1-13.
32. Reichborn-Kjennerud T, Ystrom E, Neale MC et al. Structure of genetic and environmental risk factors for symptoms of DSM-IV borderline personality disorder. JAMA Psychiatry 2013;70:1206-14.
33. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. Mol Psychiatry 2019;24:562-75.
34. Cloninger CR, Christiansen KO, Reich T et al. Implications of sex differences in the prevalences of antisocial personality, alcoholism, and criminality for familial transmission. Arch Gen Psychiatry 1978;35:941-51.
35. Carter C. An ABC of medical genetics. 6. Polygenic inheritance and common diseases. Lancet 1969;1:1252-6.
36. Goldstein RB, Wickramaratne PJ, Horwath E et al. Familial aggregation and phenomenology of 'early'-onset (at or before age 20 years) panic disorder. Arch Gen Psychiatry 1997;54:271-8.
37. Kendler KS, Gatz M, Gardner CO et al. Age at onset and familial risk for major depression in a Swedish national twin sample. Psychol Med 2005;35:1573-9.
38. Niiranen TJ, McCabe EL, Larson MG et al. Heritability and risks associated with early onset hypertension: multigenerational, prospective analysis in the Framingham Heart Study. BMJ 2017;357:j1949.
39. Piko P, Werissa NA, Fiatal S et al. Impact of genetic factors on the age of onset for type 2 diabetes mellitus in addition to the conventional risk factors. J Pers Med 2020;11:6.
40. Reid S, Alexsson A, Frodlund M et al. High genetic risk score is associated with early disease onset, damage accrual and decreased survival in systemic lupus erythematosus. Ann Rheum Dis 2020;79:363-9.
41. Lichtenstein P, Bjork C, Hultman CM et al. Recurrence risks for schizophrenia in a Swedish national cohort. Psychol Med 2006;36:1417-25.
42. Sellgren C, Landen M, Lichtenstein P et al. Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. Acta Psychiatr Scand 2011;124:447-53.
43. Ekholm B, Ekholm A, Adolfsson R et al. Evaluation of diagnostic procedures in Swedish patients with schizophrenia and related psychoses. Nord J Psychiatry 2005;59:457-64.
44. Kendler KS, Ohlsson H, Lichtenstein P et al. The genetic epidemiology of treated major depression in Sweden. Am J Psychiatry 2018;175:1137-44.
45. Kendler KS, Lönn SL, Salvatore J et al. The origin of spousal resemblance for alcohol use disorder. JAMA Psychiatry 2018;75:280-6.
46. Kendler KS, Ji J, Edwards AC et al. An extended Swedish national adoption study of alcohol use disorder. JAMA Psychiatry 2015;72:211-8.
47. Prescott CA, Kendler KS. Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. Am J Psychiatry 1999;156:34-40.
48. Tsuang MT, Lyons MJ, Eisen SA et al. Genetic influences on DSM-III-R drug abuse and dependence: a study of 3,372 twin pairs. Am J Med Genet 1996;67:473-7.
49. Sundquist J, Ohlsson H, Sundquist K et al. Attention-deficit/hyperactivity disorder and risk for drug use disorder: a population-based follow-up and co-relative study. Psychol Med 2015;45:977-83.
50. Mårild K, Størdal K, Bulik CM et al. Celiac disease and anorexia nervosa: a nationwide study. Pediatrics 2017;139:e20164367.
51. Yao S, Kuja-Halkola R, Thornton LM et al. Familial liability for eating disorders and suicide attempts: evidence from a population registry in Sweden. JAMA Psychiatry 2016;73:284-91.
52. Mellemkjaer L, Papadopoulos FC, Pukkala E et al. Cancer incidence among patients with anorexia nervosa from Sweden, Denmark and Finland. PLoS One 2015;10:e0128018.
53. Kendler KS, Ohlsson H, Bacanu S et al. Differences in genetic risk score profiles for drug use disorder, major depression, and ADHD as a function of sex, age at onset, recurrence, mode of ascertainment, and treatment. Psychol Med 2023;53:3448-60.
54. Krebs MD, Appadurai V, Hellberg K-L G et al. The relationship between genotype- and phenotype-based estimates of genetic liability to psychiatric disorders, in practice and in theory. Am J Hum Genet 2026;113:184-201.
55. Sundquist J, Ohlsson H, Sundquist K et al. Common adult psychiatric disorders in Swedish primary care (where most mental health patients are treated). BMC Psychiatry 2017;17:235.

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Long-term effects of psychotherapies for depression: an advanced meta-analysis

Pim Cuijpers[1,2], Clara Miguel[1], Esra Kaya Aglio[1], Annemieke van Straten[1], Eirini Karyotaki[3], Mathias Harrer[1]

[1]Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [2]International Institute for Psychotherapy, Babeș-Bolyai University, Cluj-Napoca, Romania; [3]Programme on Clinical Psychology, Faculty of Social and Behavioural Sciences, University of Amsterdam, Amsterdam, The Netherlands

It is well-established that psychotherapies are effective in the treatment of depression. It remains unclear, however, whether the effects persist over the long term. We conducted a comprehensive meta-analysis examining the long-term effects of psychotherapies for depression compared with control conditions. We included randomized controlled trials (RCTs) comparing psychotherapies for adult depression with control conditions (care-as-usual, waitlist, or other) that reported outcomes at six months after randomization or later. The standardized mean difference (SMD) was the main outcome, but we also examined response rates in the treatment and control groups and the relevant risk ratio (RR). We evaluated the effectiveness of psychotherapies over time using a multivariate pooling model with cubic regression splines to allow for potentially non-linear interactions. Dependencies in the true effects were modeled using continuous-time autoregressive variance-covariance matrices. We included 191 RCTs with 209 comparisons between treatment and control groups, involving 33,691 participants (17,715 in the treatment, 15,976 in the control conditions). The trials encompassed 534 follow-up measurements, of which 52 (9.7%) occurred more than 12 months after randomization. The best fitting restricted cubic spline model for long-term SMDs (5 basis functions) indicated that the SMD increased from baseline to 0.55 at 12 weeks, then gradually decreased to 0.39 at around one-year follow-up, and remained largely stable thereafter. The SMD remained statistically significant up to 8.3 years (431 months) after randomization. The RR for response went up to 1.68 after 3 months and slowly decreased over time to 1.14 at 5-year follow-up. The RR remained significant up to 4.5 years (236 weeks). We conclude that psychotherapies have moderate to large effects at 3 months after randomization, which slowly decrease during the next 9 months to a moderate level, and remain stably moderate for several years.

Key words: Psychotherapies, depression, long-term effects, standardized mean difference, response rates, cognitive behavior therapy, behavioral activation

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It is well-established that psychotherapies are effective in the treatment of depression[1]. Hundreds of randomized trials have shown that cognitive behavior therapy, interpersonal psychotherapy, behavioral activation, brief psychodynamic therapy, problem-solving therapy, and several other psychotherapies have significant effects on depression when compared with control conditions, such as waitlists, care-as-usual (CAU), and pill placebo. Psychotherapies have also been found to have comparable effects to antidepressant medications in the short term[2].

It is unclear, however, what the effects of psychotherapies are in the longer term. A previous network meta-analysis found that psychotherapies still have significant effects at one-year follow-up[1], and in two other network meta-analyses it was found that the effects of psychotherapies are superior to those of pharmacotherapy at one-year follow-up[2,3]. These studies built on earlier meta-analyses showing that psychotherapies have significant effects at 6-month and longer follow-up[4,5]. A few other meta-analyses have examined the long-term outcomes of Internet-based interventions for depression and indeed found positive effects at follow-up[6,7]. However, the number of studies with follow-up data at one year or longer was very limited.

The small number of randomized trials with long-term follow-up is a problem in all previous meta-analyses examining long-term outcomes of psychotherapies for depression. The most extensive meta-analysis included 96 trials, but few of these had a follow-up period of more than one year[1]. Furthermore, in those meta-analyses, all follow-up outcomes were clustered into time categories that were examined in separate analyses. More advanced analyses in which all time points from all studies are modelled simultaneously in one analysis have not yet been conducted in this field. Such analyses also make it possible to examine the trajectory of treatment effects over time, rather than only assessing whether the effects remain significant at specific time points.

We therefore conducted an advanced meta-analysis evaluating the long-term outcomes of psychotherapies for depression compared with control conditions, modelling all available follow-up data to estimate the course of effects over time.

METHODS

Identification and selection of studies

The current study is part of a larger meta-analytic project on psychological treatments of depression that was registered in the Open Science Framework[8]. This database has been used in a series of earlier meta-analyses[9], and is updated every four months. The protocol for the current meta-analysis was published in the Open Science Framework[10] and the Metapsy website[11]. Since data collection methods were similar to other papers using data from our main project[9], we followed reporting guidance from the Text Recycling Research Project[12].

The trials included in the current study were identified through the larger existing database of randomized trials on psychological treatment of depression. We searched four major databases (PubMed, PsycINFO, EMBASE and the Cochrane Library) up to

May 1, 2025, by combining index and free terms indicative of depression and psychological treatments, with filters for randomized controlled trials (see supplementary information).

All records were screened by two independent researchers, and all papers that could possibly meet inclusion criteria according to one of the researchers were retrieved as full-text. We checked the primary papers in our database, but also all secondary papers of the same trials. The decision to include or exclude a study in the database was done by the two independent researchers. Disagreements were resolved through discussion.

For the current meta-analysis, we selected randomized controlled trials in adults comparing a psychotherapy for depression with a control condition (waitlist, CAU, placebo, other), reporting outcomes (for treatment and control conditions) at 6 months or longer after randomization. Depression could be defined either as meeting criteria for a depressive disorder according to a diagnostic interview or as a score above the cut-off on a validated self-report depression measure. Only individual, group, telephone, and guided self-help interventions were included. Interventions without any human interaction were excluded[13]. We also excluded studies in inpatients[14], and studies in children and adolescents.

Quality assessment and data extraction

We assessed the validity of included studies using the Cochrane Risk of Bias tool (RoB 2)[15], further adapted for psychological trials[16]. The validity was assessed by two independent reviewers. Disagreements were solved through discussion and, if needed, a third or senior reviewer was consulted. Five domains were examined: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result.

We also coded participant characteristics (clinical diagnosis versus a cut-off as inclusion criterion; type of recruitment; type of target group; mean age; proportion of women); characteristics of the psychotherapies (type of therapy[17]; format; number of sessions), as

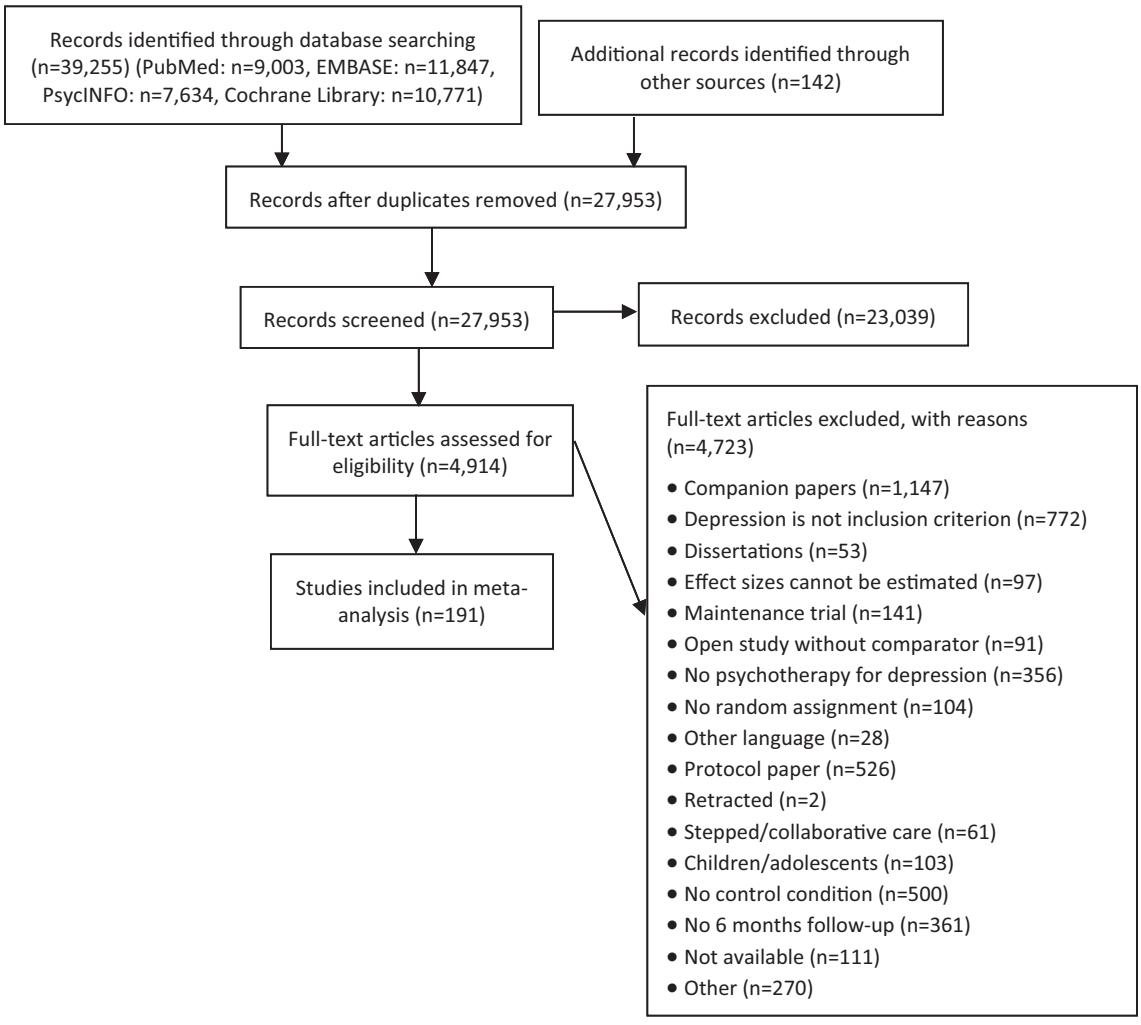

Figure 1 PRISMA flow chart

Table 1 Aggregated characteristics of included studies

Trials (n=191)	
Age, years, mean±SD	44.5±15.8
Sex, % women	72.8
Diagnosis, n (%)	
Meeting criteria for depressive disorder	91 (47.6)
Score above cut-off on self-report scale	100 (52.4)
Recruitment, n (%)	
Clinical	57 (29.8)
Community	49 (25.6)
Other	85 (44.5)
Target group, n (%)	
Adults in general	56 (29.3)
General medical patients	55 (28.8)
Perinatal depression	35 (18.3)
Other specific group	45 (23.6)
Region, n (%)	
Europe	83 (43.4)
North America	57 (29.8)
East Asia	18 (9.4)
Other	33 (17.3)
Control condition, n (%)	
Care-as-usual	141 (73.8)
Waitlist	17 (8.9)
Other	33 (17.3)
Risk of bias, n (%)	
Low	35 (18.3)
Some concerns	77 (40.3)
High	79 (41.4)
Low risk of bias, n (%)	
Randomization process	119 (62.3)
Deviations from intended interventions	155 (81.1)
Missing outcome data	112 (58.6)
Measurement of outcome	181 (94.8)
Selection of reported result	62 (32.5)
Comparisons (n=209)	
Treatment, n (%)	
Cognitive behavior therapy	106 (50.7)
Third wave therapy	14 (6.7)
Behavioral activation	22 (10.5)
Interpersonal psychotherapy	15 (7.2)
Problem-solving therapy	11 (5.3)
Other	41 (19.6)
Format, n (%)	
Individual	85 (40.7)
Group	60 (28.7)
Guided self-help	30 (14.3)
Mixed/other	34 (16.3)
Number of sessions, mean±SD	9.8±5.7
Follow-up measurements (n=534)	
1-3 months, n (%)	134 (25.1)
>3-6 months, n (%)	174 (32.6)
>6-9 months, n (%)	99 (18.5)
>9-12 months, n (%)	75 (14.0)
>12-24 months, n (%)	37 (6.9)
>24 months, n (%)	15 (2.8)

well as general characteristics of the studies (type of control condition; region where the study was conducted).

For the current study, we also extracted the time from randomization to follow-up measurement in weeks. We did this separately for each of the follow-up assessments in the study.

Outcome measures

For each time point, we calculated the standardized mean difference (SMD) between the treatment and the control condition, adjusted for small-sample bias (yielding Hedges' g). We collected all post-treatment outcomes (including those before 6 months post-randomization) and each follow-up outcome for the included studies. For trials in which the interventions lasted more than 6 months, we started to collect data points at 6 months after randomization.

When trials provided more than one depression outcome measure, we selected one measure, based on its frequency of use (1. Beck Depression Inventory, BDI[18]; 2. Revised Beck Depression Inventory, BDI-II[19]; 3. 17-item Hamilton Depression Rating Scale, HAMD-17[20]; 4. Patient Health Questionnaire-9, PHQ-9[21]; 5. Center for Epidemiologic Studies Depression Scale, CES-D[22]; 6. Edinburgh Postnatal Depression Scale, EPDS[23]; 7. Geriatric Depression Scale, GDS[24]).

When the means and standard deviations were not reported, we used change scores. If these were not reported either, we converted binary outcomes to Hedges' g (assuming a logistic distribution) or used other statistics (e.g., p-value, t-value) to calculate the effect size. When means were only reported in figures, we used PlotDigitizer 3.1.6 to extract them[25]. Missing standard deviations were imputed using the pooled standard deviations of the outcome measures from other studies in the database[26].

Response was defined as a 50% symptom reduction from baseline to post-test, and was calculated by a validated method using the baseline and post-test means and standard deviations of the continuous outcome measures, and the number of patients at post-test[27]. This method of estimating response rates has been tested in five meta-analyses of treatments of depression and anxiety[2,27], resulting

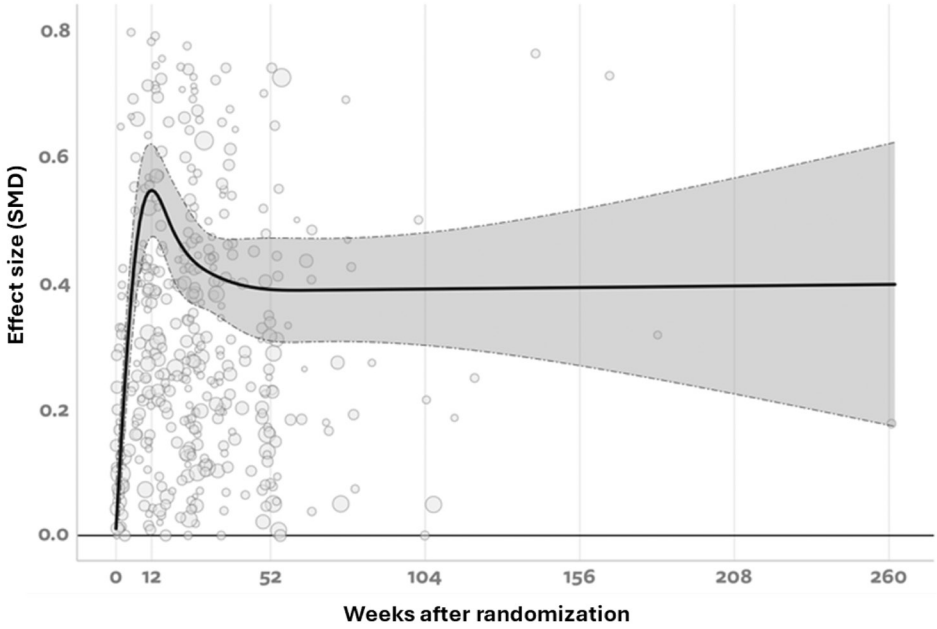

Figure 2 Standardized mean differences (SMDs) between psychotherapies and control conditions (with 95% CIs) at different times during follow-up (restricted cubic spline model with 5 basis functions)

in correlations between 0.94 and 0.97 between the estimated and true response rates.

We calculated the risk ratio (RR) for response as the response rate in the treatment groups divided by the rate in the control groups. In the main analysis, we included all randomized participants, classifying dropouts as non-responders. As a sensitivity analysis, we repeated the analyses when assuming different missingness mechanisms (see below).

Meta-analyses

The meta-analyses were conducted using the 'metapsyTools' package in R (version 4.1.1)[28]. This package was specifically developed for our meta-analytic project and imports the functionality from the 'meta'[29], 'metafor'[30], and 'dmetar'[31] packages.

To model the effectiveness of psychotherapies over time, a multivariate pooling model was applied[32]. Dependencies in the true effects were modeled using continuous-time autoregressive variance-covariance matrices. Within studies, sampling variance-covariance matrices were constructed assuming an autoregressive AR (1) process with a one-week autocorrelation of ϕ=0.9.

Within these models, we used cubic regression splines to allow for potentially non-linear interactions. We considered 4 to 8 basis functions and chose the best-fitting approximation based on the corrected Akaike's information criterion of the model. This approach was used to model both effects expressed as SMDs (Hedges' g) and differential response rates, for which we employed log-risk ratios. Using the fitted models, predicted effects of psychotherapy were calculated for each week post-randomization, along with prediction intervals.

For many of the included trials, long-term results were only available for patients who adhered to the study protocol, with substantial dropout over time. If these dropouts followed a missing not at random (MNAR) pattern, it is possible that the true effects in the intention-to-treat sample are overestimated. To account for this, RRs in the main analysis were calculated assuming that all dropouts were non-responders. Furthermore, we assessed the impact of more or less severe MNAR patterns in a tipping point analysis (δ-adjustment)[33]. To this end, we recalculated both SMDs and RRs (and their sampling variances) under the assumption that the effect among dropouts was 25%, 50% or 75% smaller than recorded, or that it was completely null (SMD=0 and RR=1, respectively).

Fixed regression coefficients were added to the main longitudinal analysis model to examine effect moderators. For categorical moderators, the meta-regression models were stratified by moderator level, and we examined whether the effects over time (linear

Table 2 Standardized mean differences (SMDs) between psychotherapies and control conditions at key follow-up time points

Follow-up time point	SMD	95% CI	PI	p
3 months	0.544	0.47-0.61	–0.28 to 1.36	<0.001
6 months	0.434	0.37-0.50	–0.38 to 1.25	<0.001
9 months	0.400	0.33-0.47	–0.42 to 1.22	<0.001
1 year	0.389	0.31-0.47	–0.43 to 1.21	<0.001
1.5 years	0.388	0.31-0.47	–0.43 to 1.21	<0.001
2 years	0.390	0.30-0.48	–0.43 to 1.21	<0.001
3 years	0.392	0.27-0.52	–0.43 to 1.22	<0.001
4 years	0.394	0.22-0.57	–0.44 to 1.23	<0.001
5 years	0.397	0.17-0.62	–0.45 to 1.24	<0.001

PI – prediction interval

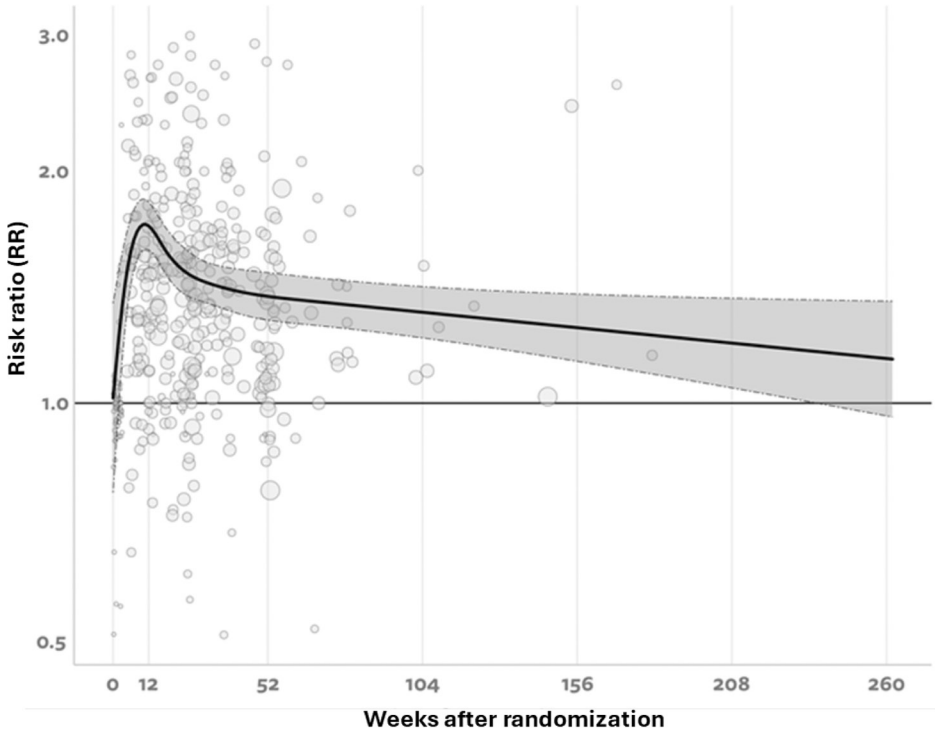

Figure 3 Risk ratios (RRs) for response in psychotherapies and control conditions (with 95% CIs) at different times during follow-up (restricted cubic spline model with 5 basis functions)

slope) differed significantly compared to a reference category by adding time-by-moderator interactions.

RESULTS

Selection and inclusion of studies

After examining 39,397 records (27,953 after removal of duplicates), we retrieved 4,914 full-text papers and excluded 4,723. The PRISMA flow chart, with reasons for exclusion, is presented in Figure 1. A total of 191 randomized trials (with 209 comparisons between a treatment and a control group) met inclusion criteria.

Characteristics of included studies

Table 1 provides the aggregated characteristics of the included 191 studies (see supplementary information for the characteristics of the individual studies). The trials included 33,691 participants (17,715 in the treatment, 15,976 in the control conditions). The mean age of participants was 44.5±15.8 years, and the proportion of women was 72.8%.

In 91 trials (47.6%), participants met criteria for a depressive disorder according to a diagnostic interview, while in the remaining trials participants scored above a cut-off on a self-report scale (100 trials, 52.4%). Participants were recruited from clinics and clinical referrals in 57 trials (29.8%), while in the other trials participants were recruited through the community (49 trials, 25.6%) or other methods (85 trials, 44.5%).

A total of 56 trials were aimed at adults in general (29.3%), while the others were aimed at specific target groups, such as general medical patients (55 trials, 28.8%); women with perinatal depression (35 trials, 18.3%); or other groups (45 trials, 23.6%).

In most studies (141 trials, 73.8%), care-as-usual was used as the control condition; 17 studies (8.9%) used waitlist, and the remaining 33 (17.3%) used another control condition. Most trials were conducted in Europe (83 trials, 43.4%); the others were carried out in North America (57 trials, 29.8%), East Asia (18 trials, 9.4%), or in other regions (33 trials, 17.3%).

Cognitive behavior therapy was examined in 106 of the 209 comparisons (50.7%), 14 examined a third-wave therapy (6.7%), 22 behavioral activation (10.5%), 15 interpersonal psychotherapy (7.2%), 11 problem-solving therapy (5.3%), and the remaining 41 examined another type of therapy (19.6%). Of the 209 comparisons, 85 examined an individual format (40.7%), 60 a group format (28.7%), 30 guided self-help (14.3%) and the remaining 34 examined a mixed or other format (16.3%). The mean number of sessions was 9.8±5.7.

Of the 191 trials, 119 (62.3%) were assessed as low risk arising from the randomization process, 155 (81.1%) as low risk due to deviations from intended interventions, 112 (58.6%) as low risk due to missing outcome data, 181 (94.8%) as low risk in the measurement of the outcome, and 62 (32.5%) as low risk in the selection of the

Table 3 Risk ratios (RRs) for response in psychotherapies and control conditions at key follow-up time points

Follow-up time point	RR	95% CI	PI	p
3 months	1.68	1.57-1.80	0.94-3.02	<0.001
6 months	1.47	1.37-1.57	0.82-2.62	<0.001
9 months	1.41	1.32-1.50	0.79-2.52	<0.001
1 year	1.38	1.28-1.48	0.77-2.47	<0.001
1.5 years	1.34	1.25-1.44	0.75-2.41	<0.001
2 years	1.31	1.22-1.42	0.73-2.35	<0.001
3 years	1.25	1.13-1.39	0.70-2.25	<0.001
4 years	1.20	1.05-1.37	0.66-2.17	0.009
5 years	1.14	0.96-1.36	0.62-2.09	0.128

PI – prediction interval

reported result. The overall risk of bias was assessed as low in 35 trials (18.3%), as "some concerns" in 77 trials (40.3%) and as high in 79 trials (41.4%).

The 209 comparisons included 534 follow-up measurements: 308 (57.7%) between 1 and 6 months since randomization, 174 (32.6%) between >6 and 12 months, and 52 (9.7%) at more than 12 months. The 52 measurements with a follow-up longer than one year included 37 between >12 and 24 months, eight between 2 and 4 years, three between 5 and 6 years, and four between 7 and 10 years. On average, each of the comparisons had 2.6 follow-up measurements (range: 1 to 8).

Long-term effects of psychological treatments of depression

The best fitting restricted cubic spline model for the long-term SMDs had 5 basis functions. Figure 2 provides a graphical representation of the estimated SMDs over 5 years post-randomization, and Table 2 lists the results of the estimated SMDs at a selection of follow-up times up to 5 years. The SMD increased from baseline to 0.55 at 12 weeks, then gradually decreased to 0.39 at around one-year follow-up, remaining largely stable thereafter. The SMD remained statistically significant up to 8.3 years (431 months) after randomization.

The SMDs of the tipping point analyses (assuming that the effect among dropouts was 25%, 50%, 75% or 100% smaller than recorded) are reported in the supplementary information. The general pattern of change was comparable to the main analyses, although the effect sizes were somewhat smaller. In the most conservative model (effects among dropout being zero), the SMD was 0.46 at 12 weeks after randomization and then decreased to 0.33 after one year, remaining largely stable at all other follow-up points.

Response rates and risk ratios

The best-fitting restricted cubic spline model for the long-term RRs for response also had 5 basis functions. Figure 3 provides a graphical representation of the estimated RRs in the treatment and control conditions over 5 years post-randomization, and Table 3 lists the estimated RRs at a selection of follow-up times up to 5 years. The RR went up to 1.68 after 3 months and then slowly decreased over time to 1.14 at 5-year follow-up. The RR remained statistically significant up to 4.5 years (236 weeks).

The RRs of the tipping point analyses are reported in the supplementary information. The pattern of change over time was comparable to the main analyses, although the absolute values were smaller. Even in the most conservative analyses (all drop-outs being non-responders and the effect among dropouts being 100% smaller than recorded), the effect remained statistically significant up to 2.6 years (133 weeks).

For the response rates in the treatment and control groups, the best-fitting restricted cubic spline models had 8 basis functions. The response rates in the treatment groups increased to 38% at week 10, decreased to 31% at week 17, and increased again to 34-35% after week 23, then remaining stable (see Table 4 and supplementary information). The response rates in the control conditions increased to 22% at week 10, declined to 18% at week 17, and increased again

Table 4 Response rates in psychotherapies and control conditions at key follow-up time points

	Psychotherapies			Control conditions		
Follow-up time point	Rate	95% CI	PI	Rate	95% CI	PI
3 months	0.34	0.31-0.37	0.10-0.70	0.19	0.17-0.21	0.06-0.46
6 months	0.34	0.31-0.37	0.10-0.71	0.23	0.20-0.25	0.07-0.51
9 months	0.34	0.31-0.37	0.10-0.70	0.24	0.22-0.26	0.08-0.53
1 year	0.35	0.32-0.38	0.10-0.71	0.24	0.21-0.26	0.08-0.53
1.5 years	0.35	0.32-0.39	0.11-0.72	0.24	0.21-0.27	0.08-0.53
2 years	0.35	0.32-0.39	0.11-0.72	0.25	0.22-0.28	0.08-0.54
3 years	0.35	0.31-0.40	0.11-0.72	0.26	0.23-0.30	0.09-0.56
4 years	0.35	0.29-0.42	0.10-0.72	0.28	0.23-0.33	0.09-0.58
5 years	0.35	0.27-0.44	0.10-0.72	0.29	0.23-0.36	0.10-0.61

PI – prediction interval

Table 5 Moderator analyses

Moderator	Coefficient	SE	p
Mean age (continuous)	–0.02	0.02	0.46
Proportion of women (continuous)	–0.03	0.02	0.27
Recruitment			
Clinical	Ref.		
Community	–0.07	0.05	0.16
Other	–0.09	0.05	0.07
Diagnosis			
Meeting criteria for depressive disorder	Ref.		
Score above cut-off on self-report scale	–0.06	0.04	0.16
Target group			
Adults in general	Ref.		
General medical patients	–0.14	0.07	0.06
Perinatal depression	–0.10	0.07	0.16
Other specific group	–0.06	0.05	0.21
Treatment			
Cognitive behavior therapy	Ref.		
Third wave therapy	–0.02	0.10	0.85
Behavioral activation	–0.27	0.12	**0.02**
Interpersonal psychotherapy	–0.04	0.14	0.76
Problem-solving therapy	–0.03	0.06	0.66
Other	0.05	0.05	0.31
Format			
Individual	Ref.		
Group	–0.06	0.05	0.18
Guided self-help	–0.05	0.08	0.53
Mixed/other	–0.03	0.07	0.67
Number of sessions (continuous)	0.03	0.02	0.14
Control condition			
Care-as-usual	Ref.		
Waitlist	0.08	0.17	0.66
Other	0.01	0.05	0.77
Region			
North America	Ref.		
Europe	0.05	0.07	0.50
East Asia	0.09	0.14	0.53
Other	–0.04	0.08	0.65
Risk of bias			
High	Ref.		
Some concerns	–0.01	0.05	0.88
Low	0.04	0.06	0.51

to 24% at week 32, then remaining stable before gradually rising to 29% at week 260 (see Table 4 and supplementary information).

Moderators

Only one of the examined moderators was significantly associated with the difference between psychotherapies and control conditions over time (see Table 5): behavioral activation (with cognitive behavior therapy as reference group) was associated with less sustained effects over time (p=0.02).

DISCUSSION

We conducted by far the largest meta-analysis of the long-term effects of psychotherapies for depression compared to control conditions. We included data from 191 randomized trials reporting outcomes at least 6 months post-randomization, including 52 studies reporting outcomes at more than one year and 15 at more than two years. These data allowed to model the longitudinal course of the effects of psychotherapies using state-of-the-art methods.

In the main analyses, we found that the effects of psychotherapies increased from baseline to 12 weeks post-randomization with an SMD of 0.55, gradually decreased to SMD=0.39 at around 1-year follow-up, and then remained relatively stable thereafter. In the main analyses, the SMD was still statistically significant up to more than 8 years after randomization. We found that the RRs for response showed a decreasing trend over time (which was not the case for SMDs), although the effects were still significant after 4.5 years. Even under the most conservative estimates, the RRs remained significant up to 2.6 years.

These findings indicate that the beneficial effects of psychotherapies for depression are sustained for several years after treatment. Caution is warranted when interpreting outcomes beyond two years post-randomization, given the relatively small number of available data points. However, our primary focus in this study was on modelling the overall course of effects rather than focusing on individual time points.

Our data are highly relevant from a clinical perspective. We already showed in previous research that one course of brief psychotherapy has more beneficial effects than taking antidepressant medications for a whole year[3]. In the current study we found that the effects of psychotherapies last beyond that one year and continue to be significant compared to control conditions over several years. This finding is encouraging for patients, although the long-lasting effects are moderate, and many individuals do not respond to therapy in the first place[34]. Furthermore, despite the long-term effects, it is well-known that many patients experience relapse after successful remission through treatment[35].

We found that behavioral activation was associated with significant worse outcomes compared to other psychotherapies. However, as in all moderator analyses, this is a correlational result and does not imply causation. The observed association may be con-

founded by other study characteristics related both to intervention type and outcome.

This study has several strengths and limitations. Strengths include the large number of included trials and long-term outcomes, and the use of sophisticated analyses to estimate the course of the effects of psychotherapies over time. However, there are also some limitations that need to be taken into account when interpreting the results. The number of measurements beyond two years was limited, and many trials had some risk of bias, although we did not find that this risk was associated with the course of the effects over time. The levels of heterogeneity were substantial in many of the analyses, and the moderator analyses identified few potential sources of this heterogeneity. Moreover, we could not examine the impact of publication bias on our results. The development of methodologies allowing to examine the impact of publication bias on the longitudinal analyses that we conducted is very much needed[36].

Despite these limitations, we can conclude that psychotherapies for adult depression have moderate to large effects at 3 months after randomization, which slowly decrease during the next 9 months to a moderate level, and thereafter remain stable at that moderate level for several years.

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REFERENCES

1. Cuijpers P, Quero S, Noma H et al. Psychotherapies for depression: a network meta-analysis covering efficacy, acceptability and long-term outcomes of all main treatment types. World Psychiatry 2021;20:283-93.
2. Cuijpers P, Noma H, Karyotaki E et al. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry 2020;19:92-107.
3. Furukawa TA, Shinohara K, Sahker E et al. Initial treatment choices to achieve sustained response in major depression: a systematic review and network meta-analysis. World Psychiatry 2021;20:387-96.
4. Karyotaki E, Smit Y, de Beurs DP et al. The long-term efficacy of acute phase psychotherapy for depression: a meta-analysis of randomized trials. Depress Anxiety 2016;33:370-83.
5. Karyotaki E, Smit Y, Henningsen KH et al. Combining pharmacotherapy and psychotherapy or monotherapy for major depression? A meta-analysis on the long-term effects. J Affect Disord 2016;194:144-52.
6. Zainal NH, Soh CP, Van Doren N et al. Do the effects of internet-delivered cognitive-behavioral therapy (i-CBT) last after a year and beyond? A meta-analysis of 154 randomized controlled trials (RCTs). Clin Psychol Rev 2024;114:102518.
7. Mamukashvili-Delau M, Koburger N, Dietrich S et al. Long-term efficacy of internet-based cognitive behavioral therapy self-help programs for adults with depression: systematic review and meta-analysis of randomized controlled trials. JMIR Ment Health 2023;10:e46925.
8. Cuijpers P, Karyotaki E. A meta-analytic database of randomised trials on psychotherapies for depression. https://doi.org/10.17605/OSF.IO/825C6.
9. Cuijpers P, Miguel C, Harrer M et al. Psychological treatment of depression: a systematic overview of a 'Meta-Analytic Research Domain.' J Affect Disord 2023;335:141-51.
10. Cuijpers P, Harrer M. Long-term effects of psychotherapies for adult depression: a meta-analysis. https://osf.io/xckwa.
11. Cuijpers P, Harrer M. Long-term effects of psychotherapies for adult depression: a meta-analysis. www.metapsy.org/registrations#rec7A2Q6LBdVgc9tZ.
12. Hall S, Moskovitz C, Pemberton M; Text Recycling Research Project. Understanding text recycling: a guide for researchers. https://textrecycling.org/resources/best-practices-for-researchers.
13. Cuijpers P, Noma H, Karyotaki E et al. Effectiveness and acceptability of cognitive behavior therapy delivery formats in adults with depression: a network meta-analysis. JAMA Psychiatry 2019;76:700-7.
14. Cuijpers P, Ciharova M, Miguel C et al. Psychological treatment of depression in institutional settings: a meta-analytic review. J Affect Disord 2021;286:340-50.
15. Sterne JAC, Savović J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
16. Miguel C, Harrer M, Karyotaki E et al. Operationalization of Cochrane's Risk of Bias 2 tool (RoB 2) in the context of psychotherapy trials. medRxiv 2025; 26.25330349.
17. Cuijpers P, Karyotaki E, de Wit L et al. The effects of fifteen evidence-supported therapies for adult depression: a meta-analytic review. Psychother Res 2020;30: 279-93.
18. Beck AT, Ward CH, Mendelson M et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
19. Beck AT, Steer RA, Brown GK. Manual for Beck Depression Inventory-II. San Antonio: Psychological Corporation, 1996.
20. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56-62.
21. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Int Med 2001;16:606-13.
22. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.
23. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987; 150:782-6.
24. Yesavage JA, Brink TL, Rose TL et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37-49.
25. PlotDigitizer. https://plotdigitizer.com/app.
26. Furukawa TA, Barbui C, Cipriani A et al. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol 2006;59:7-10.
27. Furukawa TA, Cipriani A, Barbui C et al. Imputing response rates from means and standard deviations in meta-analyses. Int Clin Psychopharmacol 2005;20: 49-52.
28. Harrer M, Kuper P, Cuijpers P. metapsyTools: several R helper functions for the "metapsy" database. R package version 0.3.2. 2022. https://tools.metapsy.org.
29. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22:153-60.
30. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1-48.
31. Harrer M, Cuijpers P, Furukawa TA et al. dmetar: companion R package for the guide "Doing Meta-Analysis in R". R package version 0.1.0. 2019. http://dmetar.protectlab.org.
32. Trikalinos TA, Olkin I. Meta-analysis of effect sizes reported at multiple time points: a multivariate approach. Clin Trials 2012;9:610-20.
33. Liu Y, Zhou K, Sims KD. Tipping point analysis: assessing the potential impact of missing data. JAMA 2025;334:265-6.
34. Cuijpers P, Miguel C, Ciharova M et al. Absolute and relative outcomes of psychotherapies for eight mental disorders: a systematic review and meta-analysis. World Psychiatry 2024;23:267-75.
35. Breedvelt JJF, Karyotaki E, Warren FC et al. An individual participant data meta-analysis of psychological interventions for preventing depression relapse. Nat Ment Health 2024;2:154-63.
36. Cuijpers P, Harrer M, Miguel C et al. Five decades of research on psychological treatments of depression: a historical and meta-analytic overview. Am Psychol 2025;80:297-310.

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Predicting long-term poor outcomes in individuals at clinical high risk for psychosis using real-world clinical data: the OASIS1000 prospective study

Yanakan Logeswaran[1,2], Andrea De Micheli[1,3], Ilaria Toniol[1], Tiexin Chen[4,5], Antonio Melillo[1,6], Maite Arribas[1], Nicholas R. Livingston[7], Kamil Krakowski[1,8], Dominic Oliver[1,9-11], Daniel Stahl[2], Paolo Fusar-Poli[1,3,8,12]

[1]Early Psychosis: Interventions and Clinical-detection (EPIC) lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [2]Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [3]OASIS Service, South London and Maudsley NHS Foundation Trust, London, UK; [4]South London and Maudsley NHS Foundation Trust, London, UK; [5]Guy's and St. Thomas' NHS Foundation Trust, London, UK; [6]Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy; [7]Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [8]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy; [9]Department of Psychiatry, University of Oxford, Oxford, UK; [10]OPEN Early Detection Service, Oxford Health NHS Foundation Trust, Oxford, UK; [11]NIHR Oxford Health Biomedical Research Centre, Oxford, UK; [12]Department of Psychiatry and Psychotherapy, University Hospital, Ludwig-Maximilian-University, Munich, Germany

Most research into the clinical high risk for psychosis (CHR-P) state has focused on predicting transition to psychosis in the short term, and largely in research samples that are not representative of real-world preventive care. However, CHR-P individuals experience a broad range of poor long-term clinical outcomes in real-world settings, such as hospitalization for psychiatric reasons, initiation of a new antipsychotic treatment, or suicide. Improving the detection of individuals at greater risk of these long-term poor outcomes is critical to advance preventive care in real-world clinical settings. This study aims to develop and internally validate a personalized clinical prediction model for real-world, long-term poor outcomes beyond transition risk in CHR-P individuals. This RECORD-compliant, real-world, long-term prospective cohort study included electronic health records (EHR) data from all CHR-P individuals receiving preventive care from the Outreach and Support in South London (OASIS) service in South London and Maudsley National Health Service Foundation Trust in the UK from 2001 to 2024. The primary outcome was the long-term cumulative risk of first real-world poor outcome, operationalized by pragmatic parameters informing clinical practice: transition to psychosis, receiving a first antipsychotic treatment at a dosage necessary to treat first-episode psychosis, receiving a first voluntary or compulsory hospitalization for psychiatric reasons, or dying by suicide. A clinical prediction model (regularized Cox regression) was developed and validated using internal-external cross-validation to predict long-term poor outcomes, utilizing real-world predictors available in routine care. Model performance was indexed by discrimination (Harrell's C), calibration (slope, intercept), overall performance (Brier score), and potential clinical utility (decision curve analysis). One thousand CHR-P OASIS patients were included (mean age: 22.51±4.99 years; 53.60% males, 44.73% White) and followed up to a maximum of 21 years. The cumulative risk of real-world poor outcome was 0.644 (95% CI: 0.547-0.742) at 14-18 years. The validated clinical prediction model showed statistically significant discrimination (C=0.69; 95% CI: 0.63-0.74), calibration (slope = 1.61, 95% CI: 0.74-2.48; intercept = –0.03, 95% CI: –0.62 to 0.55) and overall performance (Brier score = 0.18; 95% CI: 0.13-0.22). Decision curve analysis demonstrated that the model was associated with greater net benefit than the clinical alternatives at risk thresholds from 0% to 50%. These data suggest that most CHR-P individuals have long-term poor outcomes, beyond transition to psychosis, in real-world care, which should become the focus of a new generation of research. The clinical prediction model presented here can identify these individuals and facilitate the personalized provision of preventive care, thereby improving outcomes in this population. CHR-P services should extend their duration of care to address the substantial long-term clinical outcomes experienced by young individuals.

Key words: Clinical high risk for psychosis, long-term clinical outcomes, real-world settings, first-episode psychosis, clinical prediction modelling, preventive care

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Psychotic disorders are characterized by high clinical, societal and personal burden[1,2]. Approximately 78% of first-episode psychosis (FEP) cases experience prodromal symptoms prior to the onset of the disorder[3]. This is a key stage with the potential to prevent psychosis onset[4], evidenced by a population attributable fraction of 10.9%[5].

Specialized clinical high risk for psychosis (CHR-P) services aim to identify young people with attenuated psychotic symptoms[6] and poor functioning[7] during this prodromal stage, in order to provide preventive mental health care and reduce the duration of untreated psychosis for those who do develop the disorder[8,9], thus improving long-term outcomes. These services are recommended by national guidelines, such as the National Institute for Health and Care Excellence (NICE) guidelines[10] and the National Health Service England Access and Waiting Time Standard[11] in the UK.

Around 25% of CHR-P individuals transition to FEP within three years, increasing to 35% at 10 years[12], which is substantially higher than the observed incidence rate in the general population (0.317% at 10 years)[13]. Given that transition risk is greatest in the first two years, with approximately 80% of transitions occurring in that period[12], the majority of research on the CHR-P state has focused on advancing detection and prognosis in the short term[14]. Further, prognostic models for the risk of transition in this population have mostly been developed using research samples[15]. However, such samples are not representative of clinical cohorts across demographic and clinical characteristics as well as real-world outcomes[16,17], thereby limiting the real-world generalizability and applicability of these clinical prediction models.

Despite group-level improvements in symptom severity and functioning, about half of CHR-P individuals who do not transition to psychosis do not remit from the CHR-P state[18] and experience functional impairment and other psychiatric morbidity in the medium term[19,20]. However, the real-world outcomes experienced by this vulnerable population in the very long term are yet to be clearly characterized, due to the paucity of longer-term follow-up studies. Furthermore, though CHR-P psychometric assessments have excel-

lent prognostic accuracy[5,21], they are not predictive of the real-world poor outcomes experienced by CHR-P individuals as observed in clinical practice, emphasizing the need to additionally characterize the risk of these outcomes to inform real-world preventive efforts and clinical guidelines.

While several models have been developed to predict transition[22,23], there are no published models that predict the risk of the broader range of real-world poor outcomes[15]. Beyond transition, the start of antipsychotic treatment at a dosage necessary to treat FEP, hospitalization for psychiatric reasons, and suicide are similarly significant adverse outcomes that are markers of increasing distress, functional deterioration, and potential risk to self and/or others. Treatment stratification based on transition risk alone may not capture the care needs of those at greater risk of experiencing these broader, real-world poor outcomes. It is therefore clear that developing and validating a clinical prediction model for real-world, long-term poor outcomes in CHR-P individuals would provide substantial clinical benefit for improving care in this vulnerable population.

The present study aimed to develop and validate a personalized clinical prediction model for real-world, long-term poor outcomes, using clinically relevant, real-world predictors and outcome data from a sample of 1,000 CHR-P individuals, recruited from the Outreach and Support in South London (OASIS) CHR-P service (the OASIS1000 study).

METHODS

Data source

This is a clinical, real-world, prospective cohort study using routinely collected electronic health record (EHR) data from all patients receiving care from services within South London and Maudsley National Health Service Foundation Trust (SLaM) in the UK. SLaM is one of Europe's largest providers of secondary mental health care[24]. Its catchment area comprises four ethnically and socioeconomically diverse South London boroughs (Lambeth, Southwark, Lewisham and Croydon), as well as tertiary referrals from other areas of London.

The high ethnic and socioeconomic diversity in SLaM, along with one of the highest incidence rates of psychosis worldwide[25,26], provides a suitable population for developing models that are transportable to other settings characterized by a more homogeneous ethnic or social composition[27]. Indeed, our earlier clinical prediction model, which was developed in the same area, was successfully transported and generalized to other areas with diverse ethnic compositions and different health care settings – Camden and Islington (lower proportion of Black people, lack of CHR-P preventive services)[28]; Oxfordshire (lower proportion of Black people, lack of CHR-P preventive services, lower incidence of psychosis)[29] – as well as outside the UK[30,31].

The EHR system in SLaM captures every piece of information recorded by health care providers (e.g., mental health professionals, accident and emergency departments) in the area regarding a patient's presentation, received interventions, and observed outcomes, also after the individual has been discharged from the CHR-P service.

Study population

The OASIS community mental health service in SLaM, initiated in 2001, is one of the largest and longest-standing preventive services for CHR-P individuals funded by the UK National Health Service[32]. It provides early detection, standardized assessment, and preventive care (encompassing needs-based interventions such as psychoeducation and psychosocial support, psychological interventions, and pharmacotherapy) to CHR-P individuals aged 14 to 35 years for up to two years since the initial intake.

The population of this prospective cohort study comprised all individuals accessing OASIS from 2001 to 2024 who met CHR-P criteria (i.e., attenuated psychosis symptoms, APS; or brief and limited intermittent psychotic symptoms, BLIPS; or genetic risk and functional deterioration, GRD), as defined by the Comprehensive Assessment of At Risk Mental State (CAARMS) instrument[33]. Individuals were followed up from the time of access to OASIS until their final entry on the EHR.

Outcomes

The primary outcome was the time from acceptance to OASIS, which coincides with a CHR-P assessment and designation, to real-world poor outcome, operationalized as one of the following pragmatic parameters informing clinical practice: a) transition to a FEP, b) receiving a first antipsychotic treatment at a dosage necessary to treat a FEP[34], c) receiving a voluntary hospitalization for psychiatric reasons, d) receiving a compulsory hospitalization for psychiatric reasons following a Mental Health Act assessment; or e) dying by suicide. The secondary outcome was death for any reason.

Predictors

We included the following *a priori* selected baseline sociodemographic and clinical predictors that are available in routine clinical practice: age; gender; self-assigned ethnicity; employment status; marital status; index of multiple deprivation (IMD) decile; referral source; CHR-P subgroup; CAARMS severity scores (combined P1 and P2, P3, P4); duration of untreated attenuated psychotic symptoms (DUAPS); Social and Occupational Functioning Assessment Scale (SOFAS)[35] score; Health of the Nation Outcome Scale (HoNOS)[36] score; baseline substance use (alcohol, cannabis, nicotine); and baseline medication (sub-FEP-dosage antipsychotics, benzodiazepines, other) (see supplementary information for further details).

Baseline cannabis use was operationalized as a binary variable capturing current frequent cannabis use (daily or near-daily use),

given meta-analytic evidence of substantially greater risk of developing psychosis amongst daily/near-daily users compared to less frequent/non-users[37], and similar risk of psychosis observed between past and non-users[38]. Alcohol and nicotine use also followed this categorization to capture more severe instances of substance use consistently.

Statistical analysis

This study adhered to the Reporting of Studies Conducted Using Observational Routinely Collected Health Data statement (RECORD) (see also supplementary information). We first described baseline clinical and sociodemographic characteristics of the sample, reporting the mean and standard deviation (SD) for continuous variables, and counts and relative frequencies for categorical variables.

Kaplan-Meier failure functions (1-survival)[39] and Greenwood 95% confidence intervals (CIs)[40] were utilized to describe the cumulative risk of poor real-world outcomes, as well as death for any reason. Kaplan-Meier plots were truncated when there were fewer than 10 individuals at risk for each outcome (and 50 for death, given the rarity of this outcome). We reported the numbers of individuals who remained at-risk (i.e., those who had not experienced a poor outcome and were still being followed-up) at each year of follow-up, alongside the number of outcomes experienced (i.e., events) in the preceding year of follow-up, as per methodological guidelines to aid interpretation of the Kaplan-Meier plots[41].

A standardized mortality ratio (SMR) was calculated by comparing the number of observed deaths in the sample to the number of expected deaths in the general population of the four SLaM boroughs. Expected deaths were estimated using Office for National Statistics data on borough-specific mortality rates, adjusting for gender in the OASIS1000 sample and stratified for individuals aged 15-34 using 5-year age bands[42,43].

Model development and validation

Model development

We developed and internally validated a multivariate regularized Cox regression to predict the probability of and time to a poor outcome (thus controlling for the variable follow-up time), following gold-standard methodological[44] and reporting guidelines (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis, TRIPOD+AI[45]) (see also supplementary information).

For the prediction model, a cut-off of 8 years was applied to the follow-up period. Sample size and event requirements for the model were calculated *post hoc* using the *pmsampsize* (v. 1.1.3) package[46,47]. The regularized Cox regression automatically selects the minimum set of predictors that are essential to maintain high prognostic accuracy, shrinking towards zero and eventually removing the coefficients of less predictive and/or highly correlated variables. In this way, regularized regression methods preserve both prognostic accuracy and model parsimony, thus facilitating clinical interpretation and usability.

Model validation

A nested cross-validation framework was utilized for temporal internal-external validation[48]. The dataset was split into five train-test folds according to year of accepted referral at OASIS (2001-2007: N=131; 2008-2012: N=154; 2013-2016: N=180; 2017-2019: N=234; 2020-2024: N=265), to allow for similarly sized folds, whilst isolating the years affected by COVID-19 (2020-2024) (see supplementary information for further details).

Model performance was assessed by discrimination (Harrell's C-index[49]), calibration (calibration slope, calibration intercept), and an overall performance measure (Brier score). Discrimination refers to how well a model can differentiate between those with higher and lower risks of having an event (poor outcome). An Harrell's C-index of 0.5 indicates that the predictive accuracy of a model is no better than chance, while 1.0 indicates perfect predictive accuracy. Calibration refers to the agreement between predicted probabilities and observed outcomes. Calibration slopes greater than 1 suggest that risk is underestimated for individuals at high risk and overestimated for individuals at low risk, whereas calibration slopes lower than 1 suggest the opposite. Calibration intercepts indicate whether predicted risks are, on average, overestimated (<0) or underestimated (>0) compared to observed risks. Lower Brier scores denote higher precision and less bias, with scores above 0.25 suggesting a poor model. Pooled average estimates and CIs for these performance metrics across the five temporal folds were calculated by random effects meta-analyses[50,51].

The final model was fitted on the entire dataset to obtain coefficients for future validation and clinical use. Hazard ratios (HRs) for retained predictors are presented. HR values scaled by two SDs are also calculated to compare between coefficient magnitudes across categorical and continuous variables[52] and to identify the most predictive features.

Decision curve analysis

Decision curve analysis was used to assess the potential clinical utility of the model by estimating its net benefit across different threshold probabilities, compared with default strategies of assessing all or assessing none[53]. Net benefit quantifies the trade-off between the benefit of true positive predictions and the harm of false positive predictions. The net benefit was assessed within each of the five test folds of the internal-external validation framework and then combined to visualize the mean decision curves over risk thresholds ranging from 0% to 50%. It is unlikely that a clinician would need a clinical prediction model to assess a patient in whom the threshold probability to experience

a real-world poor outcome exceeds 50%.

Sensitivity analysis

There has been a recent consensus in precision medicine to incorporate ethnicity (self-assigned ethnicity in our study) in clinical prediction models, because its exclusion produces less accurate predictions in certain subgroups (e.g., Black individuals), thereby reducing model fairness and potentially exacerbating social inequalities[54-56]. Whilst we included this predictor, we also reran the model after removing ethnicity as a predictor, to assess whether this affected model performance, in line with our previous prediction modeling studies[31,57].

Exploratory analyses

We conducted several exploratory analyses to evaluate the association between real-world, long-term poor outcomes and CHR-P subtype using Cox regressions and zero-inflated negative binomial regressions[58] (for hospitalization outcomes). Due to a low event rate, the risk of suicide was not analyzed. These analyses were complete-case analyses given low levels of missingness.

Software

Analyses were performed in R 4.4.1 using the *dcurves*[59], *glmnet*[60], *metafor*[61], *survival*[62], and *VIM*[63] packages.

RESULTS

Baseline sample characteristics

Table 1 summarizes the baseline characteristics of the OASIS1000 sample, which was followed up to a maximum of 21 years. The mean age at presentation was 22.51±4.99 years, and 53.60% were male. The majority were single (81.86%), lived with their own family (53.72%), and were either unemployed (35.72%) or students (37.26%). There were similar proportions of White (44.73%) and non-White (Black: 32.65%; Asian: 8.80%; other: 13.82%) ethnicities. The majority were referred from community mental health services (25.71%), general medical practitioners (21.84%), early intervention services (17.66%), and child and adolescent mental health services (12.12%).

Regarding baseline clinical characteristics, the mean total CAARMS severity was 51.87±24.04, and the mean functioning level was poor (SOFAS score: 54.80±12.72; HoNOS score: 11.54±5.03). APS criteria were met by 80.32% of subjects, BLIPS criteria by 18.47% and GRD criteria by 1.20%. Attenuated psychotic symptoms onset occurred on average 1.67 years prior to CHR-P designation (DUAPS = 608.40 days). DUAPS was longest in the APS subgroup (683.65±916.62 days), followed by the BLIPS subgroup (294.94±739.08 days) and the GRD subgroup (233.27±202.64 days).

Risk of real-world, long-term poor outcomes

Table 2 and Figure 1 present the cumulative risk of real-world, long-term poor outcomes. The cumulative risk of a poor outcome was 0.190 (95% CI: 0.164-0.216) at 1 year and 0.254 (95% CI: 0.222-0.285) at 2 years, increasing to 0.644 (95% CI: 0.547-0.742) at 14-18 years.

As for individual outcomes, the cumulative risk of developing psychosis was 0.135 (95% CI: 0.112-0.157) at 1 year and 0.192 (95% CI: 0.164-0.220) at 2 years, increasing to 0.462 (95% CI: 0.379-0.545) at 14-18 years. The cumulative risk of first being voluntarily hospitalized for psychiatric reasons was 0.052 (95% CI: 0.037-0.067) at 1 year and 0.091 (95% CI: 0.070-0.112) at 2 years, increasing to 0.354 (95% CI: 0.245-0.463) at 14-18 years. The cumulative risk of first being compulsorily hospitalized for psychiatric reasons was 0.047 (95% CI: 0.033-0.061) at 1 year and 0.079 (95% CI: 0.059-0.099) at 2 years, increasing to 0.308 (95% CI: 0.221-0.395) at 14-18 years. Among those hospitalized for psychiatric reasons, the mean number of days spent in hospital was 110.2±227.0. The cumulative risk of receiving a first antipsychotic treatment at a dosage necessary to treat FEP was 0.143 (95% CI: 0.119-0.167) at 1 year and 0.199 (95% CI: 0.170-0.228) at 2 years, increasing to 0.411 (95% CI: 0.345-0.478) at 14-18 years.

Risk of dying for any reason

The cumulative probability of dying for any reason was 0.001 (95% CI: 0.000-0.003) at 1 and 2 years, increasing to 0.057 (95% CI: 0.023-0.091) at 15 and 16 years. Fourteen CHR-P individuals died: six of suicide, and eight of other or unknown causes. The age- and sex-standardized SMR was 5.84 (95% CI: 5.20-7.91).

Predicting real-world, long-term poor outcomes

The mean follow-up time was 841.1 days (SD = 891.6; interquartile range, IQR = 188.0-1091.5), with a total of 254 (26.3%) individuals experiencing a poor outcome by 8 years.

Table 3 shows the HRs and coefficients of the final model. The retained features, in descending order of magnitude of prognostic effect, were baseline sub-FEP-dosage antipsychotic medication (HR=2.27), BLIPS CHR subgroup (HR=1.15), CAARMS P4 total score (HR=1.11), baseline SOFAS score (HR=0.91), CAARMS P1 and P2 total score (HR=1.09), self-assigned Black ethnicity (HR=1.08), cannabis use (HR=1.06), being referred from inpatient mental health services (HR=1.05), being unemployed (HR=1.01), HoNOS total score (HR=1.01), and age (HR=1.00).

The model achieved statistically significant, moderate discrimination, with a C-index of 0.69 (95% CI: 0.63-0.74) (see Table 4). It exhibited some miscalibration, overestimating the risk of poor outcome on average (calibration intercept = –0.03; 95% CI: –0.62 to

Table 1 Sociodemographic and clinical characteristics of the clinical high risk for psychosis (CHR-P) sample

Age, years (mean±SD)	22.51±4.99
Gender, N (%)	
Female	461 (46.10)
Male	536 (53.60)
Non-binary	3 (0.30)
Self-assigned ethnicity, N (%)	
White	437 (44.73)
Asian	86 (8.80)
Black	319 (32.65)
Other	135 (13.82)
Marital status, N (%)	
Married	40 (4.12)
Separated or divorced	16 (1.65)
Single	794 (81.86)
Engaged	85 (8.76)
In a relationship	35 (3.61)
Employment status, N (%)	
Employed	264 (27.02)
Student	364 (37.26)
Unemployed	349 (35.72)
Accommodation status, N (%)	
Living with own family	505 (53.72)
Owner	11 (1.17)
Private rental	145 (15.42)
Shared flat	101 (10.74)
Council flat or hostel	132 (14.04)
Homeless	22 (2.34)
Other	24 (2.55)
IMD decile (mean±SD)	3.51±1.71
CHR-P subgroup, N (%)	
APS	800 (80.32)
BLIPS	184 (18.47)
GRD	12 (1.20)
Total CAARMS severity (mean±SD)	51.87±24.04
P1 and P2 total score	34.45±18.75
P3 total score	11.99±8.72
P4 total score	5.96±7.66
DUAPS, days (mean±SD)	608.40±896.53
SOFAS score (mean±SD)	54.80±12.72
HoNOS adjusted total score (mean±SD)	11.54±5.03
Referral source, N (%)	
Self	33 (3.45)
Caregivers or relatives	10 (1.04)
Schools or colleges	14 (1.46)
Social services or supported accommodation	22 (2.30)
General medical practitioners	209 (21.84)
Community mental health services	246 (25.71)
Child and adolescent mental health services	116 (12.12)
Early intervention for psychosis services	169 (17.66)
Accident and emergency departments or home treatment team	49 (5.12)
Assessment and liaison services	58 (6.06)
Inpatient mental health services	21 (2.19)
Police and criminal justice system	7 (0.73)
Physical health services	3 (0.31)
Baseline substance use, N (%)	
Alcohol	90 (11.04)
Cannabis	120 (14.29)
Nicotine	145 (20.63)
Baseline medication, N (%)	
Antipsychotic (sub-FEP dosage)	39 (4.04)
Benzodiazepine	31 (3.21)
Other	198 (20.60)

CAARMS – Comprehensive Assessment of at Risk Mental State, DUAPS – duration of untreated attenuated psychotic symptoms, HoNOS – Health of the Nation Outcome Scale, SOFAS – Social and Occupational Functioning Assessment Scale, IMD – index of multiple deprivation, APS – attenuated psychotic symptoms, BLIPS – brief and limited intermittent psychotic symptoms, GRD – genetic risk and deterioration syndrome, FEP – first-episode psychosis

0.55), in particular with overestimations of low risk and underestimations of high risk (calibration slope = 1.61; 95% CI: 0.74-2.48). The overall performance was adequate, with a Brier score of 0.18 (95% CI: 0.13-0.22). The decision curve analysis indicated that the model was associated with greater net benefit than the clinical alternative of assessing all, at risk thresholds from 24% to 50%, and assessing none, at risk thresholds from 0% to 50% (see Figure 2 and supplementary information).

Sensitivity analysis

Excluding the ethnicity variable as a predictor did not significantly affect the model's performance: the C-index decreased by 0.01 (see supplementary information). This indicates that the model can perform even when this predictor is disregarded.

Exploratory analyses

Compared to the APS subgroup, BLIPS individuals had a greater risk of a real-world, long-term poor outcome (HR=2.08, 95% CI: 1.59-2.72), of developing psychosis (HR=2.17, 95% CI: 1.63-2.90),

Table 2 Cumulative risk of real-world, long-term poor outcomes with 95% confidence intervals

Follow-up (years)	Transition to psychosis	Antipsychotic at dosage necessary to treat first-episode psychosis	Voluntary hospitalization for psychiatric reasons	Compulsory hospitalization for psychiatric reasons	Real-world poor outcome
1	0.135 (0.112-0.157)	0.143 (0.119-0.167)	0.052 (0.037-0.067)	0.047 (0.033-0.061)	0.190 (0.164-0.216)
2	0.192 (0.164-0.220)	0.199 (0.170-0.228)	0.091 (0.070-0.112)	0.079 (0.059-0.099)	0.254 (0.222-0.285)
3	0.241 (0.208-0.274)	0.239 (0.207-0.272)	0.105 (0.082-0.129)	0.104 (0.080-0.128)	0.301 (0.266-0.337)
4	0.274 (0.237-0.310)	0.247 (0.213-0.280)	0.132 (0.103-0.160)	0.126 (0.097-0.154)	0.338 (0.298-0.378)
5	0.299 (0.259-0.339)	0.275 (0.238-0.312)	0.152 (0.119-0.185)	0.145 (0.113-0.177)	0.363 (0.320-0.406)
6	0.311 (0.269-0.353)	0.286 (0.248-0.323)		0.154 (0.120-0.189)	0.372 (0.328-0.416)
7	0.339 (0.293-0.385)	0.298 (0.258-0.338)	0.174 (0.135-0.212)	0.175 (0.136-0.214)	0.419 (0.369-0.470)
8		0.307 (0.266-0.349)	0.180 (0.140-0.220)		0.425 (0.374-0.477)
9	0.356 (0.308-0.405)	0.318 (0.275-0.361)	0.196 (0.151-0.241)	0.182 (0.141-0.223)	0.451 (0.396-0.507)
10	0.381 (0.327-0.435)	0.337 (0.290-0.385)	0.217 (0.165-0.270)	0.207 (0.158-0.256)	0.478 (0.418-0.539)
11	0.391 (0.334-0.447)		0.230 (0.173-0.288)		0.489 (0.427-0.552)
12	0.406 (0.343-0.469)	0.356 (0.303-0.408)	0.276 (0.202-0.350)	0.222 (0.166-0.278)	0.549 (0.471-0.627)
13	0.423 (0.354-0.493)	0.377 (0.319-0.436)	0.293 (0.214-0.372)	0.270 (0.196-0.344)	0.602 (0.513-0.691)
14					
15					
16	0.462 (0.379-0.545)	0.411 (0.345-0.478)	0.354 (0.245-0.463)	0.308 (0.221-0.395)	0.644 (0.547-0.742)
17					
18					

Suicide is not reported directly due to the small number of events

of receiving a first antipsychotic treatment at a dosage necessary to treat FEP (HR=1.70, 95% CI: 1.23-2.33), and of being voluntarily and compulsorily hospitalized for psychiatric reasons (HR=1.74, 95% CI: 1.11-2.69; HR=2.48, 95% CI: 1.64-3.76) (see also supplementary information).

DISCUSSION

To our knowledge, this is the first clinical prediction model for forecasting real-world, long-term poor outcomes in CHR-P individuals. In a clinical cohort of 1,000 CHR-P subjects accessing preventive care in the UK National Health Service, there was a significant risk of real-world, long-term poor outcome, as defined by developing psychosis, receiving antipsychotic treatment at a dosage necessary to treat FEP, being voluntarily or compulsorily hospitalized for psychiatric reasons, or dying by suicide over 21 years of follow-up. Our model for predicting real-world, long-term poor outcomes was validated and demonstrated statistically significant, moderate accuracy and calibration. The model also exhibited potential clinical utility across a range of risk thresholds, showing that it may facilitate the detection of young people at risk of poor outcomes and the individualized provision of preventive care, thereby improving outcomes.

This study progresses our clinical care for CHR-P individuals in several ways. First, it provides unprecedented evidence that the large majority of CHR-P patients experience real-world, long-term poor outcomes, increasing from 0.254 at 2 years to 0.644 at 14-18 years after seeking help from a preventive clinic. The cumulative risk of developing psychosis was 0.192 at 2 years and 0.381 at 10 years – in line with meta-analytic estimates of transition risk[12] – and reached 0.462 at 14-18 years. These findings are relevant, as they contrast with recent claims that transition risk in CHR-P individuals is declining worldwide and too small to allow for preventive interventions[64].

While most previous studies were based on small, research-based samples that are more likely to recruit less severe CHR-P individuals, our cohort reflects real-world outcomes in this group. Our finding that 46% of CHR-P individuals would go on to develop psychosis in the very long term suggests that there are notable sampling biases in research studies assessing the likelihood of transitioning to psychosis in CHR-P samples. These are likely associated with different levels of risk enrichment, that have already been reported in this population[65].

Second, we investigated a clinically meaningful composite endpoint that extends beyond the narrow focus on transitioning from a CHR-P state to FEP. In real-world care, we found that CHR-P individuals also had a substantial risk of receiving a first antipsychotic treatment at a dosage necessary to treat FEP (0.411 at 14-18 years), and approximately one third were hospitalized for psychiatric reasons (voluntary hospitalization: 0.354 at 14-18 years; compulsory hospitalization: 0.308 at 14-18 years), spending an average of

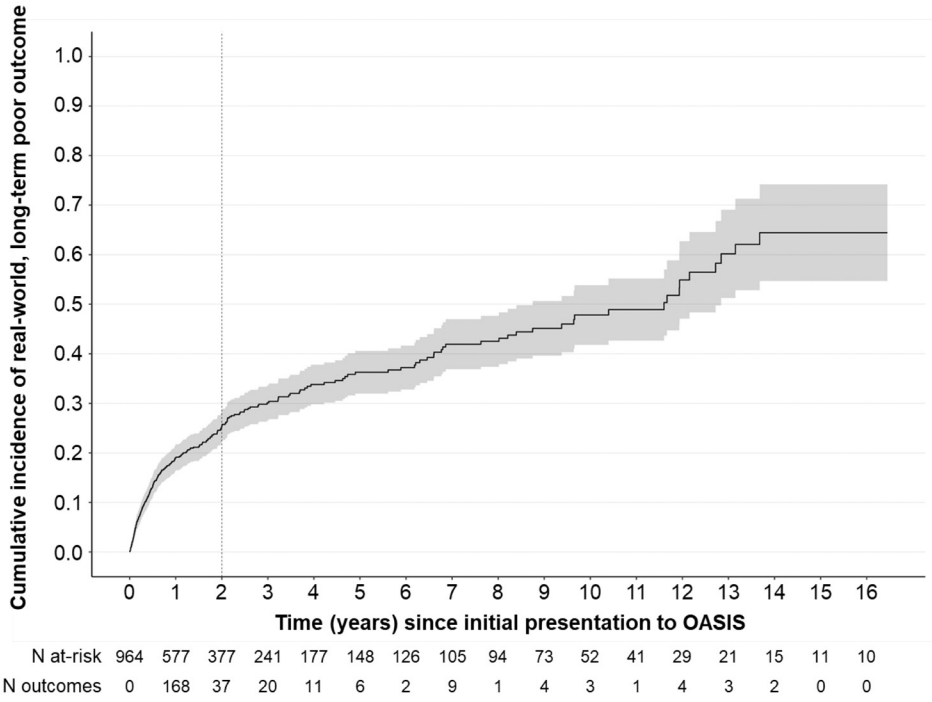

Figure 1 Cumulative incidence of real-world, long-term poor outcome in clinical high risk for psychosis (CHR-P) individuals, with 95% CIs (shade above and below the curve). The dotted vertical line denotes the median duration of care (two years) provided by CHR-P services. "N at-risk" indicates the number of individuals who remained at risk at each follow-up time. "N outcomes" indicates the number of outcomes (events) experienced at each follow-up time.

110.2 days in hospital. Notably, while the rate of real-world poor outcomes was greatest in the initial months, CHR-P individuals continued to steadily experience poor outcomes for the duration of follow-up.

These findings clearly suggest that focusing solely on the short-term risk of transition to psychosis is clinically limited in capturing and supporting the real-world needs of CHR-P individuals. These considerations are particularly concerning if studies include research samples that do not typically represent the true spectrum of the CHR-P state. The fact that most CHR-P individuals will go on to develop poor outcomes in the long term may question the efficacy of preventive interventions. However, it is essential to note that preventive care in this cohort was capped at two years (as in most CHR-P services worldwide[66]), while the follow-up extended to up to 21 years. This means that the duration of care offered by CHR-P services (median: two years) is evidently insufficient and needs to be extended to support individuals beyond this period. Careful consideration of discharge destinations and care is warranted. This consideration has already been supported by our recent meta-analysis, which shows an increase in the transition rate from CHR-P state to FEP following discharge from preventive clinics at two years[12].

Third, this study presents the first clinically-based model to comprehensively forecast poor outcomes in the longer term. Being able to predict real-world, long-term poor outcomes can aid treatment stratification and the provision of holistic preventive care in CHR-P services[67]. Capturing a range of real-world poor outcomes enables a more informed decision-making process with patients. On a practical level, it would also help streamline implementation by reducing the cost and time of using multiple models[68]. It could also address barriers such as clinician fatigue and subsequent desensitization to precision psychiatry, which impede the adoption of prediction models in clinical practice[69].

The current prediction model is based on predictors collected in the UK National Health Service as part of clinical care, thereby representing real-world practice. Therefore, the model can be utilized to identify individuals at a greater risk of real-world, long-term poor outcomes for more impactful stratification. The most predictive features of our prediction model are largely in line with known risk and protective factors for transition from the CHR-P state[70], suggesting that they are prognostically important for a broader range of real-world, long-term poor outcomes. As our prediction model has been developed on routinely available clinical information, it has the promise to be sequentially integrated with future neurobiological models for improved prognostic accuracy[71,72].

The integration of our clinical prediction model into clinical workflows can be summarized in the following steps, which are based on our earlier implementation work with similar models[73,74]. First, implementation governance would need to be established in accordance with the local regulations, and involve clinicians and experts by experience to ensure that the highest ethical, data use, and privacy standards are met[68]. We have recently co-produced, together with patients, their families, funders, health care providers, and other stakeholders, a European guidance for the ethi-

Table 3 Regularized Cox regression model coefficients and hazard ratios

Predictor	Coefficient	Hazard ratio	Hazard ratio (scaled)
Age (years)	0.00030	1.00	1.00
Gender			
Female	NA	NA	NA
Male	-	1 (ref)	1 (ref)
Self-assigned ethnicity			
White	-	1 (ref)	1 (ref)
Asian	NA	NA	NA
Black	0.07874	1.08	1.08
Other	NA	NA	NA
Employment status			
Employed or student	-	1 (ref)	1 (ref)
Unemployed	0.01407	1.01	1.01
Marital status			
In a relationship	-	1 (ref)	1 (ref)
Single or divorced	NA	NA	NA
IMD decile	NA	NA	NA
CHR-P subgroup			
APS	-	1 (ref)	1 (ref)
BLIPS	0.13701	1.15	1.15
GRD	NA	NA	NA
CAARMS P1 and P2 total score	0.00222	1.00	1.09
CAARMS P3 total score	NA	NA	NA
CAARMS P4 total score	0.00702	1.01	1.11
DUAPS (days)	NA	NA	NA
SOFAS score	-0.00456	1.00	0.91
HoNOS (adjusted total score)	0.00052	1.00	1.01
Referral source			
Self	NA	NA	NA
Caregivers or relatives	NA	NA	NA
Schools or colleges	NA	NA	NA
Social services or supported accommodation	NA	NA	NA
General medical practitioners	-	1 (ref)	1 (ref)
Community mental health services	NA	NA	NA
Child and adolescent mental health services	NA	NA	NA
Early intervention for psychosis services	NA	NA	NA
Accident and emergency departments or home treatment team	NA	NA	NA
Assessment and liaison services	NA	NA	NA
Inpatient mental health services	0.04529	1.05	1.05
Police and criminal justice system	NA	NA	NA
Physical health services	NA	NA	NA
Alcohol use	NA	NA	NA
Cannabis use	0.06188	1.06	1.06

Table 3 Regularized Cox regression model coefficients and hazard ratios *(continued)*

Predictor	Coefficient	Hazard ratio	Hazard ratio (scaled)
Nicotine use	NA	NA	NA
Antipsychotic medication (sub-FEP dosage)	0.81996	2.27	2.27
Benzodiazepine medication	NA	NA	NA
Other medication	NA	NA	NA

NA denotes predictors whose coefficients were shrunk to zero (i.e., not retained in the final model by the regularized regression). Hazard ratios are scaled by two standard deviations for continuous variables to enable comparison of coefficient magnitudes across categorical and continuous variables. CHR-P – clinical high risk for psychosis, CAARMS – Comprehensive Assessment of at Risk Mental State, DUAPS – duration of untreated attenuated psychotic symptoms, HoNOS – Health of the Nation Outcome Scale, SOFAS – Social and Occupational Functioning Assessment Scale, IMD – index of multiple deprivation, APS – attenuated psychotic symptoms, BLIPS – brief and limited intermittent psychotic symptoms, GRD – genetic risk and deterioration syndrome, FEP – first-episode psychosis

cal implementation of precision and preventive psychiatry that comprehensively accounts for the nuanced complexities of this field[75,76].

Once this step is addressed, the model could be embedded into assessment routines, Shiny apps, or EHR systems, where available, to extract relevant variables when a new CHR-P individual is assessed for suspected psychosis risk[74]. The real-world nature of our model eliminates the need for clinicians to input additional data, as the necessary information is already recorded during routine clinical practice. Importantly, our clinical prediction model is intended to complement clinician judgement, not to replace it. Previous empirical research has demonstrated that clinicians' judgment in predicting outcomes for CHR-P individuals is associated with lower prognostic accuracy compared to clinical prediction models[72,77]. Aligning with these considerations, despite the initial judgement of CHR-P clinicians, the majority of participants (up to 64% at 14-18 years) experienced a poor outcome. Currently, prognosis in this group is not personalized, but limited to a rough group-level prediction of a binary outcome (after excluding those already psychotic at baseline) of "being at CHR-P" vs. "not being at CHR-P". Notably, neither the CHR-P subgroups nor other predictors (e.g., baseline exposure to small doses of antipsychotics or specific CAARMS subscores) are currently measured and utilized by clinicians to formulate a prognosis in this group.

Therefore, the primary clinical value of our model is to educate health care professionals and enhance their mental health literacy in preventive medicine by encouraging them to assess and utilize clinical predictors that are already available within their practice. This precision psychiatry model can then support clinicians in making a more accurate prognosis based on the included predictors. This task would be challenging to complete without clinical prediction models, as it would require a complex manual interpretation and integration of all the raw data at face value. Practically speaking, the model could screen CHR-P individuals when accepted by a mental health clinic or a professional, generate a continuous risk score at a predetermined time point of clinical interest (e.g., 2 years), and flag those exceeding a set threshold[73] (see an illustrative example of the use of the model in the supplementary information).

Current guidelines recommend producing continuous risk estimates that clinicians can use to inform their decision-making, alongside all other information that informs their clinical judgment, rather than more prescriptive dichotomized outcomes[78,79]. Clinicians would then, where warranted, discuss the benefits of considering more intensive preventive support and monitoring for mental health deterioration with their patients. The decision curve analysis, which our team first introduced in CHR-P clinical prediction modelling[80], can provide additional useful information to clinicians by plotting a continuous trade-off of clinical net benefits for using our risk calculator against competing alternatives across a range of risk thresholds up to 50% (where an unnecessary intervention becomes more harmful than missing a poor outcome). We have already demonstrated that it is feasible to embed similar risk calculators for young CHR-P individuals in the UK National Health Service by completing one of the few real-world studies testing the implementation of a clinical prediction model, which demonstrat-

Table 4 Performance of the personalized clinical prediction model for predicting the risk of real-world, long-term poor outcome in clinical high risk for psychosis (CHR-P) individuals

Temporal fold (year of accepted referral)	Sample size (N)	Events, N (%)	C-index (95% CI)	Calibration intercept (95% CI)	Calibration slope (95% CI)	Brier score (95% CI)	Prognostic index, mean±SD
2001-2007	131	42 (32.1)	0.69 (0.61-0.77)	0.41 (0.04-0.79)	2.14 (1.34-2.95)	0.21 (0.17-0.25)	0.03±0.25
2008-2012	154	49 (31.8)	0.63 (0.55-0.71)	0.32 (–0.02 to 0.66)	1.47 (0.47-2.47)	0.21 (0.18-0.25)	–0.14±0.23
2013-2016	180	63 (35.0)	0.65 (0.58-0.72)	0.40 (0.09-0.72)	1.12 (0.65-1.59)	0.21 (0.18-0.24)	–0.02±0.44
2017-2019	234	57 (24.4)	0.73 (0.66-0.80)	–0.19 (–0.50 to 0.12)	0.87 (0.63-1.11)	0.16 (0.13-0.18)	0.66±0.57
2020-2024	265	43 (16.2)	0.71 (0.61-0.80)	–0.63 (–0.96 to –0.30)	2.42 (1.48-3.35)	0.13 (0.11-0.16)	0.06±0.26
Overall	964	254 (26.3)	0.69 (0.63-0.74)	–0.03 (–0.62 to 0.55)	1.61 (0.74-2.48)	0.18 (0.13-0.22)	0.15±0.27

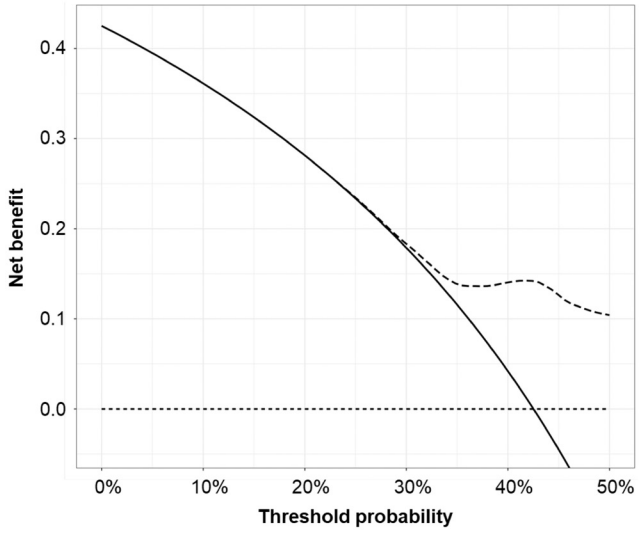

Figure 2 Potential clinical utility decision curve. The clinical prediction model (long dashed curve) was associated with greater net benefit than the alternatives of assessing all (black curve) at risk thresholds from 24% to 50%, and of assessing none (short dashed line) at risk thresholds from 0% to 50%.

ed good clinician adherence to the recommendations made by the risk calculator[73].

Fourth, referral pathways, local service configuration, and population characteristics change over time. These are known as temporal shifts, and, if not accounted for, can lead to models performing worse[22,81,82]. For example, if changes in service configuration result in fewer CHR-P individuals being referred from inpatient services, the caseload may be less unwell at presentation to the CHR-P service over the next year compared to the previous year. These differences may affect the accuracy of a prediction model. To address this, we utilized a temporal internal-external validation framework to demonstrate that model performance remained stable across the two decades of OASIS, despite these temporal shifts. This highlights its potential for prospective use in similar settings in the long term.

Fifth, our findings indicate the need for the development and availability of effective preventive treatments to address the poor prognosis across a range of clinically meaningful, real-world, long-term poor outcomes in CHR-P individuals. A recent meta-analysis of randomized controlled trials for preventive interventions in CHR-P[83] found no convincing evidence for their sustained efficacy in preventing transition, though this may have stemmed in part from high CIs and clinical improvements in treatment-as-usual care (i.e., needs-based interventions).

Needs-based interventions may be effective on several real-world outcomes analyzed by the current study. To the best of our knowledge, there are no trials testing the effect of interventions on composite poor outcomes or, for example, hospitalizations for psychiatric reasons. Given that some CHR-P individuals do not experience poor outcomes, intensive preventive interventions for this subgroup may be more harmful than necessary. Our prediction model could be utilized to identify individuals at lower risk of real-world, long-term poor outcomes for future clinical trials, for whom intensive interventions may be spared.

This study has some limitations. First, we did not conduct structured diagnostic or psychometric interviews to validate our outcomes. Nonetheless, our study findings have high ecological validity, assessing real-world outcomes in patients seen in everyday clinical practice, as opposed to research participants, which have been shown to be unrepresentative of clinical samples[16,17]. Second, although we could not follow-up all individuals for the same amount of time (e.g., those who were accepted in more recent years had a shorter follow-up compared to those who were recruited in the earlier years when the CHR-P service started), our analytic approach addressed this issue by considering the actual number of those remaining at-risk throughout the follow-up period. Furthermore, our temporal validation approach controlled for year of acceptance at the CHR-P service.

Third, the impact of pharmacological and psychological interventions provided by the local preventive clinic is undetermined. Addressing this would require randomized controlled trials, which are logistically and ethically complex to perform. However, due to the evolution of intervention provision over time, our temporal validation means that our model is somewhat robust to this. Additional independent external validation, particularly in international clinical samples, is needed to confirm this robustness[84].

In conclusion, this study demonstrates that most CHR-P individuals have long-term poor outcomes, beyond transition to psychosis, in real-world care, which should become the focus of a new generation of research. The clinical prediction model presented here can identify these individuals and facilitate the personalized provision of preventive care, thereby improving outcomes in this population. CHR-P services should also extend their duration of care to address the substantial long-term poor clinical outcomes experienced by young individuals.

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REFERENCES

1. Fusar-Poli P, Estradé A, Stanghellini G et al. The lived experience of psychosis: a bottom-up review co-written by experts by experience and academics. World Psychiatry 2022;21:168-88.
2. Estradé A, Onwumere J, Venables J et al. The lived experiences of family members and carers of people with psychosis: a bottom-up review co-written by experts by experience and academics. Psychopathology 2023;56:371-82.
3. Benrimoh D, Dlugunovych V, Wright AC et al. On the proportion of patients who experience a prodrome prior to psychosis onset: a systematic review and meta-analysis. Mol Psychiatry 2024;29:1361-81.
4. Fusar-Poli P, McGorry PD, Kane JM. Improving outcomes of first-episode psy-

chosis: an overview. World Psychiatry 2017;16:251-65.
5. Oliver D, Arribas M, Radua J et al. Prognostic accuracy and clinical utility of psychometric instruments for individuals at clinical high-risk of psychosis: a systematic review and meta-analysis. Mol Psychiatry 2022;27:3670-8.
6. Fusar-Poli P, Raballo A, Parnas J. What is an attenuated psychotic symptom? On the importance of the context. Schizophr Bull 2017;43:687-92.
7. Fusar-Poli P, Rocchetti M, Sardella A et al. Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. Br J Psychiatry 2015;207:198-206.
8. Morgan G, Thara R, Gureje O et al. Duration of untreated psychosis: a global perspective. World Psychiatry 2025;24:49-50.
9. Oliver D, Davies C, Crossland G et al. Can we reduce the duration of untreated psychosis? A systematic review and meta-analysis of controlled interventional studies. Schizophr Bull 2018;44:1362-72.
10. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. https://www.nice.org.uk/guidance/cg178.
11. National Health Service England. Implementing the early intervention in psychosis access and waiting time standard. www.england.nhs.uk.
12. Salazar de Pablo G, Radua J, Pereira J et al. Probability of transition to psychosis in individuals at clinical high risk: an updated meta-analysis. JAMA Psychiatry 2021;78:970-8.
13. Kirkbride JB, Errazuriz A, Croudace TJ et al. Incidence of schizophrenia and other psychoses in England, 1950-2009: a systematic review and meta-analyses. PLoS One 2012;7:e31660.
14. Fusar-Poli P, Salazar de Pablo G, Correll CU et al. Prevention of psychosis: advances in detection, prognosis, and intervention. JAMA Psychiatry 2020;77:755-65.
15. Sanfelici R, Dwyer DB, Antonucci LA et al. Individualized diagnostic and prognostic models for patients with psychosis risk syndromes: a meta-analytic view on the state of the art. Biol Psychiatry 2020;88:349-60.
16. Shah JL, Peters MI. Early intervention in psychiatry: scotomas, representativeness, and the lens of clinical populations. Soc Psychiatry Psychiatr Epidemiol 2019;54:1019-21.
17. Taipale H, Schneider-Thoma J, Pinzón-Espinosa J et al. Representation and outcomes of individuals with schizophrenia seen in everyday practice who are ineligible for randomized clinical trials. JAMA Psychiatry 2022;79:210-8.
18. Salazar de Pablo G, Soardo L, Cabras A et al. Clinical outcomes in individuals at clinical high risk of psychosis who do not transition to psychosis: a meta-analysis. Epidemiol Psychiatr Sci 2022;31:e9.
19. Rutigliano G, Valmaggia L, Landi P et al. Persistence or recurrence of non-psychotic comorbid mental disorders associated with 6-year poor functional outcomes in patients at ultra high risk for psychosis. J Affect Disord 2016;203:101-10.
20. Fusar-Poli P, De Micheli A, Signorini L et al. Real-world long-term outcomes in individuals at clinical risk for psychosis: the case for extending duration of care. eClinicalMedicine 2020;28:100578.
21. Fusar-Poli P, Cappucciati M, Rutigliano G et al. At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. World Psychiatry 2015;14:322-32.
22. Hartmann S, Dwyer D, Cavve B et al. Development and temporal validation of a clinical prediction model of transition to psychosis in individuals at ultra-high risk in the UHR 1000+ cohort. World Psychiatry 2024;23:400-10.
23. Rosen M, Betz LT, Schultze-Lutter F et al. Towards clinical application of prediction models for transition to psychosis: a systematic review and external validation study in the PRONIA sample. Neurosci Biobehav Rev 2021;125:478-92.
24. Perera G, Broadbent M, Callard F et al. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) case register: current status and recent enhancement of an electronic mental health record-derived data resource. BMJ Open 2016;6:e008721.
25. Jongsma HE, Gayer-Anderson C, Lasalvia A et al. Treated incidence of psychotic disorders in the multinational EU-GEI Study. JAMA Psychiatry 2018;75:36-46.
26. Stewart R, Soremekun M, Perera G et al. The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry 2009;9:51.
27. Sperrin M, Riley RD, Collins GS et al. Targeted validation: validating clinical prediction models in their intended population and setting. Diagn Progn Res 2022;6:24.
28. Fusar-Poli P, Werbeloff N, Rutigliano G et al. Transdiagnostic risk calculator for the automatic detection of individuals at risk and the prediction of psychosis: second replication in an independent national health service trust. Schizophr Bull 2019;45:562-70.
29. Puntis S, Oliver D, Fusar-Poli P. Third external replication of an individualised transdiagnostic prediction model for the automatic detection of individuals at risk of psychosis using electronic health records. Schizophr Res 2021;228:403-9.
30. Raket LL, Jaskolowski J, Kinon BJ et al. Dynamic ElecTronic hEalth reCord deTection (DETECT) of individuals at risk of a first episode of psychosis: a case-control development and validation study. Lancet Digit Health 2020;2:e229-39.
31. Oliver D, Wong CMJ, Bøg M et al. Transdiagnostic individualized clinically-based risk calculator for the automatic detection of individuals at-risk and the prediction of psychosis: external replication in 2,430,333 US patients. Transl Psychiatry 2020;10:364.
32. Fusar-Poli P, Spencer T, De Micheli A et al. Outreach and support in South-London (OASIS) 2001-2020: twenty years of early detection, prognosis and preventive care for young people at risk of psychosis. Eur Neuropsychopharmacol 2020;39:111-22.
33. Yung AR, Yuen HP, McGorry PD et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust N Z J Psychiatry 2005;39:964-71.
34. Taylor DM, Barnes TRE, Young AH. The Maudsley prescribing guidelines in psychiatry. Hoboken: Wiley, 2021.
35. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed, text revision. Washington: American Psychiatric Association, 2000.
36. Wing JK, Beevor AS, Curtis RH et al. Health of the Nation Outcome Scales (HoNOS): research and development. Br J Psychiatry 1998;172:11-8.
37. Robinson T, Ali MU, Easterbrook B et al. Risk-thresholds for the association between frequency of cannabis use and the development of psychosis: a systematic review and meta-analysis. Psychol Med 2023;53:3858-68.
38. Bond BW, Duric B, Spinazzola E et al. Cannabis use cessation and the risk of psychotic disorders: a case-control analysis from the first episode case-control EU-GEI WP2 study. Can J Psychiatry 2025;70:182-93.
39. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
40. Greenwood M. The natural duration of cancer. Rep Public Health Med Subj 1926;33:1-26.
41. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002;359:1686-9.
42. Office for National Statistics. Deaths registered by area of usual residence, UK. www.ons.gov.uk.
43. Office for National Statistics. Deaths registered in England and Wales. www.ons.gov.uk.
44. Collins GS, Dhiman P, Ma J et al. Evaluation of clinical prediction models (part 1): from development to external validation. BMJ 2024;384:e074819.
45. Collins GS, Moons KGM, Dhiman P et al. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. BMJ 2024;385:e078378.
46. Ensor J. pmsampsize: sample size for development of a prediction model. https://cran.r-project.org/web/packages/pmsampsize/index.html.
47. Riley RD, Snell KI, Ensor J et al. Minimum sample size for developing a multivariable prediction model: Part II – binary and time-to-event outcomes. Stat Med 2019;38:1276-96.
48. Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal-external, and external validation. J Clin Epidemiol 2016;69:245-7.
49. Harrell FE Jr, Califf RM, Pryor DB et al. Evaluating the yield of medical tests. JAMA 1982;247:2543-6.
50. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol 2014;14:25.
51. Riley RD, Ensor J, Snell KIE et al. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. BMJ 2016;353:i3140.
52. Gelman A. Scaling regression inputs by dividing by two standard deviations. Stat Med 2008;27:2865-73.
53. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26:565-74.
54. Khor S, Haupt EC, Hahn EE et al. Racial and ethnic bias in risk prediction models for colorectal cancer recurrence when race and ethnicity are omitted as predictors. JAMA Netw Open 2023;6:e2318495.
55. Manski CF, Mullahy J, Venkataramani AS. Using measures of race to make clinical predictions: decision making, patient health, and fairness. Proc Natl Acad Sci USA 2023;120:e2303370120.
56. van Apeldoorn JAN, Hageman SHJ, Harskamp RE et al. Adding ethnicity to cardiovascular risk prediction: external validation and model updating of SCORE2 using data from the HELIUS population cohort. Int J Cardiol 2024;417:132525.

57. Krakowski K, Oliver D, Arribas M et al. Dynamic and transdiagnostic risk calculator based on natural language processing for the prediction of psychosis in secondary mental health care: development and internal-external validation cohort study. Biol Psychiatry 2024;96:604-14.
58. Greene WH. Accounting for excess zeros and sample selection in Poisson and negative binomial regression models (March 1994). https://ssrn.com/abstract=1293115.
59. Sjoberg DD, Vertosick E. dcurves: decision curve analysis for model evaluation. https://cran.r-project.org/web/packages/dcurves/index.html.
60. Friedman J, Hastie T, Tibshirani R et al. glmnet: lasso and elastic-net regularized generalized linear models. https://cran.r-project.org/web/packages/glmnet/index.html.
61. Viechtbauer W. metafor: meta-analysis package for R. https://cran.r-project.org/web/packages/metafor/index.html.
62. Therneau TM, Lumley T, Atkinson E et al. survival: survival analysis. https://cran.r-project.org/web/packages/survival/index.html.
63. Templ M, Kowarik A, Alfons A et al. VIM: visualization and imputation of missing values. https://cran.r-project.org/web/packages/VIM/index.html.
64. Fusar-Poli P, Palombini E, Davies C et al. Why transition risk to psychosis is not declining at the OASIS ultra high risk service: the hidden role of stable pretest risk enrichment. Schizophr Res 2018;192:385-90.
65. Fusar-Poli P, Schultze-Lutter F, Cappucciati M et al. The dark side of the moon: meta-analytical impact of recruitment strategies on risk enrichment in the clinical high risk state for psychosis. Schizophr Bull 2016;42:732-43.
66. Kotlicka-Antczak M, Podgórski M, Oliver D et al. Worldwide implementation of clinical services for the prevention of psychosis: the IEPA early intervention in mental health survey. Early Interv Psychiatry 2020;14:741-50.
67. Radua J, Davies C, Fusar-Poli P. Evaluation of variability in individual response to treatments in the clinical high-risk state for psychosis: a meta-analysis. Schizophr Res 2021;227:20-7.
68. Baldwin H, Loebel-Davidsohn L, Oliver D et al. Real-world implementation of precision psychiatry: a systematic review of barriers and facilitators. Brain Sci 2022;12:934.
69. Bentley KH, Zuromski KL, Fortgang RG et al. Implementing machine learning models for suicide risk prediction in clinical practice: focus group study with hospital providers. JMIR Form Res 2022;6:e30946.
70. Oliver D, Reilly TJ, Baccaredda Boy O et al. What causes the onset of psychosis in individuals at clinical high risk? A meta-analysis of risk and protective factors. Schizophr Bull 2020;46:110-20.
71. Schmidt A, Cappucciati M, Radua J et al. Improving prognostic accuracy in subjects at clinical high risk for psychosis: systematic review of predictive models and meta-analytical sequential testing simulation. Schizophr Bull 2017;43:375-88.
72. Koutsouleris N, Dwyer DB, Degenhardt F et al. Multimodal machine learning workflows for prediction of psychosis in patients with clinical high-risk syndromes and recent-onset depression. JAMA Psychiatry 2021;78:195-209.
73. Oliver D, Spada G, Colling C et al. Real-world implementation of precision psychiatry: transdiagnostic risk calculator for the automatic detection of individuals at-risk of psychosis. Schizophr Res 2021;227:52-60.
74. Wang T, Oliver D, Msosa Y et al. Implementation of a real-time psychosis risk detection and alerting system based on electronic health records using CogStack. J Vis Exp 2020;159:10.3791/60794.
75. Fusar-Poli P, Manchia M, Koutsouleris N et al. Ethical considerations for precision psychiatry: a roadmap for research and clinical practice. Eur Neuropsychopharmacol 2022;63:17-34.
76. Kéri P, White LA, Oliver D et al. Empowering experts by experience to guide ethical precision psychiatry. Biol Psychiatry 2024;96:517-8.
77. Koutsouleris N, Kambeitz-Ilankovic L, Ruhrmann S et al. Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. JAMA Psychiatry 2018;75:1156-72.
78. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006;332:1080.
79. Efthimiou O, Seo M, Chalkou K et al. Developing clinical prediction models: a step-by-step guide. BMJ 2024;386:e078276.
80. Fusar-Poli P, Rutigliano G, Stahl D et al. Development and validation of a clinically based risk calculator for the transdiagnostic prediction of psychosis. JAMA Psychiatry 2017;74:493-500.
81. Moreno-Torres JG, Raeder T, Alaiz-Rodríguez R et al. A unifying view on dataset shift in classification. Pattern Recognit 2012;45:521-30.
82. Logeswaran Y, Oliver D. It's about time: why we need to consider temporal drift when developing and implementing clinical prediction models. Biol Psychiatry Cogn Neurosci Neuroimaging 2025;10:677-8.
83. Minichino A, Davies C, Karpenko O et al. Preventing psychosis in people at clinical high risk: an updated meta-analysis by the World Psychiatric Association Preventive Psychiatry section. Mol Psychiatry 2025;30:2773-82.
84. Oliver D. The importance of external validation to advance precision psychiatry. Lancet Reg Health Eur 2022;22:100498.

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Risk of all-cause and cause-specific mortality, and suicide attempt in people with anxiety and stress-related disorders: a systematic review, meta-analysis and meta-regression analysis of 165 studies

Elias Wagner[1,2], Matin Mortazavi[1,2], Laura Poddighe[3], David S. Baldwin[4-6], Vasileios Masdrakis[7], David J. Castle[8], Alessandro Serretti[9,10], Vincenzo Oliva[11-14], Giuseppe Fanelli[14-16], Michele Fornaro[17], Jae Il Shin[18-20], Ian Colman[21,22], Seana N. Semchishen[21], Kelly K. Anderson[23-25], Jian Li Wang[26,27], Elisa Brietzke[28], Michel Sabé[29,30], Samuele Cortese[5,31-33], Katharina Domschke[34], Alkomiet Hasan[2,35], Wing Chung Chang[36,37], Daniel T. Myran[38-41], Christoph U. Correll[42-45], Sarah Connor Gorber[46], Mikkel Højlund[47,48], Marco Solmi[40,44,49,50]

[1]Evidence-based Psychiatry and Psychotherapy, Faculty of Medicine, University of Augsburg, Augsburg, Germany; [2]Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, University of Augsburg, BKH Augsburg, Augsburg, Germany; [3]Department of Mental Health and Addiction Services, Spedali Civili of Brescia, Brescia, Italy; [4]Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK; [5]Hampshire and Isle of Wight Healthcare NHS Foundation Trust, Southampton, UK; [6]South African Medical Research Council Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa; [7]First Department of Psychiatry, Athens University Medical School, Eginition Hospital, Athens, Greece; [8]University of Tasmania and Centre for Mental Health Service Innovation, Hobart, TAS, Australia; [9]Department of Medicine and Surgery, Kore University of Enna, Enna, Italy; [10]Oasi Research Institute, Troina, Italy; [11]Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain; [12]Bipolar and Depressive Disorders Unit, Hospìtal Clinic de Barcelona, Barcelona, Spain; [13]Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; [14]Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy; [15]Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands; [16]Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands; [17]Section of Psychiatry, Department of Neuroscience, Reproductive Science and Odontostomatology, Federico II University of Naples, Naples, Italy; [18]Department of Pediatrics, Yonsei University College of Medicine, Severance Children's Hospital, Seoul, Republic of Korea; [19]Yonsei-Donggok Medical Education Institute, Seoul, Republic of Korea; [20]Severance Underwood Meta-Research Center, Institute of Convergence Science, Yonsei University, Seoul, Republic of Korea; [21]School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada; [22]Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway; [23]Department of Epidemiology and Biostatistics, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada; [24]Department of Psychiatry, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada; [25]Institute for Clinical Evaluative Sciences (ICES) Western, London, ON, Canada; [26]Department of Community Health and Epidemiology, Faculty of Medicine, Dalhousie University, Halifax, NS, Canada; [27]Department of Psychiatry, Faculty of Medicine, Dalhousie University, Halifax, NS, Canada; [28]Department of Psychiatry, Queen's University School of Medicine, Kingston, ON, Canada; [29]Department of Psychiatry, University Hospitals of Geneva, Thonex, Switzerland; [30]Faculty of Medicine, University of Geneva, Geneva, Switzerland; [31]Developmental EPI Lab, Center for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK; [32]Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, NY, USA; [33]Department of Precision and Regenerative Medicine-Jonic Area, University of Bari "Aldo Moro", Bari, Italy; [34]Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [35]German Center for Mental Health (DZPG), partner site München/Augsburg, Augsburg, Germany; [36]Department of Psychiatry, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong; [37]State Key Laboratory of Brain and Cognitive Sciences, University of Hong Kong, Hong Kong; [38]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada; [39]Department of Family Medicine, University of Ottawa, Ottawa, ON, Canada; [40]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [41]Bruyère Research Institute, Ottawa, ON, Canada; [42]Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY, USA; [43]Departments of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; [44]Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin Berlin, Berlin, Germany; [45]German Center for Mental Health (DZPG), partner site, Berlin, Germany; [46]Ottawa Hospital Research Institute, Hatching Ideas Lab, Ottawa, ON, Canada; [47]Department of Psychiatry Aabenraa, Mental Health Services Region of Southern Denmark, Aabenraa, Denmark; [48]Clinical Pharmacology, Pharmacy, and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark; [49]SCIENCES lab, Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada; [50]Regional Centre for Treatment of Eating Disorders and On Track: Champlain First Episode Psychosis Program, Department of Mental Health, Ottawa Hospital, Ottawa, ON, Canada

Anxiety disorders are the most prevalent mental health conditions worldwide. While their burden in terms of excess mortality is known to be high, a quantitative systematic evaluation of all-cause and cause-specific mortality and suicide attempt risks in people with anxiety or stress-related disorders is lacking. We performed a systematic review and random effects meta-analysis, in which co-primary outcomes were risk ratios (RRs) for all-cause and suicide-related mortality, and secondary outcomes were natural-cause mortality, other cause-specific mortality, and risk of suicide attempt. Sensitivity and meta-regression analyses were conducted. Overall, 165 studies encompassing 7,395,722 people with any anxiety or stress-related disorder and 135,059,023 controls, from 27 different countries across all continents, were included. Compared with the general population, a higher risk of all-cause mortality was associated with any anxiety or stress-related disorder (n=42, RR=1.54, 95% CI: 1.14-2.08, p=0.005), generalized anxiety disorder (n=9, RR=1.48, 95% CI: 1.23-1.78, p<0.001), and post-traumatic stress disorder (PTSD) and other stress-related disorders (n=21, RR=1.39, 95% CI: 1.15-1.67, p<0.001), but not with panic disorder, phobias, and mixed anxiety or stress-related disorders. Suicide mortality was increased in people with any anxiety or stress-related disorder (n=39, RR=2.88, 95% CI: 2.13-3.89, p<0.001), panic disorder (n=3, RR=3.58, 95% CI: 1.39-9.25, p<0.008), mixed anxiety or stress-related disorders (n=27, RR=2.77, 95% CI: 1.89-4.07, p<0.001), PTSD and other stress-related disorders (n=11, RR=3.13, 95% CI: 1.85-5.28, p<0.001), and generalized anxiety disorder (n=3, RR=1.93, 95% CI: 1.17-3.17, p<0.01). Suicide attempt risk was higher than in the general population in people with all anxiety or stress-related disorders, ranging from RR=6.33 (95% CI: 4.08-9.82, n=5) in panic disorder to RR=2.74 (95% CI: 1.72-4.35, n=5) in phobias. Natural-cause mortality was increased in any anxiety or stress-related disorder (n=19, RR=1.25, 95% CI: 1.09-1.44, p=0.002), generalized anxiety disorder (n=5, RR=1.55, 95% CI: 1.19-2.02, p=0.001), mixed anxiety or stress-related disorders (n=8, RR=1.26, 95% CI: 1.02-1.56, p=0.033), and PTSD and other stress-related disorders (n=9, RR=1.17, 95% CI: 1.03-1.33, p=0.019), but not in panic disorder. Cardiovascular-related deaths were increased in any and mixed anxiety or stress-related disorders and in generalized anxiety disorder, while cancer mortality was increased only in generalized anxiety disorder. When analyzing people with vs. without anxiety disorders with samples being matched by comorbid physical or mental disorders, results remained significant for all-cause mortality in generalized anxiety disorder and panic disorder, but not in any or mixed anxiety or stress-related disorders, and in PTSD and stress-related disorders. When compared with other mental disorders, no difference in co-primary outcomes emerged from more than two studies. Publication bias was present across several analyses, but sensitivity analyses largely confirmed the main findings. In meta-regression analyses, more recent data collection mitigated all-cause mortality, while schizophrenia-spectrum and bipolar disorder comorbidity mitigated suicide mortality risk, possibly driven by underlying treatment. This meta-analysis documents a higher all-cause, suicide and natural-cause mortality, and a higher risk of suicide attempt, in people with anxiety or stress-related disorders compared to the general population. Given the high prevalence and the recognized global treatment gap for these disorders, this finding is of great public health concern, and calls for appropriate prevention, screening and treatment strategies. More studies are needed to fill the publication bias gap and to identify modifiable risk or mitigating factors.

Key words: Anxiety disorders, stress-related disorders, mortality, suicide, suicide attempt, generalized anxiety disorder, panic disorder, post-traumatic stress disorder, mitigating factors

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Anxiety disorders are the most prevalent mental health conditions[1], affecting approximately 4.4% of the population (over 300 million people) worldwide. They contribute to 10.4% of the disability adjusted life years (DALYs) lost due to neurological, mental and substance use disorders[2]. Despite effective treatments being available, only one in four (27.6%) of individuals with an anxiety disorder receive minimally adequate treatment, due to a variety of factors, including a lack of awareness or recognition of the presence of a mental disorder, a shortage of mental health care providers, and the impact of social and self-stigma[3]. Furthermore, at least 30% of these disorders prove to be difficult-to-treat or treatment-resistant[4].

Although anxiety disorders may be associated with a lower relative increase in risk of death compared to other mental disorders, they are likely to contribute to a larger population-attributable risk of excess mortality, because of their much higher prevalence. For example, the population attributable risk of excess mortality due to anxiety disorders has been reported to be 4.3%, being more than six times higher than that due to schizophrenia[5].

While several meta-analyses have consistently quantified the risk of death in schizophrenia[6], bipolar disorder[7], and depressive disorders[8] compared with the general population, the reported mortality effect sizes are inconsistent for anxiety and stress-related disorders[5]. There is even evidence that some diagnostic subtypes (e.g., among stress-related disorders) may have protective effects on overall life expectancy, albeit this finding could reflect, at least in part, diagnostic inaccuracies in primary care settings[9].

Meta-analyses of the risk of suicidality[10,11] and all-cause mortality[5,12] in anxiety disorders have either reported significantly elevated risk ratios (RRs) in comparison with the general population or people without mental disorders[5], or found non-significantly elevated risks in people with vs. without clinically significant anxiety symptoms[12]. These differences may be due to the operationalization of case definitions in existing meta-analyses, that inconsistently included persons with full-threshold diagnoses and people with anxiety symptoms but not a disorder diagnosis[5,12,13]. Conflicting findings have also been reported on suicide risk in post-traumatic stress disorder (PTSD), with a systematic review from over a decade ago detecting no increased risk of suicide mortality[14], while a recent meta-analysis found the opposite[15].

In recent years, several new studies have reported on mortality or suicide attempts in people with anxiety disorders[9,16-18] as well as PTSD[19-23]. For instance, recent studies have reported on the association between anxiety disorders and specific mortality risk in people with cardiovascular disease[24], diabetes mellitus[25,26], or coronavirus 2019 disease (COVID-19)[27-29]. Nevertheless, the impact of moderating factors has never been quantified in a large scale meta-analysis.

A comprehensive and up-to-date appraisal of the evidence available in this area is thus warranted. To address this gap, we performed a systematic review and meta-analysis of cohort and case-control studies examining the risk of all-cause and cause-specific mortality, suicide death and suicide attempt, in individuals with anxiety or stress-related disorders versus several control groups, while considering potential risk and mitigating non-modifiable and modifiable factors, confounding variables, study quality, and time trends.

METHODS

Literature search

A PRISMA 2020-compliant[30] systematic review, searching PubMed via Ovid Medline, PsycINFO and EMBASE, with a search date up to August 15, 2024, was performed (see supplementary information for the search key). Additionally, we hand-searched the references of previously published systematic reviews for additional articles[12,13,15,31-34]. The *a priori* protocol was made publicly available at https://osf.io/59dta.

Study eligibility criteria

We included cohort or case-control studies reporting all-cause, natural-cause and cause-specific mortality risk, as well as mortality by suicide and suicide attempt risk, in people with anxiety or stress-related disorders (defined according to DSM/ICD criteria/requirements, on the basis of a diagnostic interview or medical records) compared with the general population or any other control group (e.g., group without anxiety disorder matched by comorbid physical or mental comorbid disorder, or group with other mental disorders), or reporting on mitigating/protective factors within anxiety or stress-related disorders.

We excluded cross-sectional studies, randomized controlled trials, studies not defining anxiety or stress-related disorders as specified above, and those not reporting an outcome of interest. Studies identifying anxiety or stress-related disorders by only using rating scales, such as the Hamilton Anxiety Rating Scale or the State-Trait Anxiety Inventory, were not eligible for inclusion.

Five independent raters (LP, MM, EW, MS, VM) screened and selected studies using Covidence[35], and extracted data from eligible studies. No language or time restrictions were applied.

Outcomes

Co-primary outcomes were RRs of all-cause and suicide-related mortality. Secondary outcomes included natural-cause, non-natural-cause excluding suicide (e.g., overdose or accidental

death), and cause-specific (e.g., cardiovascular disease or cancer) mortality risks, as well as history of suicide attempt. For studies investigating anxiety or stress-related disorders as a whole, without diagnostic subtype differentiation in their analyses, the term "mixed anxiety or stress-related disorders" was used.

We kept multiple studies reporting on the same representative population and the same outcome only if the study dates overlapped for less than 50%. In case of larger overlap, we prioritized the largest sample size. If one (larger) study reported on an unadjusted outcome and another on an adjusted outcome, both studies were kept (the larger study in the main analyses and the study with the adjusted results in sensitivity analyses). In representative studies, if the control group was not provided, we extracted data from census sources corresponding to the study period, as done in previous research[6].

We conducted three types of analyses, one for each type of control group, to avoid mixing heterogeneous control groups. Specifically, the exposed group consisted of people meeting diagnostic criteria/requirements for an anxiety or stress-related disorder, and the control groups consisted of: a) the general population, regardless of underlying comorbid physical diseases (from here on, "general population"), or b) people without anxiety disorders, matched with the exposed group by comorbid physical or mental disorders (see supplementary information), or c) other mental disorders.

Main, sensitivity and subgroup analyses

The main analyses were conducted for any anxiety or stress-related disorder, as well as for specific diagnoses. In the case of several observations, estimates with the most extended follow-up were used.

Sensitivity analyses were performed on the co-primary outcomes excluding case-control studies, poor-quality studies, and studies with extreme estimates (RR>20). Subgroup analyses were conducted on the co-primary outcomes across different study designs (retrospective or prospective cohorts, case-control studies), quality rating (good/fair/poor), representativeness (nationwide/not nationwide), study region, and presence of adjusted estimates (yes/no).

When at least ten studies were available for each outcome, univariate mixed-effects meta-regression analyses investigated the following potential moderators: sample size, median year of data collection, mean follow-up (years), mean age of the whole sample, proportion of females, proportion of people with Caucasian race, and proportion of individuals with comorbid depression, bipolar disorder, schizophrenia-spectrum disorder, alcohol/substance use disorder, cardiovascular disease, or cancer.

Data analysis

We pooled any ratio measure: RR, odds ratio, standardized mortality ratio, hazard ratio, and incidence rate ratio (IRR). Adjusted ratio measures were preferred if available. If not reported as ratio measures, we calculated either RR or IRR from raw data (events/totals/follow-up). If association measures were presented for various strata, we aggregated results before conducting the meta-analysis using aggregate study-level data (from the *metafor* package[36]).

Using a random-effects model[37], a RR with a 95% confidence interval (CI) for each outcome was estimated. I^2 was used to assess heterogeneity[38]. Publication bias was evaluated by Egger's test[39]. The fail-safe number was calculated when Egger's test was suggestive of publication bias (i.e., $p<0.1$) and at least ten studies were reported. Trim-and-fill[40] adjusted RRs were calculated if at least ten studies were reported.

For the anxiety disorder vs. general population comparison, meta-regression, sensitivity and subgroup analyses were conducted to explore sources of heterogeneity. Subgroup analyses were also conducted for the anxiety vs. no anxiety disorder samples matched by underlying comorbidity comparison. Univariate mixed-effects meta-regression analyses investigated the abovementioned potential moderators, when at least ten studies reported each of them for each outcome.

The quality of the included studies was measured using the design-appropriate US National Institutes of Health (NIH) quality rating tool[41]. R 4.4.0 and the *metafor* package were used for all statistical analyses[29,42] .

RESULTS

Included studies

Overall, 165 studies were identified by our systematic search and after manual search[9,17-29,43-192] (see PRISMA chart in Figure 1). These studies (cohort: n=133, 80.6%; case-control: n=32, 19.4%) comprised 7,395,722 people with any anxiety or stress-related disorder and 135,059,023 controls from 27 different countries across all continents.

A total of 87 studies included persons with mixed anxiety or stress-related disorders (3,677,433 patients and 35,533,803 controls), while there were 63 studies on PTSD and other stress-related disorders (with 3,247,478 patients and 99,958,248 controls), 22 studies on generalized anxiety disorder (with 64,678 patients and 1,812,823 controls), 18 studies on panic disorder (with 364,122 patients and 2,307,240 controls), and eight studies on phobias – including social anxiety disorder, agoraphobia and specific phobias (with 42,011 patients and 714,962 controls). Some studies included more than one population.

Studies were conducted in the US (n=71), Sweden (n=13), the UK (n=9), Canada (n=9), South Korea (n=8), Denmark (n=6), the Netherlands (n=6), Taiwan (n=6), France (n=5), Italy (n=4), Germany (n=4) and Spain (n=3). Two studies each emanated from Japan, Norway, Finland, China, Australia and Czech Republic, and one each from New Zealand, Lithuania, South Africa, Iran, Israel, Hungary, Northern Ireland, Switzerland and Brazil. Studies reported on observation time windows between 1947 and 2023.

There were 49 (29.7%) prospective and 84 (50.9%) retrospective cohort studies – with 32 (24.1%) being nationwide studies – and 32

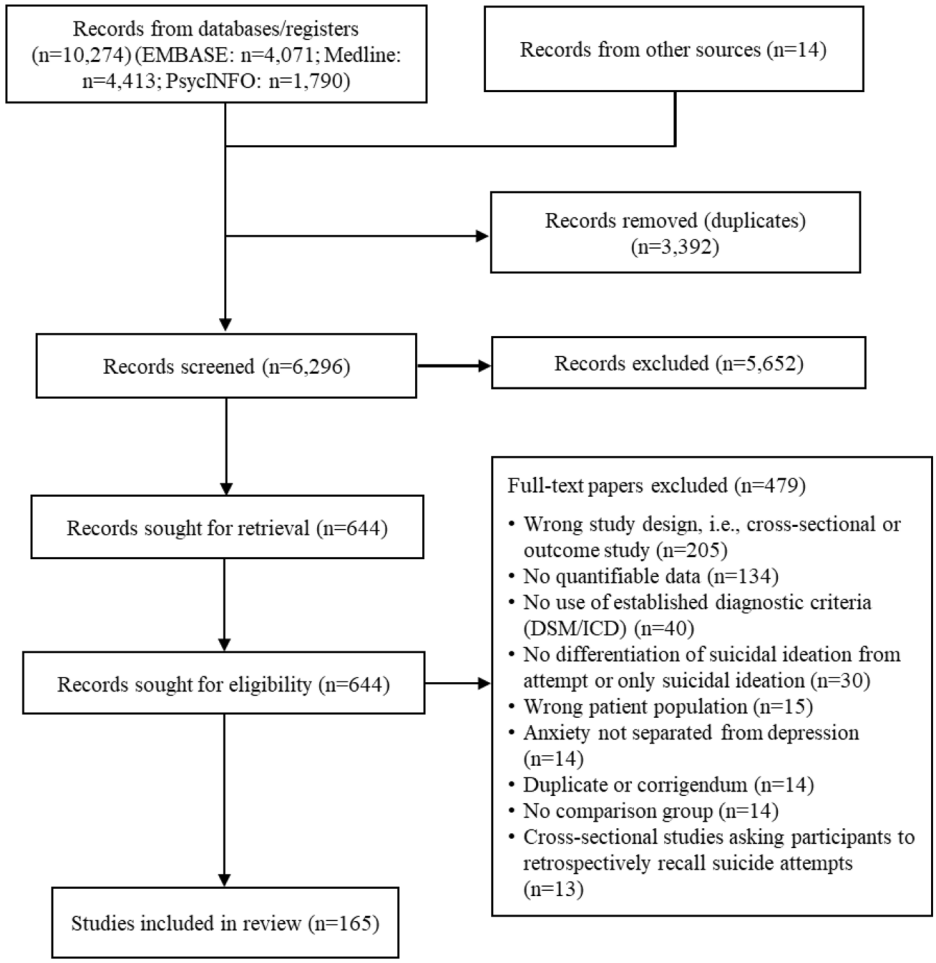

Figure 1 PRISMA study selection diagram

(19.4%) case-control studies. In total, 96 studies were rated regarding their quality as fair, 62 as good and 7 as poor according to the NIH tool. Median follow-up was 7.5 (interquartile range, IQR: 3 to 11) years. Mean age of people with any anxiety or stress-related disorder was 49.9 years, and 35.7% of them were women.

Overall, 89 out of 165 studies (53.9%) reported all-cause mortality (see supplementary information). Only seven studies investigated the association between different risk or protective factors and mortality in subjects with anxiety or stress-related disorders[22,47,57,87,108,160,179], using heterogeneous factors and outcomes, which precluded meta-analytic pooling. The comorbid physical or mental disorders considered in relevant studies were also highly heterogeneous (see supplementary information).

Meta-analyses comparing people with anxiety or stress-related disorders versus the general population

All-cause mortality

Any anxiety or stress-related disorder was associated with a significantly elevated all-cause mortality compared to the general population (n=42, RR=1.54, 95% CI: 1.14-2.08, I^2=99%, p=0.005) (see Figure 2).

Among specific diagnostic categories, generalized anxiety disorder (n=9, RR=1.48, 95% CI: 1.23-1.78, I^2=81%, p<0.001), and PTSD and other stress-related disorders (n=21, RR=1.39, 95% CI: 1.15-1.67, I^2=98%, p<0.001) were associated with significantly higher all-cause mortality rates, whereas panic disorder (n=7, p=0.073) and phobias (n=6, p=0.074) were not. The category "mixed anxiety or stress-related disorders" was not associated with significantly increased all-cause mortality (n=19, p=0.088) (see Figure 2).

Publication bias emerged only for the association between any anxiety or stress-related disorder and all-cause mortality, which became non-significant with a fail-safe N of 42 (see supplementary information).

Suicide-related mortality

Any anxiety or stress-related disorder was associated with significantly higher suicide-related mortality compared to the general population (n=39, RR=2.88, 95% CI: 2.13-3.89, I^2=100%, p< 0.001), as were panic disorder (n=3, RR=3.58, 95% CI: 1.39-9.25,

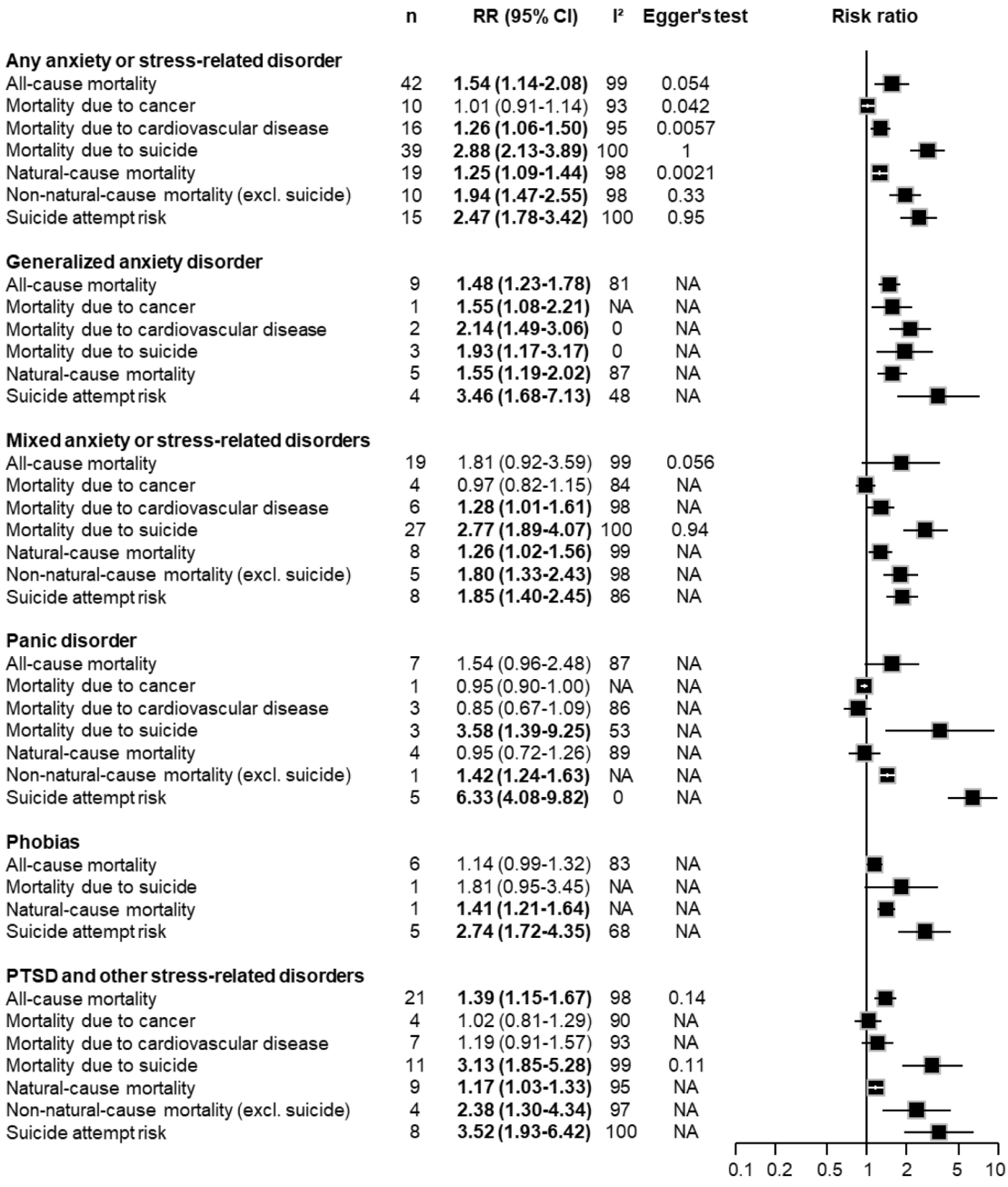

Figure 2 All-cause and cause-specific mortality, and suicide attempt risk in people with anxiety or stress-related disorders versus the general population. RR – risk ratio, NA – not assessed, PTSD – post-traumatic stress disorder. Significant values are highlighted in bold prints.

I^2=53%, p=0.008), mixed anxiety or stress-related disorders (n=27, RR=2.77, 95% CI: 1.89-4.07, I^2=100%, p<0.001), PTSD and other stress-related disorders (n=11, RR=3.13, 95% CI: 1.85-5.28, I^2=99%, p<0.001), and generalized anxiety disorder (n=3, RR=1.93, 95% CI: 1.17-3.17, I^2=0%, p=0.01) (see Figure 2). No evidence of publication bias was found.

Suicide attempt risk

Any anxiety or stress-related disorder was significantly associated with a higher suicide attempt risk in comparison with the general population (n=15, RR=2.47, 95% CI: 1.78-3.42, I^2=100%, p<0.001). Moreover, panic disorder (n=5, RR=6.33, 95% CI: 4.08-9.82, I^2=0%, p<0.001), PTSD and other stress-related disorders (n=8, RR=3.52, 95% CI: 1.93-6.42, I^2=100%, p<0.001), mixed anxiety or stress-related disorders (n=8, RR=1.85, 95% CI: 1.40-2.45, I^2=86%, p<0.001), phobias (n=5, RR=2.74, 95% CI: 1.72-4.35, I^2=68%, p<0.001) and generalized anxiety disorder (n=4, RR=3.46, 95% CI: 1.68-7.13, I^2=48%, p<0.001) were all associated with significantly higher suicide attempt rates (see Figure 2). There was no evidence of publication bias.

Natural-cause mortality

Any anxiety or stress-related disorder was significantly associated with higher natural-cause mortality as compared with the general population (n=19, RR=1.25, 95% CI: 1.09-1.44, I^2=98%, p=0.002). Significant associations with higher natural-cause mortality were also found for generalized anxiety disorder (n=5, RR=1.55, 95% CI: 1.19-2.02, I^2=87%, p=0.001) and phobias (n=1, RR=1.41, 95% CI: 1.21-1.64, p<0.001), as well as for mixed anxiety or stress-related disorders (n=8, RR=1.26, 95% CI: 1.02-1.56, I^2=99%, p=0.033), and PTSD and other stress-related disorders (n=9, RR=1.17, 95% CI: 1.03-1.33, I^2=95%, p=0.019). No association emerged for panic disorder (n=4, p=0.73) (see Figure 2).

The association between any anxiety or stress-related disorder and higher natural-cause mortality became non-significant after adjusting for publication bias, with a fail-safe N of 23. No additional publication bias was found.

Non-natural-cause mortality (excluding suicide)

A higher non-natural-cause (excluding suicide) mortality risk emerged for any anxiety or stress-related disorder (n=10, RR=1.94, 95% CI: 1.47-2.55, I^2=98%, p<0.001), as well as for PTSD and other stress-related disorders (n=4, RR=2.38, 95% CI: 1.30-4.34, I^2=97%, p=0.005), mixed anxiety or stress-related disorders (n=5, RR=1.80, 95% CI: 1.33-2.43, I^2=98%, p<0.001), and panic disorder (n=1, RR=1.42, 95% CI: 1.24-1.63, p<0.001). No studies were available for generalized anxiety disorder and phobias (see Figure 2).

Cancer-related mortality

There was no significant association between any anxiety or stress-related disorder and higher cancer-related mortality compared to the general population (n=10, p=0.81). No association was also found for mixed anxiety or stress-related disorders (n=4, p=0.75), panic disorder (n=1, p=0.056), and PTSD and other stress-related disorders (n=4, p=0.84). Generalized anxiety disorder was associated with higher cancer-related mortality, though in one study only (n=1, RR=1.55, 95% CI: 1.08-2.21, p=0.017).

Cardiovascular disease-related mortality

Any anxiety or stress-related disorder was associated with a significantly higher risk of mortality from cardiovascular disease compared to the general population (n=16, RR=1.26, 95% CI: 1.06-1.50, I^2=95%, p=0.006). This association was also found for generalized anxiety disorder (n=2, RR=2.14, 95% CI: 1.49-3.06, I^2=0%, p<0.001), and mixed anxiety or stress-related disorders (n=6, RR=1.28, 95% CI: 1.01-1.61, I^2=98%, p=0.04). PTSD and other stress-related disorders (n=7, p=0.21) and panic disorder (n=3, p=0.20) were not associated with cardiovascular disease-related mortality, and no data were available for phobias (see Figure 2).

For any anxiety or stress-related disorder, the association became non-significant after adjusting for publication bias, with a fail-safe N of 10. No publication bias emerged for other analyses.

Sensitivity, subgroup and meta-regression analyses of comparisons versus the general population

In sensitivity analyses, after excluding case-control studies, all-cause mortality (n=40, RR=1.51, 95% CI: 1.10-2.08, I^2=99%, p=0.01), suicide-related mortality (n=17, RR=3.47, 95% CI: 2.08-5.77, I^2=100%, p<0.001), natural-cause mortality (n=18, RR=1.23, 95% CI: 1.07-1.42, I^2=98%; p<0.001), and suicide attempt risk (n=9, RR=2.44, 95% CI: 1.69-3.53, I^2=92%, p<0.001) were still significantly higher in anxiety or stress-related disorders when compared with the general population. When poor quality studies and studies with extreme estimates (RR>20) were excluded, results remained significant for both co-primary outcomes (all p<0.006) (see Table 1).

Subgroup comparisons for all-cause mortality regarding quality rating, study design, study region, representativeness, and presence of adjusted estimates did not reveal any significant differences (all p>0.073). Subgroup comparisons for suicide-related mortality show-

Table 1 Sensitivity analyses for co-primary outcomes (anxiety and stress-related disorders vs. general population)

	n	RR (95% CI)	p	I^2
All-cause mortality				
Main analysis	42	1.54 (1.14-2.08)	0.005	99%
Excluding case-control studies	40	1.51 (1.10-2.08)	0.01	99%
Excluding poor quality studies	40	1.56 (1.14-2.14)	0.0056	99%
Excluding extreme estimates (RR>20)	40	1.25 (1.12-1.40)	<0.001	99%
Mortality due to suicide				
Main analysis	39	2.88 (2.13-3.89)	<0.001	100%
Excluding case-control studies	17	3.47 (2.08-5.77)	<0.001	100%
Excluding poor quality studies	39	2.88 (2.13-3.89)	<0.001	100%
Excluding extreme estimates (RR>20)	38	2.61 (2.03-3.96)	<0.001	99%
Natural-cause mortality				
Main analysis	19	1.25 (1.09-1.44)	0.0017	98%
Excluding case-control studies	18	1.23 (1.07-1.42)	<0.001	98%
Excluding poor quality studies	17	1.24 (1.06-1.44)	0.0057	98%
Excluding extreme estimates (RR>20)	19	1.25 (1.09-1.44)	0.0017	98%
Suicide attempt risk				
Main analysis	15	2.47 (1.78-3.42)	<0.001	100%
Excluding case-control studies	9	2.44 (1.69-3.53)	<0.001	92%
Excluding poor quality studies	15	2.47 (1.78-3.42)	<0.001	100%
Excluding extreme estimates (RR>20)	15	2.47 (1.78-3.42)	<0.001	100%

RR – risk ratio

ed significantly higher mortality risks in studies with a good quality rating (p=0.02) and those with adjusted estimates (p<0.001). Suicide attempt risk was significantly higher in prospective cohort studies compared to retrospective cohort and case-control studies (p=0.002), and significantly lower in nationwide compared to non-nationwide cohorts (p=0.002) (see also supplementary information).

In meta-regression analyses, a significant decrease in all-cause mortality was observed with increasing median year of data collection (n=42, beta=–0.039, 95% CI: –0.070 to –0.008, p=0.015). Sample size (p=0.67), mean age of the sample (p=0.21), mean follow-up in years (p=0.42), proportion of females (p=0.87), proportion of people with Caucasian (p=0.61) or Black (p=0.49) race, and the proportion of individuals with comorbid depression (p=0.55) all had no significant impact on all-cause mortality risk (see also supplementary information).

A longer mean follow-up (n=10, beta=–0.023, 95% CI: –0.046 to –0.000, p=0.047), and a higher proportion of comorbid schizophrenia-spectrum disorders (n=15, beta=–0.148, 95% CI: –0.220 to –0.076, p<0.001) and bipolar disorder (n=11, beta=–0.122, 95% CI: –0.229 to –0.016, p=0.024) significantly decreased suicide-related mortality. Proportions of people with comorbid substance use disorder (p=0.25), alcohol use disorder (p=0.80) or depression (p=0.59) had no significant impact on suicide mortality risk.

No potential moderators had significant effects on natural-cause mortality (all p>0.13) or suicide attempt risk (all p>0.14).

Meta-analyses in samples matched by comorbid physical or mental disorders

In meta-analyses where anxiety vs. no anxiety disorder groups were matched by comorbid physical or mental disorders, any anxiety or stress-related disorder (n=40, p=0.3), mixed anxiety or stress-related disorders (n=22, p=0.68), and PTSD and other stress-related disorders (n=12, p=0.16) were not significantly associated with higher all-cause mortality. However, a significantly higher all-cause mortality risk was observed for generalized anxiety disorder (n=7, RR=1.46, 95% CI: 1.23-1.73, I^2=54%, p<0.001) and panic disorder (n=2, RR=1.12, 95% CI: 1.04-1.21, I^2=0%, p=0.003) (see Figure 3).

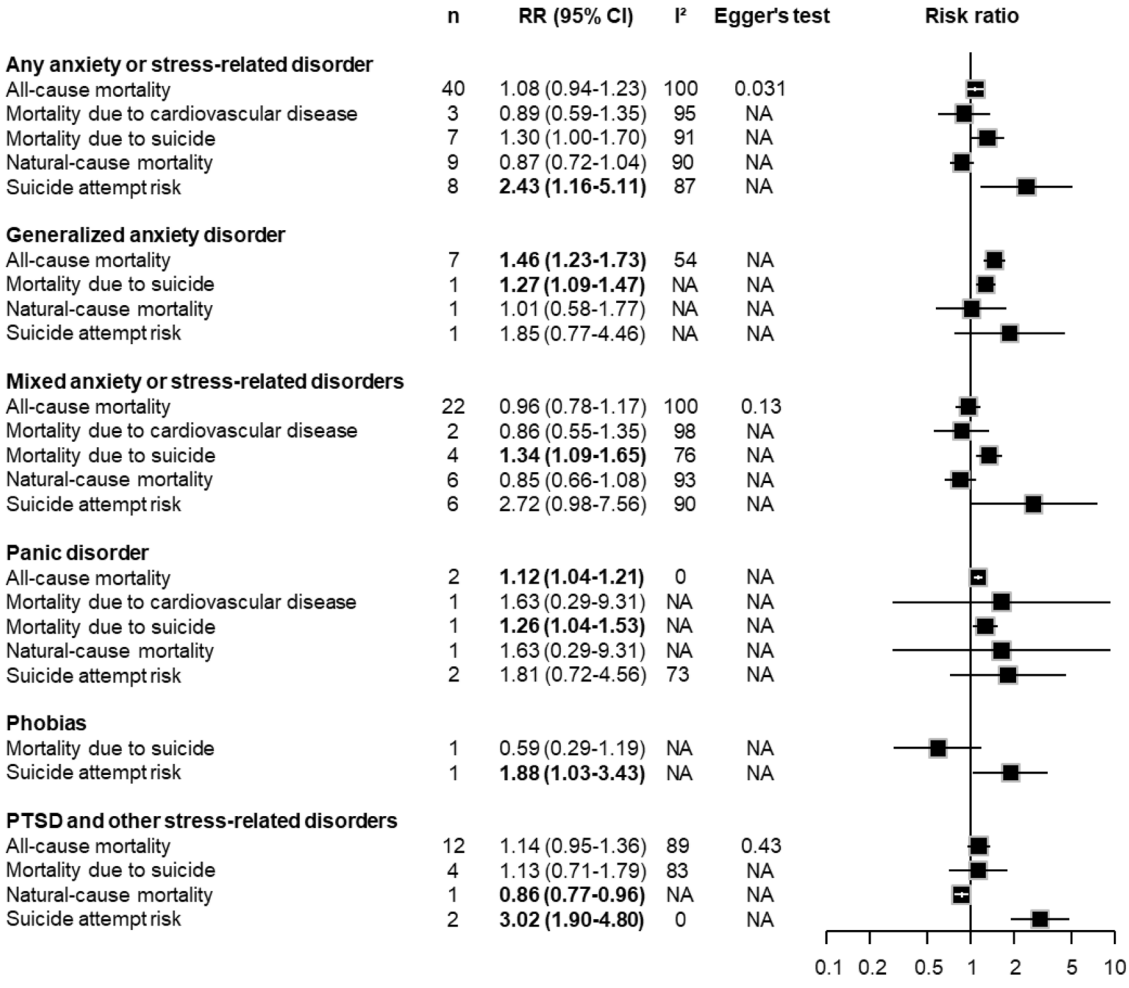

Figure 3 All-cause and cause-specific mortality, and suicide attempt risk in people with vs. without anxiety or stress-related disorders with samples being matched by comorbid disorders. RR – risk ratio, NA – not assessed, PTSD – post-traumatic stress disorder. Significant values are highlighted in bold prints.

There was no evidence of publication bias.

Mixed anxiety or stress-related disorders remained significantly associated with higher suicide-related mortality (n=4, RR=1.34, 95% CI: 1.09-1.65, I^2=76%, p=0.005), as were generalized anxiety disorder (n=1, RR=1.27, 95% CI: 1.09-1.47, p=0.002) and panic disorder (n=1, RR=1.26, 95% CI: 1.04-1.53, p=0.019). No higher risk emerged for any anxiety or stress-related disorder (n=7, p=0.054) as well as for PTSD and other stress-related disorders (n=4, p=0.62) and phobias (n=1, p=0.14) (see Figure 3). No evidence of publication bias was present.

Any anxiety or stress-related disorder remained significantly associated with a higher rate of suicide attempts (n=8, RR=2.43, 95% CI: 1.16-5.11, I^2=87%, p=0.019). A higher rate of suicide attempts was also observed for PTSD and other stress-related disorders (n=2, RR=3.02, 95% CI: 1.90-4.80, I^2=0%, p<0.001) and phobias (n=1, RR=1.88, 95% CI: 1.03-3.43, p=0.038), but not for mixed anxiety or stress-related disorders (n=6, p=0.056), generalized anxiety disorder (n=1, p=0.17) and panic disorder (n=2, p=0.21) (see Figure 3). There was no evidence of publication bias.

Natural-cause mortality was not significantly elevated for any anxiety or stress-related disorder (n=9, p=0.13), mixed anxiety or stress-related disorders (n=6, p=0.18), generalized anxiety disorder (n=1, p=0.97) and panic disorder (n=1, p=0.58). Natural-cause mortality was significantly decreased in a single study on PTSD and other stress-related disorders (n=1, RR=0.86, 95% CI: 0.77-0.96, p=0.007) (see Figure 3). There was no evidence of publication bias.

No study was available for cancer-related mortality risk in the matched-by-comorbidity comparison. No significant association with cardiovascular disease-related mortality emerged for any anxiety or stress-related disorder, mixed anxiety or stress-related disorders, and panic disorder (all p>0.57). No publication bias emerged.

Analyses comparing people with anxiety or stress-related disorders versus those with other mental disorders

PTSD and other stress-related disorders (n=2, RR=0.94, 95% CI: 0.90-0.98, p=0.007), as well as mixed anxiety or stress-related disorders (n=1, RR=0.71, 95% CI: 0.53-0.96, p=0.026) were associated with significantly lower all-cause mortality risk compared with other mental disorders. No association emerged for any anxiety or stress-related disorder (n=3, p=0.093) (see Figure 4).

Suicide-related mortality was not significantly different for any anxiety or stress-related disorder (n=6, p=0.82), mixed anxiety or stress-related disorders (n=5, p=0.71) or generalized anxiety disorder (n=1, p=0.48) compared with other mental disorders.

Suicide attempt risk was not significantly different for any anxiety or stress-related disorder (n=4, p=0.73), mixed anxiety or stress-related disorders (n=2, p=0.32), generalized anxiety disorder (n=1, p=0.2), and panic disorder (n=1, p=0.93), compared with other mental disorders. Only phobias (n=1, RR=2.35, 95% CI: 1.08-5.14, p=0.032) and PTSD and other stress-related disorders (n=1, RR=2.12, 95% CI: 1.20-3.74, p=0.01) were associated with a significantly higher risk of suicide attempts, but with only one study each.

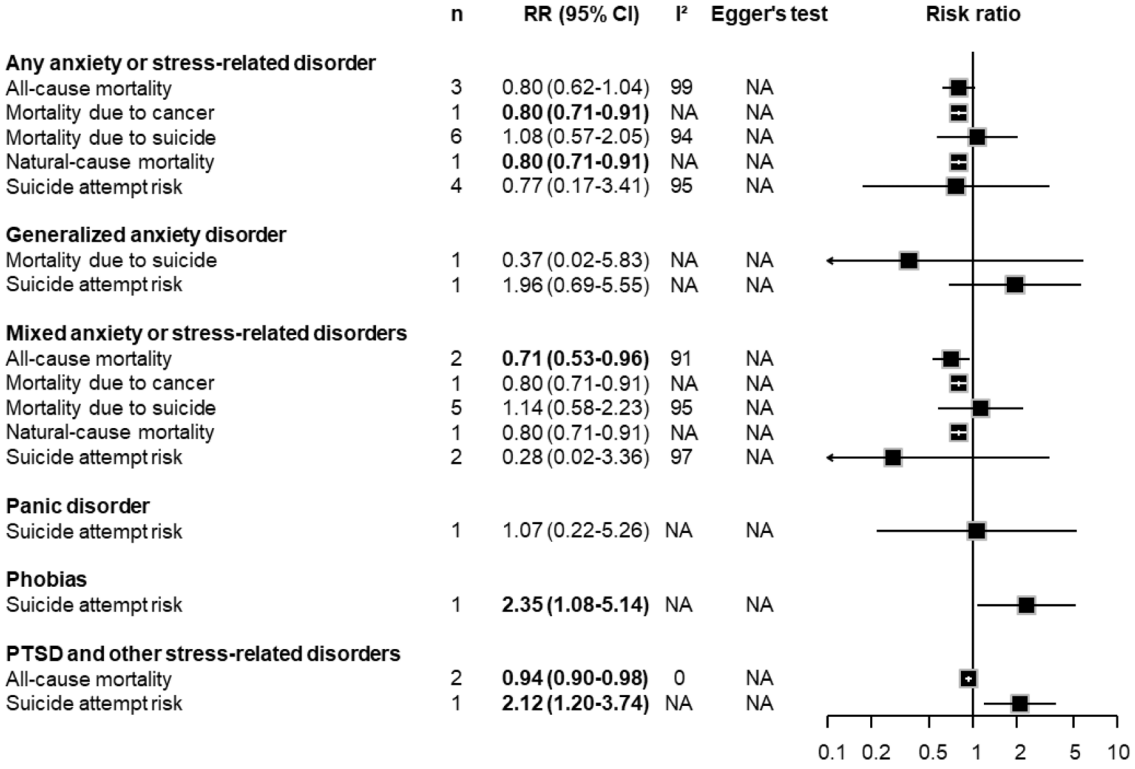

Figure 4 All-cause and cause-specific mortality, and suicide attempt risk in people with anxiety or stress-related disorders versus other mental disorders. RR – risk ratio, NA – not assessed, PTSD – post-traumatic stress disorder. Significant values are highlighted in bold prints.

A single study on any anxiety or stress-related disorder reported an association with significantly lower risk of natural-cause and cancer mortality compared with other mental disorders (n=1, RR= 0.80, 95% CI: 0.71-0.91, p<0.001).

DISCUSSION

This systematic review and meta-analysis, which included 165 studies, is the largest and most comprehensive to date assessing all-cause and cause-specific mortality, as well as suicide attempt risk, in people with anxiety or stress-related disorders. Our findings indicate a higher risk of all-cause, suicide-related, natural-cause and non-natural-cause (excluding suicide) mortality, as well as of suicide attempt, in individuals with anxiety or stress-related disorders compared with the general population. Differences in risk estimates exist across disorders, and some outcomes lost significance when analyses were matched by specific comorbid disorders. When compared with other mental disorders, no difference in co-primary outcomes emerged from more than two studies.

These results are highly relevant for several reasons. First, anxiety disorders have the highest lifetime prevalence of any mental health condition[193], with a significant impact on mental health care settings and societies[194]. Therefore, the higher mortality risk reported in this study applies to a far larger population than for schizophrenia or bipolar disorder, representing a finding of high public health concern.

This is also the case for the increased suicide-related mortality associated with anxiety disorders, which is in line with the evidence from both cross-sectional and longitudinal studies that the presence of anxiety disorders constitutes an independent risk factor for suicidal ideation and attempts[164,195], and that comorbid anxiety disorders significantly increase the risk of suicide attempts in individuals suffering from mood disorders[196].

Anxiety disorders need to be taken into account when assessing suicide risk. Currently, these disorders are not included as an independent risk factor for suicide in clinical prediction models, such as that enshrined in the Oxford Mental Illness and Suicide tool[197]. Moreover, screening and treatment of anxiety disorders are not adequately addressed in current evidence-based strategies for suicide prevention[198].

In our meta-analysis, the presence of depressive disorders did not significantly alter the association between anxiety disorders and all-cause or cause-specific mortality outcomes, which confirms that the impact of anxiety disorders on mortality may be largely independent of depressive symptoms[195]. However, severe depressive disorders are commonly treated with pharmacological interventions, many of which are also effective for anxiety symptomatology[199-201]. Thus, it is possible that an association between depressive comorbidity and death in people with anxiety disorders might be overshadowed by the treatment of depression. This hypothesis deserves further investigation, given the suboptimal reporting of eligible studies in terms of proportion of people taking antidepressants.

The association between any anxiety or stress-related disorder and natural-cause and cardiovascular disease-related mortality highlights the importance of general medical care for people with anxiety disorders, whose higher risk for physical conditions than the general population has been confirmed by recent evidence from Danish population-based cohort studies[202-204]. Physical comorbidities are rarely explored and addressed in the management of people with anxiety or stress-related disorders. Ensuring appropriate prevention, screening and treatment of these comorbidities can help mitigate the mortality gap. Still, we found evidence of some publication bias, highlighting the need for future cohort or registry studies to strengthen the body of evidence.

We explored several potential aggravating or mitigating factors for higher mortality risk. We found a slight but significant decrease of the excess mortality in people with anxiety or stress-related disorders by the median study year of investigation (ranging between 1947 and 2023). This result might be interpreted as the effect of improved access to mental health care over time for individuals with anxiety disorders, and advances in the management of these disorders, as well as a consequence of reduced stigma surrounding mental health. Regarding all-cause mortality, we could not detect significant moderating effects of comorbid mental disorders, except schizophrenia-spectrum and bipolar disorders, whose association with reduced suicide mortality risk was probably driven by underlying treatment. Still, it must be mentioned that potential moderators were underreported in the available individual studies.

The association between any anxiety or stress-related disorder and higher all-cause mortality was lost in meta-analyses when groups were matched by comorbid physical or mental disorders. However, the non-significant findings in matched analyses do not necessarily conflict with the main findings. In fact, the anxiety disorders vs. general population comparison consistently yielded higher specific-cause mortality risks in our subgroup analyses when only studies with adjusted estimates were selected. Moreover, the comorbid disorders considered in matched studies were highly heterogeneous, and matched analyses included few studies, possibly missing statistical power. Indeed, when looking at individual studies, several of them reported significant associations[26,46,75,95,101,117,146,162] that were, however, neutralized by the conservative random-effects model that we used in our analyses.

Among the strengths of this meta-analysis is the fact that we excluded studies in which patients were recruited on the basis of arbitrary symptom cut-offs assessed at variable time points, as well as confounding cross-sectional studies that were instead included in previous meta-analyses[205]. On the other hand, we could not dissect the effects of lifestyle factors (such as smoking) or psychological interventions on mortality estimates, since these were markedly underreported in the included studies. Moreover, our studies had a rather low proportion of females compared to the prevalence reported in the literature[206], which might be influenced by the inclusion of PTSD studies among male US veterans. Furthermore, due to lack of available studies, we were not able to differentiate phobias into specific phobias, agoraphobia and social anxiety disorder.

Although we applied broad inclusion criteria, our selected studies were mainly from high-income countries in North America and Western Europe. Thus, studies from low- and middle-income

countries are under-represented in this analysis and should be a priority in the future. Finally, our meta-analyses revealed evidence of publication bias in several instances. This finding underscores the importance of conducting further cohort studies to provide a more comprehensive understanding of the association of anxiety or stress-related disorders and mortality risk.

In summary, this meta-analysis can guide clinical practice by emphasizing the importance of reducing mortality in patients with anxiety and stress-related disorders, through appropriate prevention, screening and treatment strategies. Moreover, causal and likely bidirectional relationships between anxiety disorders and suicidal behavior should be investigated from a biological, psychological and societal perspective to guide further suicide prevention strategies.

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REFERENCES

1. Institute for Health Metrics and Evaluation. Global Burden of Disease. https://vizhub.healthdata.org.
2. Whiteford HA, Ferrari AJ, Degenhardt L et al. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. PLoS One 2015;10:e0116820.
3. Alonso J, Liu Z, Evans-Lacko S et al. Treatment gap for anxiety disorders is global: results of the World Mental Health Surveys in 21 countries. Depress Anxiety 2018;35:195-208.
4. Domschke K, Seuling PD, Schiele MA et al. The definition of treatment resistance in anxiety disorders: a Delphi method-based consensus guideline. World Psychiatry 2024;23:113-23.
5. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 2015;72:334-41.
6. Correll CU, Solmi M, Croatto G et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry 2022;21:248-71.
7. Biazus TB, Beraldi GH, Tokeshi L et al. All-cause and cause-specific mortality among people with bipolar disorder: a large-scale systematic review and meta-analysis. Mol Psychiatry 2023;28:2508-24.
8. Machado MO, Veronese N, Sanches M et al. The association of depression and all-cause and cause-specific mortality: an umbrella review of systematic reviews and meta-analyses. BMC Med 2018;16:112.
9. Russell R, Minhas S, Chandan JS et al. The risk of all-cause mortality associated with anxiety: a retrospective cohort study using 'The Health Improvement Network' database. BMC Psychiatry 2023;23:400.
10. Tietbohl-Santos B, Chiamenti P, Librenza-Garcia D et al. Risk factors for suicidality in patients with panic disorder: a systematic review and meta-analysis. Neurosci Biobehav Rev 2019;105:34-8.
11. Angelakis I, Gooding P, Tarrier N et al. Suicidality in obsessive compulsive disorder (OCD): a systematic review and meta-analysis. Clin Psychol Rev 2015;39:1-15.
12. Miloyan B, Bulley A, Bandeen-Roche K et al. Anxiety disorders and all-cause mortality: systematic review and meta-analysis. Soc Psychiatry Psychiatr Epidemiol 2016;51:1467-75.
13. Celano CM, Millstein RA, Bedoya CA et al. Association between anxiety and mortality in patients with coronary artery disease: a meta-analysis. Am Heart J 2015;170:1105-15.
14. Krysinska K, Lester D. Post-traumatic stress disorder and suicide risk: a systematic review. Arch Suicide Res 2010;14:1-23.
15. Nilaweera D, Phyo AZZ, Teshale AB et al. Lifetime posttraumatic stress disorder as a predictor of mortality: a systematic review and meta-analysis. BMC Psychiatry 2023;23:229.
16. Meier SM, Mattheisen M, Mors O et al. Increased mortality among people with anxiety disorders: total population study. Br J Psychiatry 2016;209:216-21.
17. Kaye AJ, Patel SJ, Meyers SR et al. Outcomes of patients hospitalized for acute diverticulitis with comorbid generalized anxiety disorder. Cureus 2023;15:e35461.
18. Ruffieux Y, Wettstein A, Maartens G et al. Life-years lost associated with mental illness: a cohort study of beneficiaries of a South African medical insurance scheme. J Affect Disord 2023;340:204-12.
19. Fox V, Dalman C, Dal H et al. Suicide risk in people with post-traumatic stress disorder: a cohort study of 3.1 million people in Sweden. J Affect Disord 2021;279:609-16.
20. Bager L, Agerbo E, Skipper N et al. Are migrants diagnosed with a trauma-related disorder at risk of premature mortality? A register-based cohort study in Denmark. J Migr Health 2023;8:100197.
21. Clark R, Kuffel RL, Neylan TC et al. Posttraumatic stress disorder, suicide, and unintended overdose death in later life: a national cohort study of veterans aged 50 and older. J Am Geriatr Soc 2023;71:1462-72.
22. Lee J-M, Lee J, Lim J et al. Increased suicide risk of psychiatric patients following the recent utilization of health care services: results from a nationwide cohort study in South Korea. Front Public Health 2023;11:1118135.
23. Sala-Hamrick KJ, Braciszewski JM, Yeh H-H et al. Diagnosed posttraumatic stress disorder and other trauma-associated stress disorders and risk for suicide mortality. Psychiatr Serv 2023;74:936-42.
24. Otoya D, Lele S, Boyd S et al. Diagnosis of mental illness does not affect postoperative outcomes in patients undergoing endovascular aortic aneurysm repair in the VA healthcare system. J Vasc Surg 2023;78:1221-7.
25. Kim H, Lee K-N, Shin DW et al. Association of comorbid mental disorders with cardiovascular disease risk in patients with type 2 diabetes: a nationwide cohort study. Gen Hosp Psychiatry 2022;79:33-41.
26. Um YH, Han K-D, Kim T-W et al. Does panic disorder increase the risk of cardiovascular diseases in diabetics?: A nationwide population-based study. J Affect Disord 2023;325:604-10.
27. Schwarzinger M, Luchini S, Teschl M et al. Mental disorders, COVID-19-related life-saving measures and mortality in France: a nationwide cohort study. PLoS Med 2023;20:e1004134.
28. Kostev K, Hagemann-Goebel M, Gessler N et al. Is there an association between depression, anxiety disorders and COVID-19 severity and mortality? A multicenter retrospective cohort study conducted in 50 hospitals in Germany. J Psychiatr Res 2023;157:192-6.
29. Xu H, Li S, Mehta HB et al. Excess deaths from COVID-19 among Medicare beneficiaries with psychiatric diagnoses: community versus nursing home. J Am Geriatr Soc 2023;71:167-77.
30. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
31. Moitra M, Santomauro D, Degenhardt L et al. Estimating the risk of suicide associated with mental disorders: a systematic review and meta-regression analysis. J Psychiatr Res 2021;137:242-9.
32. Sokoreli I, de Vries JJG, Pauws SC et al. Depression and anxiety as predictors of mortality among heart failure patients: systematic review and meta-analysis. Heart Fail Rev 2016;21:49-63.
33. Sutar R, Kumar A, Yadav V. Suicide and prevalence of mental disorders: a systematic review and meta-analysis of world data on case-control psychological autopsy studies. Psychiatry Res 2023;329:115492.
34. Wang YH, Li JQ, Shi JF et al. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. Mol Psychiatry 2020;25:1487-99.
35. Veritas Health Innovation. Covidence systematic review software. www.covidence.org.
36. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1-48.
37. Serghiou S, Goodman SN. Random-effects meta-analysis: summarizing evidence with caveats. JAMA 2019;321:301-2.
38. von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC Med Res Methodol 2015;15:35.
39. Egger M, Davey Smith G, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
40. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455-63.
41. US National Heart, Lung, and Blood Institute. Study quality assessment tools. www.nhlbi.nih.gov.
42. R Core Team 2023. R: a language and environment for statistical computing. www.R-project.org.

43. Aboumrad M, Shiner B, Mucci L et al. Posttraumatic stress disorder and suicide among veterans with prostate cancer. Psychooncology 2021;30:581-90.
44. Abrams TE, Vaughan-Sarrazin M, Rosenthal GE. Influence of psychiatric comorbidity on surgical mortality. Arch Surg 2010;145:947-53.
45. Adhikari K, Metcalfe A, Bulloch AGM et al. Mental disorders and subsequent suicide events in a representative community population. J Affect Disord 2020; 277:456-62.
46. Ahmadi N, Hajsadeghi F, Mirshkarlo HB et al. Post-traumatic stress disorder, coronary atherosclerosis, and mortality. Am J Cardiol 2011;108:29-33.
47. Ahmadi N, Moss L, Simon E. Efficacy and long-term clinical outcome of comorbid posttraumatic stress disorder and major depressive disorder after electroconvulsive therapy. Depress Anxiety 2016;33:640-7.
48. Ahman A, Karlsson A, Berge J et al. Mortality, morbidity, and predictors of death among amphetamine-type stimulant users – a longitudinal, nationwide register study. Addict Behav Rep 2024;19:100553.
49. Akaishi T, Tarasawa K, Fushimi K et al. Risk factors associated with peripartum suicide attempts in Japan. JAMA Netw Open 2023;6:e2250661.
50. Allgulander C. Suicide and mortality patterns in anxiety neurosis and depressive neurosis. Arch Gen Psychiatry 1994;51:708-12.
51. Almasi K, Belso N, Kapur N et al. Risk factors for suicide in Hungary: a case-control study. BMC Psychiatry 2009;9:45.
52. Anderberg J, Bogren M, Mattisson C et al. Long-term suicide risk in anxiety – the Lundby Study 1947-2011. Arch Suicide Res 2016;20:463-75.
53. Baldessarini RJ, Tondo L. Suicidal risks in 12 DSM-5 psychiatric disorders. J Affect Disord 2020;271:66-73.
54. Bergman BP, Mackay DF, Pell JP. Suicide among Scottish military veterans: follow-up and trends. Occup Environ Med 2022;79:88-93.
55. Bishop TM, Walsh PG, Ashrafioun L et al. Sleep, suicide behaviors, and the protective role of sleep medicine. Sleep Med 2020;66:264-70.
56. Boden JM, Fergusson DM, Horwood LJ. Anxiety disorders and suicidal behaviours in adolescence and young adulthood: findings from a longitudinal study. Psychol Med 2007;37:431-40.
57. Bohnert KM, Ilgen MA, Rosen CS et al. The association between substance use disorders and mortality among a cohort of veterans with posttraumatic stress disorder: variation by age cohort and mortality type. Drug Alcohol Depend 2013;128:98-103.
58. Bolton JM, Cox BJ, Afifi TO et al. Anxiety disorders and risk for suicide attempts: findings from the Baltimore Epidemiologic Catchment area follow-up study. Depress Anxiety 2008;25:477-81.
59. Bolton JM, Pagura J, Enns MW et al. A population-based longitudinal study of risk factors for suicide attempts in major depressive disorder. J Psychiatr Res 2010;44:817-26.
60. Boscarino JA. Posttraumatic stress disorder and mortality among U.S. Army veterans 30 years after military service. Ann Epidemiol 2006;16:248-56.
61. Boscarino JA. Psychobiologic predictors of disease mortality after psychological trauma: implications for research and clinical surveillance. J Nerv Ment Dis 2008;196:100-7.
62. Boscarino JA. A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: implications for surveillance and prevention. Psychosom Med 2008;70:668-76.
63. Boscarino JA, Figley CR. The impact of repression, hostility, and post-traumatic stress disorder on all-cause mortality: a prospective 16-year follow-up study. J Nerv Ment Dis 2009;197:461-6.
64. Boschesi Barros V, Fortti Vianna Schmidt F, Chiavegatto Filho ADP. Mortality, survival, and causes of death in mental disorders: comprehensive prospective analyses of the UK Biobank cohort. Psychol Med 2023;53:3480-9.
65. Bradley SM, Stanislawski MA, Bekelman DB et al. Invasive coronary procedure use and outcomes among patients with post-traumatic stress disorder: insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. Am Heart J 2014;168:381-90.e6.
66. Reutfors J, Andersson TML, Tanskanen A et al. Risk factors for suicide and suicide attempts among patients with treatment-resistant depression: nested case-control study. Arch Suicide Res 2021;25:424-38.
67. Brent DA, Baugher M, Bridge J et al. Age- and sex-related risk factors for adolescent suicide. J Am Acad Child Adolesc Psychiatry 1999;38:1497-505.
68. Bronisch T, Wittchen HU. Suicidal ideation and suicide attempts: comorbidity with depression, anxiety disorders, and substance abuse disorder. Eur Arch Psychiatry Clin Neurosci 1994;244:93-8.
69. Bull Bringager C, Arnesen H, Friis S et al. A long-term follow-up study of chest pain patients: effect of panic disorder on mortality, morbidity, and quality of life. Cardiology 2008;110:8-14.
70. Bullman T, Schneiderman A, Gradus JL. Relative importance of posttraumatic stress disorder and depression in predicting risk of suicide among a cohort of Vietnam veterans. Suicide Life Threat Behav 2019;49:838-45.
71. Butnoriene J, Bunevicius A, Saudargiene A et al. Metabolic syndrome, major depression, generalized anxiety disorder, and ten-year all-cause and cardiovascular mortality in middle aged and elderly patients. Int J Cardiol 2015;190:360-6.
72. Carriere I, Ryan J, Norton J et al. Anxiety and mortality risk in community-dwelling elderly people. Br J Psychiatry 2013;203:303-9.
73. Castelpietra G, Bovenzi M, Clagnan E et al. Diagnoses and prescriptions of antidepressants in suicides: register findings from the Friuli Venezia Giulia Region, Italy, 2002-2008. Int J Psychiatry Clin Pract 2016;20:121-4.
74. Catalan A, Aymerich C, Bilbao A et al. Psychosis and substance abuse increase the COVID-19 mortality risk. Psychol Med 2023;53:4236-44.
75. Cha S, Chang WK, Lee K et al. Prevalence and impact of depression and anxiety among older myocardial infarction survivors: a nationwide cohort study. J Affect Disord 2024;354:408-15.
76. Chang CF, Lai ECC, Yeh MK. Fractures and the increased risk of suicide: a population-based case-control study. Bone Joint J 2018;100-B:780-6.
77. Chang H-M, Pan C-H, Chen P-H et al. Premature death and causes of death among patients with panic disorder and comorbid psychiatric disorders: a nationwide cohort study. J Psychiatr Res 2022;148:340-7.
78. Chang WH, Lee IH, Chen WT et al. Coexisting geriatric anxiety and depressive disorders may increase the risk of ischemic heart disease mortality – a nationwide longitudinal cohort study. Int J Geriatr Psychiatry 2017;32:e25-33.
79. Cho J, Copeland LA, Stock EM et al. Protective and risk factors for 5-year survival in the oldest veterans: data from the Veterans Health Administration. J Am Geriatr Soc 2016;64:1250-7.
80. Chwastiak LA, Rosenheck RA, Desai R et al. Association of psychiatric illness and all-cause mortality in the National Department of Veterans Affairs Health Care System. Psychosom Med 2010;72:817-22.
81. Conner KR, McCarthy MD, Bajorska A et al. Mood, anxiety, and substance-use disorders and suicide risk in a military population cohort. Suicide Life Threat Behav 2012;42:699-708.
82. Conwell Y, Duberstein PR, Hirsch JK et al. Health status and suicide in the second half of life. Int J Geriatr Psychiatry 2010;25:371-9.
83. Copeland LA, Sako EY, Zeber JE et al. Mortality after cardiac or vascular operations by preexisting serious mental illness status in the Veterans Health Administration. Gen Hosp Psychiatry 2014;36:502-8.
84. Crump C, Sundquist K, Winkleby M et al. Mental disorders increase the risk of accidental death: a Swedish nationwide cohort study. Br J Psychiatry 2013; 203:297-302.
85. Cully JA, Johnson M, Moffett ML et al. Depression and anxiety in ambulatory patients with heart failure. Psychosomatics 2009;50:592-8.
86. Dao TK, Chu D, Springer J et al. Clinical depression, posttraumatic stress disorder, and comorbid depression and posttraumatic stress disorder as risk factors for in-hospital mortality after coronary artery bypass grafting surgery. J Thorac Cardiovasc Surg 2010;140:606-10.
87. Deka R, Bryan CJ, LaFleur J et al. Benzodiazepines, health care utilization, and suicidal behavior in veterans with posttraumatic stress disorder. J Clin Psychiatry 2018;79:17m12038.
88. Demesmaeker A, Chazard E, Vaiva G et al. Risk factors for reattempt and suicide within 6 months after an attempt in the French ALGOS cohort: a survival tree analysis. J Clin Psychiatry 2021;82:20m13589.
89. Descamps A, Frenkiel J, Zarca K et al. Association between mental disorders and COVID-19 outcomes among inpatients in France: a retrospective nationwide population-based study. J Psychiatr Res 2022;155:194-201.
90. Dobscha SK, Denneson LM, Kovas AE et al. Correlates of suicide among veterans treated in primary care: case-control study of a nationally representative sample. J Gen Intern Med 2014;29(Suppl. 4):853-60.
91. Drescher KD, Rosen CS, Burling TA et al. Causes of death among male veterans who received residential treatment for PTSD. J Trauma Stress 2003;16:535-43.
92. Eaton WW, Roth KB, Bruce M et al. The relationship of mental and behavioral disorders to all-cause mortality in a 27-year follow-up of 4 epidemiologic catchment area samples. Am J Epidemiol 2013;178:1366-77.
93. Fang S-C, Hung C-C, Huang C-Y et al. Influence of baseline psychiatric disorders on mortality and suicide and their associations with gender and age in patients with methamphetamine use disorder. Int J Ment Health Addict 2025;23:263-80.
94. Favaro A, Gerosa G, Caforio ALP et al. Posttraumatic stress disorder and depression in heart transplantation recipients: the relationship with outcome and adherence to medical treatment. Gen Hosp Psychiatry 2011;33:1-7.
95. Fernando SM, Qureshi D, Sood MM et al. Suicide and self-harm in adult survivors of critical illness: population based cohort study. BMJ 2021;373:n973.

96. Finley EP, Bollinger M, Noel PH et al. A national cohort study of the association between the polytrauma clinical triad and suicide-related behavior among US veterans who served in Iraq and Afghanistan. Am J Public Health 2015;105:380-7.
97. Flood AM, Boyle SH, Calhoun PS et al. Prospective study of externalizing and internalizing subtypes of posttraumatic stress disorder and their relationship to mortality among Vietnam veterans. Compr Psychiatry 2010;51:236-42.
98. Forehand JA, Peltzman T, Westgate CL et al. Causes of excess mortality in veterans treated for posttraumatic stress disorder. Am J Prev Med 2019;57:145-52.
99. Formanek T, Potocar L, Wolfova K et al. Deaths with COVID-19 and from all-causes following first-ever SARS-CoV-2 infection in individuals with pre-existing mental disorders: a national cohort study from Czechia. PLoS Med 2024;21:e1004422.
100. Foster T, Gillespie K, McClelland R et al. Risk factors for suicide independent of DSM-III-R Axis I disorder. Case-control psychological autopsy study in Northern Ireland. Br J Psychiatry 1999;175:175-9.
101. Fudim M, Cerbin LP, Devaraj S et al. Post-traumatic stress disorder and heart failure in men within the Veteran Affairs Health System. Am J Cardiol 2018;122:275-8.
102. Gau SS, Cheng AT. Mental illness and accidental death. Case-control psychological autopsy study. Br J Psychiatry 2004;185:422-8.
103. Goldston DB, Daniel SS, Erkanli A et al. Psychiatric diagnoses as contemporaneous risk factors for suicide attempts among adolescents and young adults: developmental changes. J Consult Clin Psychol 2009;77:281-90.
104. Gradus JL, Antonsen S, Svensson E et al. Trauma, comorbidity, and mortality following diagnoses of severe stress and adjustment disorders: a nationwide cohort study. Am J Epidemiol 2015;182:451-8.
105. Gradus JL, Qin P, Lincoln AK et al. Posttraumatic stress disorder and completed suicide. Am J Epidemiol 2010;171:721-7.
106. Gradus JL, Qin P, Lincoln AK et al. Acute stress reaction and completed suicide. Int J Epidemiol 2010;39:1478-84.
107. Grasbeck A, Rorsman B, Hagnell O et al. Mortality of anxiety syndromes in a normal population. The Lundby Study. Neuropsychobiology 1996;33:118-26.
108. Hawkins EJ, Goldberg SB, Malte CA et al. New coprescription of opioids and benzodiazepines and mortality among Veterans Affairs patients with posttraumatic stress disorder. J Clin Psychiatry 2019;80:18m12689.
109. Herweijer E, Wang J, Hu K et al. Overall and cervical cancer survival in patients with and without mental disorders. JAMA Netw Open 2023;6:e2336213.
110. Hirokawa S, Kawakami N, Matsumoto T et al. Mental disorders and suicide in Japan: a nation-wide psychological autopsy case-control study. J Affect Disord 2012;140:168-75.
111. Horoub A, Jabiri YA, Yusuf M et al. Patients characteristics, predictors, and hospital outcomes of Takotsubo cardiomyopathy patients with concomitant anxiety disorders. J Card Fail 2023;29:680.
112. Horoub A, Sholi T, Aldiabat M et al. The burden of anxiety disorders on acute heart failure hospitalizations: a retrospective analysis of 1.1 million admissions. J Card Fail 2023;29:684-5.
113. Huang C-J, Hsieh H-M, Chiu H-C et al. Impact of anxiety disorders on mortality for persons with diabetes: a national population-based cohort study. Psychosomatics 2017;58:266-73.
114. John U, Rumpf HJ, Hanke M et al. Mental disorders and total mortality after 20 years in an adult general population sample. Eur Psychiatry 2020;63:e30.
115. Johnson J, Weissman MM, Klerman GL. Panic disorder, comorbidity, and suicide attempts. Arch Gen Psychiatry 1990;47:805-8.
116. Kaslow N, Thompson M, Meadows L et al. Risk factors for suicide attempts among African American women. Depress Anxiety 2000;12:13-20.
117. Kaye AJ, Patel SJ, Meyers SR et al. Outcomes of inflammatory bowel disease in hospitalized patients with generalized anxiety disorder. Cureus 2022;14:e27656.
118. Kim K, Tsai AC, Sumner JA et al. Posttraumatic stress disorder, cardiovascular disease outcomes and the modifying role of socioeconomic status. J Affect Disord 2022;319:555-61.
119. Kimbrell T, Pyne JM, Kunik ME et al. The impact of Purple Heart commendation and PTSD on mortality rates in older veterans. Depress Anxiety 2011;28:1086-90.
120. Kinder LS, Bradley KA, Katon WJ et al. Depression, posttraumatic stress disorder, and mortality. Psychosom Med 2008;70:20-6.
121. Kingsbury M, Sucha E, Horton NJ et al. Lifetime experience of multiple common mental disorders and 19-year mortality: results from a Canadian population-based cohort. Epidemiol Psychiatr Sci 2019;29:e18.
122. Kjelsberg E. Adolescent psychiatric in-patients. A high-risk group for premature death. Br J Psychiatry 2000;176:121-5.
123. Laan W, Termorshuizen F, Smeets HM et al. A comorbid anxiety disorder does not result in an excess risk of death among patients with a depressive disorder. J Affect Disord 2011;135:284-91.
124. Lee DJ, Kearns JC, Wisco BE et al. A longitudinal study of risk factors for suicide attempts among Operation Enduring Freedom and Operation Iraqi Freedom veterans. Depress Anxiety 2018;35:609-18.
125. Lesage AD, Boyer R, Grunberg F et al. Suicide and mental disorders: a case-control study of young men. Am J Psychiatry 1994;151:1063-8.
126. Li P, Lu X, Kranis M et al. The association between anxiety disorders and in-hospital outcomes in patients with myocardial infarction. Clin Cardiol 2020;43:622-9.
127. MacConnell AE, Tran D, Hand R et al. The association between mental health, substance use disorder, and outcomes after total joint arthroplasty. J Arthroplasty 2023;39:619-24.
128. Madsen T, Erlangsen A, Hjorthoj C et al. High suicide rates during psychiatric inpatient stay and shortly after discharge. Acta Psychiatr Scand 2020;142:355-65.
129. Markkula N, Härkänen T, Perälä J et al. Mortality in people with depressive, anxiety and alcohol use disorders in Finland. Br J Psychiatry 2012;200:143-9.
130. Marrie RA, Walld R, Bolton JM et al. Psychiatric comorbidity increases mortality in immune-mediated inflammatory diseases. Gen Hosp Psychiatry 2018;53:65-72.
131. Martens EJ, De Jonge P, Na B et al. Scared to death? Generalized anxiety disorder and cardiovascular events in patients with stable coronary heart disease: the Heart and Soul Study. Arch Gen Psychiatry 2010;67:750-8.
132. Mash HBH, Ursano RJ, Kessler RC et al. Predictors of suicide attempt within 30 days after first medically documented suicidal ideation in U.S. Army soldiers. Am J Psychiatry 2021;178:1050-9.
133. Mathew AG, Kaye AJ, Patel SJ et al. Outcomes of gastroparesis in hospitalized patients with generalized anxiety disorder. Cureus 2023;15:e35832.
134. May AM, Klonsky ED, Klein DN. Predicting future suicide attempts among depressed suicide ideators: a 10-year longitudinal study. J Psychiatr Res 2012;46:946-52.
135. Miche M, Hofer PD, Voss C et al. Mental disorders and the risk for the subsequent first suicide attempt: results of a community study on adolescents and young adults. Eur Child Adolesc Psychiatry 2018;27:839-48.
136. Mills KL, Marel C, Darke S et al. The long-term impact of post traumatic stress disorder on recovery from heroin dependence. J Subst Abuse Treat 2018;89:60-6.
137. Mollica RF, Sarajlic N, Chernoff M et al. Longitudinal study of psychiatric symptoms, disability, mortality, and emigration among Bosnian refugees. JAMA 2001;286:546-54.
138. Siwakoti A, Potutkuchi PK, Thomas F et al. History of posttraumatic stress disorder and outcomes after kidney transplantation. Am J Transplant 2019;19:2294-305.
139. Monnin J, Thiemard E, Vandel P et al. Sociodemographic and psychopathological risk factors in repeated suicide attempts: gender differences in a prospective study. J Affect Disord 2012;136:35-43.
140. Mortier P, Conde S, Alayo I et al. Premature death, suicide, and nonlethal intentional self-harm after psychiatric discharge. JAMA Netw Open 2024;7:e2417131.
141. Mutz J, Choudhury U, Zhao J et al. Frailty in individuals with depression, bipolar disorder and anxiety disorders: longitudinal analyses of all-cause mortality. BMC Med 2022;20:274.
142. Na EJ, Lee H, Myung W et al. Risks of completed suicide of community individuals with ICD-10 disorders across age groups: a nationwide population-based nested case-control study in South Korea. Psychiatry Investig 2019;16:314-24.
143. Nardi AE, Nascimento I, Freire RC et al. Demographic and clinical features of panic disorder comorbid with bipolar I disorder: a 3-year retrospective study. J Affect Disord 2008;106:185-9.
144. Nemani K, Li C, Olfson M et al. Association of psychiatric disorders with mortality among patients with COVID-19. JAMA Psychiatry 2021;78:380-6.
145. Nilsson J, Östling S, Waern M et al. The 1-month prevalence of generalized anxiety disorder according to DSM-IV, DSM-V, and ICD-10 among nondemented 75-year-olds in Gothenburg, Sweden. Am J Geriatr Psychiatry 2012;20:963-72.
146. Nishimi K, Neylan TC, Bertenthal D et al. Post-traumatic stress disorder and risk for hospitalization and death following COVID-19 infection. Transl Psychiatry 2022;12:482.
147. Ofman P, Hoffmeister P, Kaloupek DG et al. Posttraumatic stress disorder and mortality in VA patients with implantable cardioverter-defibrillators. Clin Cardiol 2018;41:652-9.
148. Oh T-K, Park H-Y, Song I-A. Association between preoperative psychiatric morbidities and mortality after oncologic surgery: a nationwide cohort study from 2002 to 2019 in South Korea. J Pers Med 2023;13:1069.

149. Olaya B, Moneta MV, Plana-Ripoll O et al. Association between mental disorders and mortality: a register-based cohort study from the region of Catalonia. Psychiatry Res 2023;320:115037.
150. Oude Voshaar RC, Aprahamian I, Borges MK et al. Excess mortality in depressive and anxiety disorders: the Lifelines Cohort Study. Eur Psychiatry 2021; 64:e54.
151. Page A, Morrell S, Hobbs C et al. Suicide in young adults: psychiatric and socio-economic factors from a case-control study. BMC Psychiatry 2014;14:68.
152. Pelletier R, Bacon SL, Arsenault A et al. Relative associations between depression and anxiety on adverse cardiovascular events: does a history of coronary artery disease matter? A prospective observational study. BMJ Open 2015;5:e006582.
153. Pfeiffer PN, Ganoczy D, Ilgen M et al. Comorbid anxiety as a suicide risk factor among depressed veterans. Depress Anxiety 2009;26:752-7.
154. Phillips AC, Batty GD, Gale CR et al. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam experience study. Psychosom Med 2009; 71:395-403.
155. Randall JR, Walld R, Finlayson G et al. Acute risk of suicide and suicide attempts associated with recent diagnosis of mental disorders: a population-based, propensity score-matched analysis. Can J Psychiatry 2014;59:531-8.
156. Rasouli N, Malakouti SK, Rezaeian M et al. Risk factors of suicide death based on psychological autopsy method; a case-control study. Arch Acad Emerg Med 2019;7:e50.
157. Remes O, Wainwright N, Surtees P et al. Generalised anxiety disorder and excess cancer deaths: findings from a large, longitudinal population study. Lancet 2016;388:S100.
158. Rivlin A, Hawton K, Marzano L et al. Psychiatric disorders in male prisoners who made near-lethal suicide attempts: case-control study. Br J Psychiatry 2010;197:313-9.
159. Roest AM, Zuidersma M, de Jonge P. Myocardial infarction and generalised anxiety disorder: 10-year follow-up. Br J Psychiatry 2012;200:324-9.
160. Ronzitti S, Loree AM, Potenza MN et al. Gender differences in suicide and self-directed violence risk among veterans with post-traumatic stress and substance use disorders. Womens Health Issues 2019;29(Suppl. 1):S94-102.
161. Rosenberger EM, DiMartini AF, DeVito Dabbs AJ et al. Psychiatric predictors of long-term transplant-related outcomes in lung transplant recipients. Transplantation 2016;100:239-47.
162. Saiganesh P, Kaye AJ, Patel SJ et al. Outcomes of acute pancreatitis in hospitalized patients with generalized anxiety disorder. Cureus 2023;15:e43795.
163. Sani G, Tondo L, Koukopoulos A et al. Suicide in a large population of former psychiatric inpatients. Psychiatry Clin Neurosci 2011;65:286-95.
164. Sareen J, Cox BJ, Afifi TO et al. Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. Arch Gen Psychiatry 2005;62:1249-57.
165. Schoepf D, Heun R. Anxiety disorders and physical comorbidity: increased prevalence but reduced relevance of specific risk factors for hospital-based mortality during a 12.5-year observation period in general hospital admissions. Eur Arch Psychiatry Clin Neurosci 2015;265:387-98.
166. Séguin M, Renaud J, Lesage A et al. Youth and young adult suicide: a study of life trajectory. J Psychiatr Res 2011;45:863-70.
167. Simon GE, Hunkeler E, Fireman B et al. Risk of suicide attempt and suicide death in patients treated for bipolar disorder. Bipolar Disord 2007;9:526-30.
168. Skopp NA, Zhang Y, Smolenski DJ et al. Risk factors for self-directed violence in US soldiers: a case-control study. Psychiatry Res 2016;245:194-9.
169. Song I-A, Park HY, Oh TK. Effect of preoperative psychiatric morbidity on postoperative outcomes of lung cancer surgery: a nationwide cohort study in South Korea. J Psychosom Res 2022;161:111002.
170. Street AE, Jiang T, Horvath-Puho E et al. Stress disorders and the risk of nonfatal suicide attempts in the Danish population. J Trauma Stress 2021;34:1108-17.
171. Szymanski BR, Hein TC, Schoenbaum M et al. Facility-level excess mortality of VHA patients with mental health or substance use disorder diagnoses. Psychiatr Serv 2021;72:408-14.
172. ten Have M, de Graaf R, van Dorsselaer S et al. Incidence and course of suicidal ideation and suicide attempts in the general population. Can J Psychiatry 2009;54:824-33.
173. Teppo K, Jaakkola J, Biancari F et al. Mental health conditions and risk of first-ever ischaemic stroke and death in patients with incident atrial fibrillation: a nationwide cohort study. Eur J Clin Invest 2022;52:e13801.
174. Tian F, Fang F, Shen Q et al. Stress-related disorders and subsequent cancer risk and mortality: a population-based and sibling-controlled cohort study in Sweden. Eur J Epidemiol 2022;37:947-58.
175. Tidemalm D, Langstrom N, Lichtenstein P et al. Risk of suicide after suicide attempt according to coexisting psychiatric disorder: Swedish cohort study with long term follow-up. BMJ 2008;337:a2205.
176. Tong Y, Phillips MR. Cohort-specific risk of suicide for different mental disorders in China. Br J Psychiatry 2010;196:467-73.
177. Trivedi RB, Post EP, Piegari R et al. Mortality among veterans with major mental illnesses seen in primary care: results of a national study of veteran deaths. J Gen Int Med 2020;35:112-8.
178. Tyerman Z, Mehaffey JH, Hawkins RB et al. History of serious mental illness is a predictor of morbidity and mortality in cardiac surgery. Ann Thorac Surg 2021;111:109-16.
179. Ursano RJ, Kessler RC, Stein MB et al. Risk factors, methods, and timing of suicide attempts among US Army soldiers. JAMA Psychiatry 2016;73:741-9.
180. van Hout HPJ, Beekman ATF, de Beurs E et al. Anxiety and the risk of death in older men and women. Br J Psychiatry 2004;185:399-404.
181. Vance MC, Wiitala WL, Sussman JB et al. Increased cardiovascular disease risk in veterans with mental illness. Circulation 2019;12:e005563.
182. von Below A, Hallstrom T, Sundh V et al. Association between anxiety and depression and all-cause mortality: a 50-year follow-up of the Population Study of Women in Gothenburg, Sweden. BMJ Open 2023;13:e075471.
183. Waern M, Runeson BS, Allebeck P et al. Mental disorder in elderly suicides: a case-control study. Am J Psychiatry 2002;159:450-5.
184. Walters K, Rait G, Petersen I et al. Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. Eur Heart J 2008;29:2981-8.
185. Wandell P, Carlsson AC, Gasevic D et al. Depression or anxiety and all-cause mortality in adults with atrial fibrillation – A cohort study in Swedish primary care. Ann Med 2016;48:59-66.
186. Wedegaertner F, Arnhold-Kerri S, Sittaro N-A et al. Depression- and anxiety-related sick leave and the risk of permanent disability and mortality in the working population in Germany: a cohort study. BMC Public Health 2013;13:145.
187. Winkler P, Mlada K, Csemy L et al. Suicides following inpatient psychiatric hospitalization: a nationwide case control study. J Affect Disord 2015;184:164-9.
188. Xue Y, Taub PR, Iqbal N et al. Cardiac biomarkers, mortality, and post-traumatic stress disorder in military veterans. Am J Cardiol 2012;109:1215-8.
189. Yeh H-H, Westphal J, Hu Y et al. Diagnosed mental health conditions and risk of suicide mortality. Psychiatr Serv 2019;70:750-7.
190. Zhang J, Xiao S, Zhou L. Mental disorders and suicide among young rural Chinese: a case-control psychological autopsy study. Am J Psychiatry 2010; 167:773-81.
191. Zivin K, Kim HM, McCarthy JF et al. Suicide mortality among individuals receiving treatment for depression in the Veterans Affairs health system: associations with patient and treatment setting characteristics. Am J Public Health 2007;97:2193-8.
192. Zohar J, Fostick L, Israeli Consortium on PTSD. Mortality rates between treated post-traumatic stress disorder Israeli male veterans compared to non-diagnosed veterans. Eur Neuropsychopharmacol 2014;24:117-24.
193. Kessler RC, Berglund P, Demler O et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593-602.
194. Yang X, Fang Y, Chen H et al. Global, regional and national burden of anxiety disorders from 1990 to 2019: results from the Global Burden of Disease Study 2019. Epidemiol Psychiatr Sci 2021;30:e36.
195. Sareen J. Anxiety disorders and risk for suicide: why such controversy? Depress Anxiety 2011;28:941-5.
196. Masdrakis VG, Konstantopoulou S, Baldwin DS. Could improved recognition and treatment of anxiety disorders lead to a reduction in suicide? Hum Psychopharmacol 2023;38:e2879.
197. Fazel S, Wolf A, Larsson H et al. The prediction of suicide in severe mental illness: development and validation of a clinical prediction rule (OxMIS). Transl Psychiatry 2019;9:98.
198. Mann JJ, Michel CA, Auerbach RP. Improving suicide prevention through evidence-based strategies: a systematic review. Am J Psychiatry 2021;178:611-24.
199. Gomez AF, Barthel AL, Hofmann SG. Comparing the efficacy of benzodiazepines and serotonergic anti-depressants for adults with generalized anxiety disorder: a meta-analytic review. Expert Opin Pharmacother 2018;19:883-94.
200. Bighelli I, Castellazzi M, Cipriani A et al. Antidepressants versus placebo for panic disorder in adults. Cochrane Database Syst Rev 2018;4:CD010676.
201. Curtiss J, Andrews L, Davis M et al. A meta-analysis of pharmacotherapy for social anxiety disorder: an examination of efficacy, moderators, and mediators. Expert Opin Pharmacother 2017;18:243-51.

202. Momen NC, Plana-Ripoll O, Agerbo E et al. Association between mental disorders and subsequent medical conditions. N Engl J Med 2020;382:1721-31.
203. Momen NC, Østergaard SD, Heide-Jorgensen U et al. Associations between physical diseases and subsequent mental disorders: a longitudinal study in a population-based cohort. World Psychiatry 2024;23:421-31.
204. Wimberley T, Horsdal HT, Brikell I et al. Temporally ordered associations between type 2 diabetes and brain disorders – a Danish register-based cohort study. BMC Psychiatry 2022;22:573.
205. Kanwar A, Malik S, Prokop LJ et al. The association between anxiety disorders and suicidal behaviors: a systematic review and meta-analysis. Depress Anxiety 2013;30:917-29.
206. Penninx BW, Pine DS, Holmes EA et al. Anxiety disorders. Lancet 2021;397:914-27.

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Towards a shared diagnostic process: whose diagnosis is it anyway?

Diagnosis is powerful. It colors everything, from identity to social functioning to hope, and can profoundly change people's lives. For the most part, research related to mental and behavioral diagnosis has tended to focus on the content, validity and reliability of diagnostic systems. This has largely been done from the clinician viewpoint, due to a historical medical perspective that has dictated the language and framing of diagnostic features, whilst lived experience perspectives have largely been neglected[1].

The process of diagnosis – how it is delivered and framed, how it is applied to treatment decisions, and how this is navigated between clinician and service user – is often not considered in the literature on the utility of diagnosis. However, the diagnostic process is likely at least as strong a determinant of individual impact as the diagnosis itself. A better understanding of the benefits and negative impacts of the experience of the diagnostic process could inform improvements to systems of diagnostic classification and service provision[2].

In clinical systems, diagnosis remains a powerful tool in conceptualizing mental health and delivering care and treatment. There are compelling reasons for this. Diagnosis has value for clinicians who are attempting to work within the complexity and messiness of human mental suffering. The categorization and description of mental illness have been argued to be particularly useful for macro-level health care delivery and research, including for establishing population-level evidence, policy making and the purchasing, billing and commissioning of services, but has different utility on a micro- or individual level[3].

On an individual level, mental health diagnosis may be experienced as valuable to those trying to make sense of their own mental suffering. Amidst the confusion and pain of mental ill health, it can offer a foundation or starting point for recovery, or indeed hope that treatment and recovery are possible. Personal recovery has been defined as a profound and unique process to achieve a satisfactory, hopeful and productive way of life, within the possible limitations of illness[4]. Diagnosis can help make sense of difficult experiences. It offers a way for engaging with services, for explaining symptoms and challenges to others, and for decisions concerning treatment choice and eligibility. This extends to connection with those who have similar experiences, peer support, and the role modelling of recovery. However, the historical neglect of lived experience perspectives means that the clinical language of diagnosis may be in common use, but the underlying construction of what diagnoses represent is not necessarily shared[1].

Assimilation is the process of absorption or integration of new information or ideas. How diagnoses are assimilated is critical to their impact on identity and social functioning, including intimate relationships, friendships and occupational interactions[5]. Diagnostic assimilation also refers to an iterative impact on meaning-making (that is, what the diagnosis means for me, my functioning, my relationships, and my future) and feelings of agency and control. Critically, this involves domains that are known to be important to mental well-being and personal recovery, including identity, hope, social connection, and agency[2,6]. Diagnostic systems are founded on medical principles that are more attuned to symptom reduction than to personal recovery[2]. It has long been recognized that mental health diagnoses can overshadow clinical understanding[7], but we argue that this can extend further, as internalized stigma can come to shape, constrain, or even dominate a person's identity.

Additional empirical work is needed to establish the impact of the diagnostic process on how individuals are able to integrate diagnoses into their identity and functioning. We argue that the extent of collaborative meaning-making (or the co-construction of meaning) between clinicians and service users in relation to the diagnostic features is critical to this[2]. For example, a diagnostic process that involves explanation of the diagnostic features and how they may relate to the individual's experience supports the development of a shared understanding.

This meaning-making process is nested within the relationship between service user and clinician. The clinician holds a significant amount of power both over the decision-making process and the construction and framing of the diagnosis for the individual. Relational factors are also likely to be critical to feelings of agency associated with the diagnosis. A more collaborative process is intended to foster a more trusting and therapeutic relationship[2], which in turn can positively affect ongoing engagement with support services and treatment. In this context, a life-long individual dynamic process of relating to the diagnosis, sharing it with others, and considering how it relates to social and occupational functioning, could be framed and initiated.

According to this perspective, diagnosis could be viewed as a co-constructive social process[8] that should be sensitive to the way that communication, framing, and relational factors impact ongoing assimilation[5]. The significant knowledge and expertise accumulated by clinicians could be sensitively integrated with the specific idiographic knowledge of the service user in a shared meaning-making process as a part of clinical formulation.

Additionally, a more shared and phenomenological construction and language for the diagnostic features[9] could extend to classification systems and delivery tools. This would inform individual consultation, models of mental health care delivery, and wider policy, as well as dominant social narratives. However, this requires a shift in values and perspectives. Diagnosis evolved from a need to manage and respond to complexity, and it provides both a structure for meaning-making and a language to communicate this.

We suggest a philosophical repositioning that understands diagnosis to be a shared constructive process between clinician and service user. This requires a systematic and empirical understanding of the function of diagnosis for individual service users, clinicians, health care systems, and public policy. Integrating more phenomenological understanding into diagnostic features[9] could be foundational for the co-production of language, tools, and delivery systems that better meet these needs[1]. This requires research method-

ologies that rigorously respond to complexity and overcome biases that maintain inequality around both diagnostic research and clinical practice.

Corinna Hackmann[1,2], Hannah Zeilig[3,4], Cary S. Kogan[5], Geoffrey M. Reed[6]

[1]Norfolk and Suffolk Foundation Trust, Norwich, UK; [2]School of Medicine, University of East Anglia, Norwich, UK; [3]University of the Arts London, London, UK; [4]School of Health Sciences, University of East Anglia, Norwich, UK; [5]School of Psychology, University of Ottawa, Ottawa, ON, Canada; [6]Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

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1. Hackmann C, Balhara YPS, Clayman K et al. Lancet Psychiatry 2019;6:778-85.
2. Hackmann C, Wilson J, Perkins A et al. BJPsych Adv 2019;25:214-22.
3. Foulkes L. What mental illness really is… (and what it isn't). New York: Random House, 2022.
4. Anthony WA. Psychosoc Rehabil J 1993;16:11-23.
5. Kiehl I, Pease R, Hackmann C. Autism 2024;28:1060-74.
6. Leamy M, Bird V, Le Boutillier C et al. Br J Psychiatry 2011;199:445-52.
7. Jones S, Howard L, Thornicroft G. Acta Psychiatr Scand 2008;118:169-71.
8. Hayes J, Ford T, McCabe R et al. Autism 2022;26:488-98.
9. Fusar-Poli P, Estradé A, Stanghellini G et al. World Psychiatry 2022;21:168-88.

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The neurodiversity movement vs. the medical model of autism

The autism rights branch of the neurodiversity movement arose from autistic people to challenge autism's parent-led cure movement[1]. Yet, the neurodiversity movement's views tend to be supported by autistic parents of autistic people[2], and by those close to autistic people with high support needs[3]. Indeed, the neurodiversity movement acts in creative tension with, rather than in opposition to, the medical model. Here we present an overview of the distinctions and overlaps between the neurodiversity movement and the medical model, as related to autism.

In its approach to autism, the neurodiversity movement begins with its goal of quality of life. This includes but surpasses "objective" quality of life, otherwise known as adaptive functioning (e.g., self-determination and personal development, social relationships, education, employment, and daily living). It also includes subjective well-being (e.g., satisfaction with one's life). The neurodiversity movement works backward from the goal of quality of life to address the individual and social factors that interact to produce disability[4].

While many representations of (the) neurodiversity (movement) differ in the extent to which their *rhetoric* describes societal oppression as causing vs. contributing to or exacerbating disability (so-called "strong" or "weak" forms of the social model of disability), in practice empirical research suggests that nearly all neurodiversity supporters endorse certain individual-level interventions[2]. Nevertheless, the neurodiversity movement and its supporters oppose normalization and "cure" of autism[2,5], and argue that social misunderstandings or breakdowns occur *between* people[6].

In contrast, a "pure" medical model would assume that an individual's "symptoms" (behaviors or traits) directly and specifically cause dysfunction or disability, and it seeks to eliminate autism (dehumanized as separate from the person). It works to disrupt this supposed linear relationship between so-called deficits and disability by preventing or curing the "disease" or "disorder". This starkly opposes the neurodiversity movement's perspective on autism as an inseparable identity. This does *not* mean viewing autism as simply positive, but viewing it as complex, with autistic people holistically endorsing both strengths *and* challenges[7]. The neurodiversity movement helps people find pride or community in being autistic, without necessarily reducing endorsement of negative emotions that may have complex causes[5].

Autistic individuals are more likely than non-autistic people to define autism in a neurodiversity-affirming way that privileges experiential expertise (from the lived experience of being autistic), in terms of neurocognitive differences[7]. Regardless of the neurodiversity movement, autistic people tend to view autism as a natural part of themselves[5]. From a neurodiversity-aligned perspective – that places social communication problems between autistic people and interaction partners, and views what the medical model calls "restricted, repetitive behaviors"[8] as potentially within autistic people, but also arising in response to or in interaction with the environment – autism may be viewed as innate[6].

In contrast, the mainstream autism cure movement, supported by scientific research, views autism as arising from an interaction between biological and environmental factors. The alternative health offshoot of the medical model emphasizes theorized (but empirically baseless despite extensive research) "environmental triggers" such as vaccines or heavy metals, endorsing dangerous (potentially lethal) interventions such as opposing vaccines or supporting chelation therapy to bind to and remove the toxic metals[1].

In practice, basic science cannot be reliably applied to the assessment of autism. So, through psychiatric classification systems such as the DSM, autism is defined by behavior[8]. Therefore, according to some proponents of the medical model, autistic people who "successfully" (and sustainably) mask their autism, and camouflage as non-autistic, have "lost" their autism diagnosis, while admitting that they show no evidence of neural "normalization" but instead "compensation". Yet, such autistic people may recognize more than observers their ongoing cognitive or sensory processing challenges and stress from camouflaging[6]. Furthermore, the criteria of classification systems allow diagnosis by history, recognizing that people may no longer *appear* autistic but still experience disability[8]. Beyond ongoing challenges, people said to have "lost" a diagnosis often had subtler or fewer differences to begin with, may be compliant and people-pleasing to their own detriment, and may only appear that way through extensive normalization-focused therapy or (family or societal) pressure[6]. They

may only be masking with the help of support they may be receiving, which undiagnosing them may remove. Paradoxically, autistic people who mask may experience more victimization than more obviously autistic people, as they may be judged under a moral rather than medical or neurodiversity model[1].

So, while the neurodiversity movement supports intervention, it disagrees with certain principles, means and goals of clinical or biomedical interventions. Supporters may have nuanced ideas on *what* to target (e.g., inherently detrimental behaviors such as self-injurious head-banging, rather than inherently harmless behaviors that function as coping mechanisms such as hand-flapping), *why* (to improve quality of life and interdependence rather than "passing" as neurotypical), and *how* (e.g., supporting strengths and respecting individuals' preferences[4]). Neurodiversity movement supporters emphasize the need for society to change and for autistic leadership[2]. Certainly societal investment and systems change for rights enforcement (such as supports and services) are required to achieve the movement's aims, especially for autistic people with speech divergence who may require inclusive communication systems, community living, and supported decision-making[4].

The neurodiversity movement is not anti-psychiatry, but instead sometimes paradoxically embraces aspects of the Western biomedical model *more* than most researchers and practitioners aligned with that model[1]. This includes biological essentialism for the cause of autism, as noted[5]. It also tends to be more literal about autism's diagnostic criteria when opposing a cure for "autism". For example, the autism diagnosis does not include self-injurious stimming as part of autism itself; arguably this warrants its own diagnosis of stereotypic movement disorder[8]. Similarly, the autism diagnosis describes perseverative or restricted interests; many autistic people distinguish this from the ego-dystonic and anxiety-provoking obsessions of obsessive-compulsive disorder[6].

Diagnosable medical conditions such as epilepsy are seen as needing recognition in their own right, not as part of autism, but in need of a cure[2]. Rather than expressions of pain being dismissed as "autism" through diagnostic overshadowing, or not recognized because of autistic people often (falsely) being interpreted as appearing insensitive to pain[6,8], it is important to understand truly "medical" conditions, so that autistic people get the care they need. Furthermore, neurodiversity advocates may ironically show flexibility in exercising relative support for certain "autistic traits" such as inflexibility as an intervention target[9].

Autistic neurodiversity supporters tend to exhibit more scientifically based knowledge[7] and support well-established uses of science and medicine more than most of the autism community, for example in terms of vaccines for preventable diseases (and viewing autism as *not* caused by vaccines[1]).

The neurodiversity movement and the medical model may overlap at times pragmatically. For instance, autistic people may choose to camouflage or lose their autism diagnosis. As a survival mechanism, an autistic person might "pass" for "neurotypical" for contexts such as job interviews. Autism diagnoses are sometimes discriminated against regarding health or life insurance, travel or immigration, or custody.

While a world free of stigma or discrimination may remain pursuable but elusive, neurodiversity and mainstream cure proponents can maximize common ground in the autism community to fight for shared values in science and services (even if their goals are different) at a time when both are threatened.

Steven K. Kapp
Centre for Interaction, Development and Diversity, School of Psychology, Sport and Health Sciences, Faculty of Science, University of Portsmouth, Portsmouth, UK

1. Kapp SK. In: Milton D, Ryan S (eds). The Routledge international handbook of critical autism studies. London: Routledge, 2022:255-69.
2. Dwyer P, Gurba AN, Kapp SK et al. Autism 2025;29:2297-14.
3. Hersh L, Dwyer P, Kapp SK et al. Autism Adulthood 2024;6:253-71.
4. Kapp SK, Gudknecht J. Infant Child Dev 2025;34:e70017.
5. Kapp SK, Gillespie-Lynch K, Sherman LE et al. Dev Psychol 2013;49:59-71.
6. Kapp SK. Front Integr Neurosci 2025;19:1489322.
7. Gillespie-Lynch K, Kapp SK, Brooks PJ et al. Front Psychol 2017;8:438.
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed, text revision. Washington: American Psychiatric Association, 2022.
9. Kapp SK, Ne'eman A. In: Kapp SK (ed). Autistic community and the neurodiversity movement. Singapore: Palgrave Macmillan, 2020:167-94.

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Chronic pain and mental disorders: a frequent comorbidity requiring a new comprehensive approach

Chronic pain and mental disorders constitute a complex comorbidity posing significant challenges to the conventional compartmentalized approach in medicine[1].

Chronic pain – operationalized as persistent nociceptive signaling extending beyond three months – has a population prevalence of 20-25%, but presents significantly elevated rates among individuals with mental disorders[1,2]. In post-traumatic stress disorder (PTSD), epidemiological data indicate prevalence rates approaching 90%, frequently manifesting as visceral nociception[3]. Within depressive disorders, prevalence ranges from 53 to 65%, with bidirectional pathophysiological mechanisms creating reciprocal amplification[1,4].

In bipolar disorder and schizophrenia spectrum conditions, prevalence rates range from 25 to 60%, although accurate detection is frequently confounded by perceptual processing aberrations or diagnostic overshadowing[1,5]. In neurodevelopmental conditions, including attention-deficit/hyperactivity and autism spectrum disorders, pain prevalence reaches 76%, potentially attributable to sensory integration abnormalities.

These epidemiological patterns remain consistent across meth-

odologically rigorous population-based investigations, establishing pain as a pervasive yet frequently neglected comorbidity across psychiatric diagnostic categories[1].

The clinical implications are substantial. Pain comorbidity doubles functional impairment metrics in psychiatric populations and significantly reduces the probability of symptomatic remission[1,4]. In depressive disorders, concurrent pain symptomatology triples suicide risk, through mechanisms that may include heightened negative cognition and perceived interpersonal burden[6]. Individuals with schizophrenia experience clinically significant diagnostic delays for several physical conditions, including neoplastic and cardiovascular pathologies, when pain manifestations are erroneously attributed to psychotic processes[1].

Economic analyses yield concerning data: depression with comorbid pain generates incremental health care expenditures of approximately $5,200 per patient annually in the US, exceeding utilization patterns observed in numerous chronic physical conditions[6]. In low- and middle-income countries, inadequately addressed pain complicates psychiatric management and strains limited infrastructure, exacerbating health care disparities[7].

Risk factor analysis reveals a complex multidimensional matrix. Female sex consistently emerges as a significant demographic variable in pain-psychiatric comorbidity, potentially reflecting neurobiological differences, health care access disparities, and sociocultural mediators, with PTSD investigations demonstrating doubled risk ratios for female subjects[2]. Symptom severity – particularly in disorders characterized by heightened autonomic arousal – has a positive correlation with pain intensity, suggesting shared neurobiological mechanisms[4]. Socioeconomic indicators and allostatic load further potentiate this association, as documented in cross-sectional epidemiological investigations[1,4].

Functional neuroimaging studies have identified neural activation patterns in the amygdala, anterior cingulate cortex, and insular cortex – regions implicated in both nociceptive processing and affective regulation – frequently mediated through inflammatory cascade activation[8]. Significant investigative gaps remain evident, particularly regarding atypical sensory processing in autism spectrum disorders and cross-cultural variability in pain phenomenology.

The therapeutic armamentarium remains fragmented and methodologically suboptimal. Cognitive behavioral therapy (CBT), while established as an empirically validated intervention for depression and anxiety disorders, produces modest analgesic effects (effect sizes approximating 0.3), with primary mechanisms targeting affective regulation rather than nociceptive processing[1,4]. Pharmacological agents, particularly serotonin-norepinephrine reuptake inhibitors, demonstrate efficacy in approximately 60% of people with depression and comorbid pain, but have limitations regarding tolerability profiles[1]. Mindfulness-based interventions show preliminary efficacy for attenuating distress in anxiety disorders, while meditation combined with light movement practices (e.g., yoga, tai chi) demonstrates potential utility for PTSD-associated nociception, though trials remain underpowered and methodologically heterogeneous[9].

Prescription of opioid analgesics – reaching a prevalence of 40% in some bipolar disorder cohorts – introduces potential iatrogenic sequelae, including substance use disorders and affective destabilization, without long-term therapeutic benefit[7]. Emerging neuromodulatory techniques demonstrate potential utility for dementia-associated nociception, but lack methodologically rigorous evaluation across other psychiatric diagnostic categories[6].

This therapeutic heterogeneity indicates a field requiring conceptual integration. Most current chronic pain interventions represent methodologically inadequate adaptations of protocols originally developed for individuals without psychiatric comorbidities[9].

Clinicians encounter significant implementation barriers. Psychiatric training curricula typically provide insufficient education regarding pain assessment and management methodologies, while pain medicine specialists frequently have inadequate expertise regarding psychiatric complexity[1,5]. Standardized psychometric instruments, such as the Brief Pain Inventory, should be systematically incorporated into psychiatric assessment protocols to facilitate early identification of pain comorbidity[9].

Integrated care models – involving psychiatrists, psychologists, pain medicine specialists, and allied health professionals within coordinated treatment teams – represent a potentially efficacious approach. They have demonstrated favorable cost-utility ratios and enhanced clinical outcomes in depression trials[6], and could potentially be adapted across diverse health care systems, including resource-constrained environments where stigmatization frequently impedes appropriate service utilization. Inadequate attention to pain phenomenology potentially compromises not only clinical outcomes but also therapeutic engagement parameters.

Recent methodological advances enhance clinical conceptualization, with longitudinal cohort studies demonstrating that ongoing nociceptive input is associated with a 30% increased risk of depressive relapse[4]. Genetic and molecular studies implicate inflammatory pathway dysregulation as a potential pathophysiological mechanism, with interleukin-6 concentrations demonstrating significant correlations with both pain intensity parameters and psychotic symptom severity[1,8].

Cross-cultural investigations document substantial variability in pain phenomenology, ranging from attenuated expression in East Asian populations to amplified behavioral manifestations in Latin American contexts. Yet, clinical trials for mental health interventions, including those addressing pain, are predominantly conducted in Western settings, limiting insights into diverse pain experiences across global populations[1,7]. Investigations utilizing animal models elucidate stress-induced hyperalgesia mechanisms that parallel PTSD phenomenology, although significant human translational limitations persist[8].

Health services research consistently identifies systemic deficiencies: diagnostic misattribution, access limitations, and inadequate treatment, disproportionately affecting displaced populations and ethnic minorities[7]. These convergent empirical observations necessitate coordinated multinational research initiatives.

Future research requires a methodological transformation. Multinational longitudinal investigations could elucidate causal mechanisms and temporal sequencing between nociceptive onset and psychiatric symptomatology, incorporating objective biomarkers, including inflammatory mediators and neuroendocrine param-

eters[8]. Psychometrically validated, culturally calibrated nociceptive assessment instruments would remediate current measurement heterogeneity[9].

Clinical trials should evaluate multimodal intervention protocols, such as integrated pharmacological, mindfulness-based and digital therapeutic approaches for depression with comorbid pain; and sensory processing-informed interventions for autism spectrum disorders. Schizophrenia-associated nociception – a significantly under-investigated domain – warrants systematic evaluation of antipsychotic compounds with potential analgesic properties[1,5]. Digital health technologies – particularly wearable devices enabling synchronous monitoring of nociceptive and affective parameters – could enhance intervention accessibility, particularly relevant for geographically isolated populations[7]. Implementation science methodologies prioritizing equity parameters should be considered to ensure intervention dissemination across diverse socioeconomic contexts.

In conclusion, chronic pain in psychiatric populations constitutes not merely a comorbidity but a global public health phenomenon requiring systematic attention. It exacerbates psychopathology, fragments service delivery systems, and transcends geographical and cultural boundaries. Clinicians across disciplinary domains must adopt an integrated biopsychosocial framework, implementing empirically validated assessment methodologies and coordinated treatment protocols. For populations globally – across metropolitan and rural contexts – this integration represents a fundamental clinical and scientific necessity that acknowledges the neurobiological and phenomenological inseparability of nociceptive processing and psychiatric symptomatology.

Brendon Stubbs[1,2], Davy Vancampfort[3-5]
[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [2]Division of Social Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria; [3]Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium; [4]University Psychiatric Centre KU Leuven, Leuven, Belgium; [5]Leuven Brain Institute, Leuven, Belgium

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1. Ma R, Romano E, Ashworth M et al. J Pain 2024;25:104421.
2. Mills SEE, Nicolson KP, Smith BH. Br J Anaesth 2019;123:e273-83.
3. Afari N, Ahumada SM, Wright LJ et al. Psychosom Med 2014;76:2-11.
4. Werneck AO, Stubbs B. Gen Hosp Psychiatry 2024;89:49-54.
5. Firth J, Siddiqi N, Koyanagi A et al. Lancet Psychiatry 2019;6:675-712.
6. Greenberg PE, Fournier AA, Sisitsky T et al. J Affect Disord 2020;267:102-10.
7. Okasha T, Okasha A, El-Sheikh M et al. World Psychiatry 2022;21:345-56.
8. Walker AK, Kavelaars A, Heijnen CJ et al. Pharmacol Rev 2014;66:80-101.
9. Raja SN, Carr DB, Cohen M et al. Pain 2020;161:1976-82.

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A multilevel systems approach to resilience after childhood adversity

Resilience has never been more important. In recent years, the world has seen severe threats to society in the form of poverty, inequality, climate disaster, conflict, war, and terrorist attacks. Such adversity can negatively impact individuals in a myriad of ways, and has particularly strong effects on those growing up.

Globally, more than half of all children and young people report having experienced some form of adversity whilst growing up. Adversity in childhood is one of the strongest predictors of problems in later life, including (mental) health problems, lower educational attainment, behavioral problems, crime and suicide[1,2]. These problems often first emerge in the adolescent time-period.

Adolescence is a period of rapid, dynamic change through school transitions, and often the first transition into the workplace. These changes require independence, and bring social and financial responsibilities and expectations. At the same time, adolescents start building their own social network, forging friendships and increasingly stronger and more reciprocal stable social bonds. The influence of peers becomes more and more important for their sense of self, opinions and behavior. As peers are so important, adolescent behavior is in part influenced by a tendency to avoid social rejection from peers[3]. These social changes coincide with major hormonal and brain developmental changes, with the brain networks that aid the regulation of stress and emotions becoming increasingly more efficient. Due to these major social and neurodevelopmental changes, adolescence can be seen as both a time of opportunity and of increased sensitivity.

Sadly, an estimated 13% of young people globally suffer from a mental disorder[4]. The number of young people with mental health problems has increased in recent years, and particularly so in young people identifying as lesbian, gay, bisexual, transgender and queer or questioning (LGBTQ+). Critically, suicide is a leading cause of death in young people. Mental health issues that arise in adolescence are often more severe and more recurrent and can trigger lifelong trajectories of further mental health problems, absenteeism, economic hardship, violence and crime.

The burden of these problems is in a large part borne by youth who grow up in families affected by adversity in the form of poverty or childhood maltreatment[5]. As such, increasing resilience in young people with childhood adverse experiences should be prioritized as a critical public health priority.

To boost resilience, the appropriate conceptualization is an important first step. In child development, the field of resilience science started with the pioneering work of, amongst others, E. Werner, M. Rutter and N. Garmezy. These researchers investigated the etiology of mental illness in children growing up in high-risk environments. One particularly influential study was the Children of Kauai Study led by E. Werner, in which almost 700 babies born in 1955 on the Island of Kauai were studied until age 32[6]. About 200 of these children grew up in families struggling with poverty, discord, mental illness, or criminality. Strikingly, one-third of these children demonstrated academic success, social competence, and mental well-being in both adolescence and adulthood. Werner and colleagues subsequently shifted their attention to studying the factors that had helped these children show such resilience.

Over the course of the next 50 years, many studies focusing on resilience in children growing up in difficult circumstances have followed. These studies have often used different ways to quantify resilience. To move the field forward, these conceptualizations have been brought together by a large group of researchers in the "resilience framework"[7].

In this framework, resilience refers to the dynamic process of maintaining or regaining mental health in response to significant adversity. Protective, or resilience, factors aid an individual's capacity to respond well to stress. Resilience mechanisms refer to the dynamic process of adaptation to stress, such as increased stress regulatory brain activity, lower pro-inflammatory cytokine responses to stress, or the re-appraisal of a stressor. Finally, resilient functioning refers to an outcome of good mental health in the aftermath of stress.

Such resilient functioning outcomes are especially important in the context of childhood adversity, where the stressor has already taken place. Resilient functioning should then refer to functioning across a range of (stressor relevant) domains (such as thoughts, feelings, mood and behavior). Such functioning may be examined in comparison to others who have similar experiences, as well-being can be improved (e.g., stress inoculation) or decreased (e.g., stress sensitization, scarring) depending on the type or severity of the stressor experienced. Resilience science focuses on the identification of the protective factors and resilience mechanisms that aid resilient functioning outcomes.

Protective or resilience factors are known to reside at multiple biological, psychological and sociocultural levels[8]. Resilience is aided by internal predispositions (such as genotype, brain structure and function, personality traits, self-efficacy skills, cognitive control of emotions, and executive functioning skills). In addition, there are critical external social and cultural influences that aid a child's capacity to respond well in the aftermath of adversity.

Supportive family environments help shape resilience in the face of disaster when caregivers are warm and supportive, have clear routines, rules and expectations, model coping skills, and help build self-efficacy and self-esteem. Schools strengthen resilience in young people by providing structure, social connection, and essential cognitive skills such as language, aspects that are also crucial in the aftermath of crises such as war or environmental disasters. Community support systems aid resilience through access to health care, and by providing the infrastructure for food and safety, but also through societal values and belief systems which can provide hope and meaning.

These factors are inextricably intertwined. For example, friendships can help increase self-esteem, and family support can lower stress perceptions and responses. As such, resilient children require resilient families, and are reliant on resilient societies, cultures and policy-making, and these systems influence each other in bidirectional dynamic ways[9].

Thus, a young person's ability to show resilience to childhood adversity relies on complex and dynamic interactions among a large number of internal and external factors. This explains why we cannot yet, with good accuracy, predict who will show resilience, despite the fact that many protective factors are well known – a phenomenon known as the "resilience paradox".

However, this also means that there are many aspects and nodes in the network that can be investigated and potentially targeted in our efforts to boost resilience in young people. To do so, large scale collaboration and integration across fields are needed to investigate multiple levels of biological and social cultural organization and their temporal dynamics in a longitudinal or prospective manner. In other words, just as it takes a village to raise a child, it takes a village of scientists, clinicians and communities to fully understand and support resilience in young people with a history of adversity.

Anne-Laura van Harmelen
Department of Child and Education Studies, Leiden University, Leiden, The Netherlands

1. Kessler RC, McLaughlin KA, Green JG et al. Br J Psychiatry 2010;197:378-85.
2. Grummitt LR, Kreski NT, Kim SG et al. JAMA Pediatr 2021;175:1269-78.
3. Blakemore SJ. Curr Dir Psychol Sci 2018;27:116-22.
4. Kieling C, Buchweitz C, Caye A et al. JAMA Psychiatry 2024;81:347-56.
5. Caspi A, Houts RM, Belsky DW et al. Nat Hum Behav 2016;1:0005.
6. Werner EE. Sci Am 1989;260:106-11.
7. Kalisch R, Baker DG, Basten U et al. Nat Hum Behav 2017;1:784-90.
8. Ioannidis K, Askelund AD, Kievit RA et al. BMC Med 2020;18:1-16.
9. Masten AS. Dev Psychopathol 2024;36:2542-50.

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A framework for clinical validation of generative artificial intelligence therapeutics

While established frameworks exist for assessing the clinical efficacy and effectiveness of human-delivered interventions, and standards are in place for pre-artificial intelligence (AI) chatbots that have achieved clearance from the US Food and Drug Administration (FDA) as companions to psychological treatment, a significant void remains. There are currently no defined standards to determine the efficacy of an AI agent in delivering validated treatment approaches, whether it is assisting with medication management, supporting clinicians, or directly delivering talk therapy. This gap leaves the field vulnerable, confronting a surge of emerging technologies without the necessary tools to ascertain their safety, and if – or for whom – they genuinely work.

Autonomous or semi-autonomous AI agents, capable of interacting across diverse modalities – text, voice and images – can both understand and mirror the complex cues that human therapists utilize, thereby enhancing both engagement and assessment capabilities. This positions generative AI (GenAI) as a deeply promising solution for delivering psychological interventions, with the potential to significantly broaden treatment reach and reduce costs.

However, the rapid proliferation of digital applications claiming therapeutic effects, coupled with their increasing adoption by the public[1], underscores a crucial concern: the absence of established clinical standards for rigorously evaluating the safety and effectiveness of these GenAI agents. This regulatory void creates potential risks for patients and impedes the responsible and ethical integration of this transformative technology into validated clinical practice. Therefore, a robust evaluation framework, one that thoughtfully adapts established psychotherapy trial design principles to the unique characteristics of AI, is not only beneficial but urgently required.

While sharing some commonalities with general wellness and coaching applications, GenAI agents explicitly intended for treatment of clinical disorders face distinct and amplified validation challenges. These encompass the intricate management of high-risk safety scenarios, the imperative for strict adherence to empirically supported therapeutic approaches, and the inherent complexities of clinical reasoning. Unlike traditional, deterministic chatbots that follow rigid decision trees, generative models operate probabilistically. Their dynamic, non-deterministic nature, while powerful, necessitates a novel dual approach to validation that seamlessly integrates meticulous human oversight with sophisticated agent-based evaluation, thereby ensuring uncompromised safety, efficacy and effectiveness.

The concepts of efficacy (an intervention's effect under ideal conditions) and effectiveness (its performance in real-world settings) are foundational to therapeutic development. However, GenAI agents, with their dynamic, evolving models, directly challenge traditional validation paradigms. Their non-deterministic therapeutic actions mean that an agent may not produce identical responses to seemingly similar prompts. Consequently, the intervention cannot be defined by verbatim replication, but rather by the consistent and principled application of established therapeutic frameworks within clearly defined guardrails, much akin to how human-delivered treatments are evaluated for fidelity.

Furthermore, the assumption that AI models can seamlessly mimic human clinical reasoning is inherently flawed. GenAI models are demonstrably prone to factual errors (often termed "hallucinations"), can inadvertently inherit biases embedded in their training data, and may exhibit deficits in episodic memory or subtle concept differentiation – all of which are critically important for sound clinical reasoning and avoiding problematic cognitions.

Evaluating the cumulative impact of micro-interactions over extended periods is paramount, requiring analysis beyond simplistic single-turn benchmarks, to truly understand how an agent maintains therapeutic coherence, fosters an alliance, and effectively mitigates risks such as model sycophancy or the perpetuation of unhelpful thought patterns. Longitudinal studies, moreover, are particularly vulnerable to "model drift", where updates to the underlying large language model (LLM) subtly alter the agent's therapeutic characteristics, necessitating rigorous version control and proactive clinical impact assessments.

A particularly salient challenge, and potentially an opportunity, is the concept of the therapeutic alliance, which is an essential component of human-to-human treatment[2], within human-AI interaction. Unlike humans, LLMs are not capable of complex cognitions that humans rely on to interact relationally[3]. Therefore, the nature of AI's alliance may rely on more concrete markers of trust and support – such as explicit goal-setting, the use of collaborative and validating language, and adaptive responsiveness. The "emotional bond" component, in this context, shifts from reciprocal human affection to the user's trust in the AI's consistency, reliability, helpfulness, and its demonstrated ability to deliver contextually appropriate and empathetic language. Evaluation, therefore, must involve analyzing the AI's dialogue for clear markers of active listening, validation, and empathetic resonance, alongside objective user interaction patterns such as sustained engagement and task adherence as robust behavioral proxies for a perceived positive alliance.

To build patient confidence and ensure both safety and effectiveness, these core concepts must be rigorously adapted for GenAI. The efficacy of a GenAI therapeutic agent can be precisely defined as the capacity of a specific, version-controlled agent – meticulously characterized by its explicit model, knowledge grounding, therapeutic principles, and interaction protocols – to produce statistically and clinically significant improvement on validated primary outcome measures, relative to a robust control, in a randomly assigned population under optimized study conditions. This demands transparent documentation of the LLM version, fine-tuning data, and clearly defined guardrails[4].

Effectiveness is the extent to which an agent, deployed in representative real-world settings (including controlled updates),

achieves clinically meaningful benefits across diverse outcome domains, demonstrates sustained user engagement, and consistently maintains an acceptable safety profile. Effectiveness studies therefore necessitate pragmatic designs that accurately reflect typical use-cases and heterogeneous populations, requiring robust strategies for managing model evolution through performance thresholds that trigger re-validation or continuous monitoring.

To accelerate the responsible translation of GenAI into evidence-based mental health care, a multi-stage, hybrid validation process is essential, meticulously integrating rigorous technical AI evaluation with established clinical research methodologies. This comprehensive framework should be conceptualized in phases analogous to traditional therapeutic development: iterative development, pre-clinical validation, clinical trials, and post-deployment monitoring.

The first phase, iterative development and benchmarking, involves rapid model refinement using simpler, initial benchmarks such as single-turn adherence checks. This phase focuses on foundational capabilities and preliminary alignment.

The second phase, pre-clinical AI validation, moves beyond simple accuracy to rigorous *in silico* and simulated validation of the agent's behavior in complex, dynamic scenarios. This critical stage includes using LLM-to-LLM role-playing or human actors to simulate diverse therapeutic interactions, rigorous adversarial "red teaming" to proactively identify safety-critical failure modes[5] (e.g., mismanaging crisis cues or providing harmful advice), and systematic bias and fairness audits to prevent the perpetuation or amplification of health disparities[6].

The third phase, clinical efficacy and effectiveness trials, establishes direct patient benefit. These demands validating longitudinal therapeutic coherence, as clinically relevant behaviors, therapeutic benefits, and potential risks often emerge and evolve over time. Trials must employ sophisticated methods to assess context retention, dialogue coherence, and task completion across extended, multi-session interactions. Human evaluation frameworks are paramount for assessing information quality, clinical reasoning, expression style, overall safety, and patient trust, alongside crucial ethical and practical considerations such as clinical credibility, user experience, user agency, equity, transparency, and crisis management protocols.

The fourth phase, post-deployment and continuous validation, ensures sustained safety and efficacy in real-world use. GenAI agents require ongoing, vigilant monitoring to detect any performance degradation, drift, or the emergence of new risks. A one-time demonstration of effectiveness is insufficient for these rapidly evolving technologies. This phase demands pragmatic trial designs that accurately reflect real-world conditions[7], clear and actionable protocols for re-validation when the underlying model is substantially updated or performance metrics fall below a pre-defined threshold, and robust continuous validation processes to re-establish therapeutic effects and comprehensively assess risk profiles.

GenAI agents that interact directly with clinicians, caregivers and patients offer significant and transformative opportunities for psychotherapy. However, their responsible translation into validated clinical tools necessitates a clinically specific and robust research framework[8,9]. The above-mentioned stages of development, which integrate traditional sequential clinical trial norms with emerging state-of-the-art AI validation strategies, provide a crucial path forward. The ultimate aim is to develop common standards and methodologies that facilitate unwavering transparency and engender deep trust across the entire ecosystem of mental health care.

Isaac R. Galatzer-Levy[1], Nenad Tomasev[1], Carolyn Rodriguez[2], John Torous[3]
[1]Google DeepMind, London, UK; [2]Stanford Medicine, Stanford, CA, USA; [3]Harvard Medical School, Boston, MA, USA

1. Hua Y, Siddals S, Ma Z et al. World Psychiatry 2025;24:383-94.
2. Horvath AO, Del Re AC, Flückiger C et al. Psychotherapy 2011;48:9-16.
3. Galatzer-Levy IR, Munday D, McGiffin J et al. arXiv 2024;2410.07391.
4. Pfohl SR, Cole-Lewis H, Sayres R et al. Nat Med 2024;30:3590-600.
5. Laskar MTR, Alqahtani S, Bari MS et al. arXiv 2024;2407.04069.
6. Nathan PE, Stuart SP, Dolan SL. Psychol Bull 2000;126:964-81.
7. Hotopf M. Adv Psychiatr Treat 2002;8:326-33.
8. Stade EC, Stirman SW, Ungar LH et al. Npj Ment Health Res 2024;3:12.
9. Torous J, Linardon J, Goldberg SB et al. World Psychiatry 2025;24:156-74.

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Artificial intelligence and the problem of physician burnout: a double-edged scalpel

Physician burnout is a public health problem that affects a high proportion of practitioners. It is linked to early departure from the profession, reduced productivity, more frequent medical errors, and lower patient satisfaction[1]. There is no established definition of burnout, but criteria typically include emotional exhaustion, depersonalization, and diminished sense of accomplishment. Female, young, and emergency room providers appear particularly prone, with psychiatrists and ophthalmologists relatively less impacted[1]. While the overlap with depression is clear, burnout is considered job-related, whereas depression is less context-dependent, although the greater stigma of psychiatric diagnoses may have helped popularize burnout as a more "acceptable" condition.

The tangled psychological, demographic, specialty and systemic factors have made solutions elusive and prompted some to look to artificial intelligence (AI) for innovative remedies that could address physician burnout across its myriad fronts and contributors[2,3]. But what if the very tools we hope will alleviate burnout inadvertently create new, more insidious sources of strain? Analyzing AI's impact on time and mental demands – two key dimensions of the NASA Task Load Index[4], a standard tool for assessing workload in health care – provides a path for understanding its effects on burnout.

A critical factor in high-burnout specialties is overwhelming

time demands, characterized by having insufficient time to see patients and meet the charting, billing, credentialing, continuing education, and other administrative and teaching responsibilities, leading to work extending into personal and family time. AI might alleviate time demands by automating clinical charting, billing forms, medical leave requests, and insurance correspondence. Automating note generation, for example, could free up a significant portion of a physician's day, reducing the need to extend work hours. By using ambient scribes to write summaries or natural language tools to access patient data (e.g., "give me this patient's hospitalization history"), AI could make physicians more efficient.

AI could also aid in efficiently communicating with patients by adjusting text to match literacy level. In the emergency department's high-burnout context, AI could improve workflow by prioritizing critical cases, rapidly identifying urgent findings on imaging studies, and performing emergency triage tasks, thereby speeding up initial patient assessments. The resulting time savings could mean more time spent in direct patient interactions – an activity that has been considered protective against burnout[5].

However, it is also possible that some new tools may end up becoming an AI-age example of the "productivity paradox", a long-identified problem with adoption of information technologies in medicine[6]. If AI tools are poorly designed, not seamlessly integrated into existing workflows and electronic health records, or have usability issues, they could introduce new inefficiencies, disrupt established routines, diminish physicians' control over their day, and *increase* time demands.

The initial phase of implementation of AI systems also often requires a time investment for training, which could temporarily accentuate time pressures. In the case of AI scribes, high "hallucination" rates necessitate that physicians spend considerable effort editing and correcting, potentially requiring more time than if the assessment had been done manually.

Mental demands are another common source of physician burnout. By using clinical decision support systems that increase the efficiency of information synthesis, present critical data clearly, offer diagnostic suggestions, propose treatment interventions, and highlight potential risks, AI can reduce the cognitive load associated with complex case management. Similarly, by enhancing information retrieval from dense electronic health records through data visualization, and by automating the tracking of patient progress and pending results, AI can allow physicians to maintain better situational awareness with less mental effort. Early research suggests significant potential for AI in this arena, with large language models demonstrating a strong capacity for complex medical reasoning and multi-step clinical decision-making[7].

But AI tools can also *increase* mental demands, including via "alert fatigue" from excessive or low-specificity notifications or a need for hyper-vigilance. It is entirely possible that physicians will increasingly face an overwhelming volume of AI-generated data that requires extensive cognitive processing to assess for relevance and accuracy. While AI tools may reduce cognitive load in one area, it is conceivable that overall cognitive effort may actually increase due to the need to vigilantly monitor AI outputs for errors that can negatively impact care or make it into the medical record, thereby also increasing practitioners' medico-legal risks.

Such vigilance will likely need to heighten to confront a dangerous phenomenon being borne out in research, namely the tendency to over-trust AI-generated medical advice when it appears to "think" or when it generates inaccurate but believable-seeming citations to support its reasoning[8]. To avoid this automation bias and prevent medical errors that can harm patients or lead to malpractice claims against doctors, physicians may be forced into a taxing, high-alert state that compounds mental strain.

In the context of an overstretched health care system, it is not surprising that AI has been seen as a potential panacea. In the most optimistic scenario, AI could automate burdensome or tedious tasks, freeing up precious physician time. AI may also act as a powerful cognitive partner, assisting with complex diagnostics and personalizing management and care. Still, it would be simplistic to assume a mostly positive outcome on burnout from the medical AI tools that many health systems are rolling out.

The integration of new technologies into medical practice has often been a double-edged scalpel, and the widespread adoption of electronic health records nearly 20 years ago is one cautionary lesson. They were intended to streamline information and strengthen care coordination, and early versions were lauded for their real-time alerts and helpful reminders[9]. Since then, however, electronic health records have emerged as a rather consistent culprit in physician burnout studies, largely due to the substantial increase in administrative tasks that they have enabled, cumbersome system interfaces, and workflows that detract from direct patient engagement and extend physicians' workdays[9].

Such stories should serve as a reminder that tools designed to improve care can inadvertently introduce new burdens if not implemented with careful consideration for the human end-user and without an attempt to predict, and protect against, potential downsides.

AI holds meaningful promise to alleviate some drivers of physician burnout, but the promise is contingent on addressing significant challenges. These include ensuring high levels of accuracy to prevent increased verification burdens or medical errors, mitigating the risk of over-trust in imperfect systems, ensuring seamless workflow integration to avoid new inefficiencies, controlling the "task creep" that may happen because a new technology has now made new tasks possible, and protecting against the more insidious intrusions suddenly feasible, such as increased surveillance of physician productivity by AI-empowered administrators. There is also the real concern of deskilling, where over-reliance on AI could reduce physician proficiency, and the psychologically destabilizing fear of total physician displacement by AI in some medical specialties.

For medical AI tools to be a genuine solution rather than another source of physician burnout – or even a trigger for a mental health crisis – the development and deployment of these systems must be physician-centered and informed by high-quality research. Along the way, input from psychiatrists, who seem to have lower burnout rates themselves and may understand burnout par-

ticularly well due to its overlap with depression, could be uniquely helpful. Until then, circumspection around the adoption of medical AI as a sort of anti-burnout cure-all would seem in order.

Ayoub Bouguettaya[1], Elias Aboujaoude[2,3]
[1]Monash University, School of Nursing and Midwifery, Melbourne, VIC, Australia; [2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA; [3]Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA

1. Shanafelt TD, West CP, Sinsky C et al. Mayo Clin Proc 2023;100:1142-58.
2. Gallani S. Can AI save physicians from burnout? Harvard Business Review, August 13, 2024.
3. You JG, Dbouk RH, Landman A et al. JAMA Netw Open 2025;8:e2528056.
4. Hart SG, Staveland LE. Adv Psychol 1988;52:139-83.
5. Hiefner AR, Constable P, Ross K et al. J Am Board Fam Med 2022;35:716-23.
6. Brynjolfsson E. Commun ACM 1993;36:66-77.
7. Gilson A, Safranek CW, Huang T et al. JMIR Med Educ 2023;9:e45312.
8. Rosenbacke R, Melhus A, McKee M et al. JMIR AI 2024;3:e53207.
9. Budd J. J Prim Care Community Health 2023;14:21501319231166921.

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A longitudinal analysis of quality and longevity of mental health apps indexed in MIND, the largest database

Patient and clinician interest in mental health apps continues to drive market expansion, with projections estimating growth from $6.1 billion in 2023 to $26.5 billion by 2032[1]. Apps are also beginning to incorporate artificial intelligence (AI)[2]. Historically, however, mental health apps have faced criticism for inadequate privacy safeguards, a lack of clinical evidence, and safety concerns, including the potential to exacerbate self-harm behaviors[3].

While increased regulatory action and competition from AI have likely reshaped the app landscape, assessing whether the industry has addressed historical shortcomings remains challenging, due to a lack of standardized reporting[4]. A leading framework for assessment is the American Psychiatric Association's app evaluation model[5], which has been translated into a dynamic and user-friendly database, the M-Health Index and Navigation Database (MIND)[6], which has itself been used in over 20 studies and accessed by millions of people around the world.

Today, MIND (mindapps.org) is the largest freely accessible database of mental health apps, indexing over 400 apps. To be indexed on this database, apps must be downloadable in the US (iOS or Android), cost $10 or less, have been updated within four years, and remain free of stigmatizing content. Every six months, trained raters systematically re-evaluate apps to verify these eligibility standards, and assess them across 105 quality dimensions, ranging from clinical foundation to data privacy. This semi-annual review ensures continuous compliance, triggering an expert review for archiving if eligibility criteria are unmet, while generating a longitudinal dataset on the evolution of the digital mental health field.

Most research on the mental health marketplace offers only static snapshots that fail to capture the field's volatility. Although longevity is likely a prerequisite for clinical benefit[7], research applying survival analysis to quantify an app's "half-life" and identify characteristics associated with longevity remains scarce.

We extracted data from MIND on November 14, 2025, to perform a three-part analysis: a) a cross-sectional evaluation of the mental health app marketplace (including 402 apps); b) a three-year (2022-2025) longitudinal comparison across two timepoints to identify marketplace changes; and c) a five-year (2020-2025) longitudinal survival analysis of all 865 apps listed since MIND's inception (defined as remaining active on MIND vs. being archived).

From a cross-sectional lens, our findings show that over one-third of the 402 currently listed mental health apps are non-specific in their intended purpose (n=144, 35.8%). Only a small number of apps specifically target severe mental illness (SMI), with six addressing bipolar disorder (n=6; 1.5%) and none supporting individuals with schizophrenia. The tendency for apps to avoid claims of targeting specific pathologies has been well documented in recent years[2], as it allows developers to navigate the boundary between unregulated wellness products and regulated medical devices, effectively deferring regulatory oversight until a strategic pivot is required[8].

Although 379 (94.3%) apps had a privacy policy, we identified 287 apps (71.4%) that shared personal health information with third parties. Evidence supporting feasibility or clinical benefit was scarce, with only 56 apps (13.9%) reporting at least one study. Regarding the level of evidence, a majority of this subset (n=34, 60.7%) was supported by randomized controlled trials (RCTs).

We found that most apps are developed by for-profit companies (n=349, 86.8%). Notably, non-commercial developers (including academic, governmental and non-profit organizations) demonstrate a significantly higher propensity for adequate data handling (odds ratio, OR=2.46, 95% CI: 1.35-4.46) and are significantly more likely to employ evidence-based practices (OR=5.89, 95% CI: 3.07-11.30) (see also supplementary information).

When investigating the functional models that apps employ, we found that self-guided, low-intensity approaches predominate: the two most common features are journaling and goal setting or habit tracking (n=216, 53.7%), suggesting that developers prioritize tools that require minimal clinical governance. Despite the prevailing technological discourse, we identified only 48 apps (11.9%) that incorporated an AI chatbot.

From a three-year marketplace longitudinal assessment, there has been a profound economic shift toward "freemium model" apps (apps that are free to download but require in-app purchases or subscription; n=270, 67.2%). Their commercial dominance appears to come at the expense of user privacy. Freemium model apps are associated with poorer data handling practices, defined as

having a privacy policy and not sharing personal health information with third parties, compared to apps that require an upfront payment (OR=7.29, 95% CI: 2.74-19.45) or are provided entirely free (OR=2.64, 95% CI: 1.62-4.29).

Consequently, privacy concerns remain widespread: although more apps now publish a privacy policy than in 2022, they also increasingly share personal health information. This "transparency paradox" highlights that, while formal adherence to documentation has reached near-saturation, substantive data protection has diminished (see also supplementary information).

When looking across five years of data on app longevity, we found that non-specific apps exhibit significantly greater longevity (median survival time of 1,664 days, 95% CI: 1,403-2,053) than those targeting specific disorders, suggesting that developers prioritize their maintenance. Users with SMI may be particularly disadvantaged by these dynamics. While the few remaining apps for bipolar disorder (n=6, 1.5%) demonstrate survival comparable to non-specific tools, every app targeting schizophrenia in our sample was eventually archived.

Empirical validation is significantly associated with app survival (hazard ratio, HR=0.52, 95% CI: 0.37-0.74). Even among for-profit developers, apps lacking published studies face nearly double the hazard of being archived compared to those with validation (HR=1.79, 95% CI: 1.19-2.68). When investigating evidence quality, we found that apps supported by RCTs demonstrate the greatest longevity (HR=0.38, 95% CI: 0.23-0.64). Scientific validation may thus be not only an ethical imperative, but also a financially prudent strategy, as recent research identifies longitudinal survival and financial viability as decisive success factors for digital health enterprises[9].

We replicated previous findings[7] indicating that iOS apps (median survival time of 951 days, 95% CI: 783-1079) exhibit greater longevity than their Android counterparts, and extend these findings by demonstrating that cross-platform applications (designed for both iOS and Android) achieve the highest persistence of all (almost 80% had a two-year survival probability).

Despite the pre-selection bias inherent in MIND eligibility criteria, we argue that its filtering process strengthens the study's real-world relevance. By excluding non-functional or abandoned tools, this database provides a user-oriented framework that offers a representative view of the viable mental health app marketplace.

While this marketplace remains heterogeneous in terms of both app quality and longevity, our findings suggest that conducting studies may offer a dual benefit for developers: aligning with higher standards of user and academic trust, while potentially mitigating the risk of app obsolescence. Our insights provide a practical roadmap for stakeholders to select apps that are not only safe and evidence-based but, crucially, enduring.

Julian Herpertz[1,2], Bridget Dwyer[1], Jane Mikkleson[1], Matthew Flathers[1], Nils Opel[2,3], Christian Otte[2,3], Stefan M. Gold[2,3], Ulrich W. Ebner-Priemer[4-6], Julian Schwarz[7,8], Jake Linardon[9], Ayomide Egbejoda[10], Sean Ryan[1], John Torous[1]

[1]Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA, USA; [2]Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, Berlin, Germany; [3]German Center for Mental Health, partner site Berlin-Potsdam, Berlin, Germany; [4]Mental mHealth Lab, Institute of Sports and Sports Science, Karlsruhe Institute of Technology, Karlsruhe, Germany; [5]Department of Psychiatry and Psychotherapy, Medical Faculty Mannheim, Central Institute of Mental Health, Heidelberg University, Mannheim, Germany; [6]German Center for Mental Health, partner site Mannheim, Mannheim, Germany; [7]Department of Psychiatry and Psychotherapy, Brandenburg Medical School T. Fontane, Rüdersdorf bei Berlin, Germany; [8]Faculty of Health Sciences Brandenburg, Brandenburg Medical School T. Fontane, Neuruppin, Germany; [9]School of Psychology, Deakin University, Geelong, VIC, Australia; [10]Sargent College of Health and Rehabilitation Sciences, Boston University, Boston, MA, USA

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1. Camacho E, Cohen A, Torous J. JAMA Netw Open 2022;5:e2248784.
2. Torous J, Linardon J, Goldberg SB et al. World Psychiatry 2025;24:156-74.
3. Herpertz J, Stern AD, Opel N. Npj Mental Health Res 2025;4:62.
4. Torous J, Bucci S, Bell IH et al. World Psychiatry 2021;20:318-35.
5. Henson P, David G, Albright K et al. Lancet Digit Health 2019;1:e52-4.
6. Herpertz J, Dwyer B, Wagner E et al. Internet Interv 2025;42:100888.
7. Larsen ME, Nicholas J, Christensen H. JMIR Mhealth Uhealth 2016;4:e96.
8. Simon DA, Shachar C, Cohen IG. J Law Biosci 2022;9:lsac015.
9. Pfitzer E, Bitomsky L, Nißen M et al. J Med Internet Res 2024;26:e60473.

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Interventions for common mental disorders tested in Cochrane reviews: an analysis of quality of evidence and efficacy

In a recent analysis[1] of a random sample of 2,428 (35%) Cochrane reviews published between January 2008 and March 2021, only two of 48 interventions (4.2%) for common mental disorders were found to show a high quality of evidence, to be significantly superior to a comparator, and to be regarded as effective by Cochrane authors. The high-quality GRADE standard, however, could be too demanding. In particular, the assessment of risk of bias may be too stringent, leading to a downgrade of the evidence[1].

In the present analysis, we included not just a random sample, but all systematic reviews of interventions for common mental disorders published by the Common Mental Disorder Cochrane group between January 1, 2008 and June 24, 2025. We focused on interventions showing either a high or a moderate quality of evidence.

Interventions were included if they were compared to placebo, no treatment or treatment as usual, in randomized or quasi-randomized trials, and received GRADE ratings for their primary outcome. The study was carried out in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA)[2]. The protocol was registered at PROSPERO

(CRD42024547340).

For each Cochrane report, we extracted the GRADE rating of the first listed primary outcome[1,3]. If this rating was not high, we inspected the GRADE ratings of up to three further primary or secondary outcomes. We included only those secondary outcomes that addressed target symptoms. For the outcome with the highest GRADE rating, we extracted additional data (e.g., number of trials, number of patients, effect size, confidence interval). As an addition to the original protocol, we also extracted information on whether the Cochrane authors recommended the intervention as effective.

The identified Cochrane reports were randomly allocated to five pairs of raters. For each report, two reviewers extracted the data independently and compared the results. Discrepancies were solved by consensus or, if necessary, by involving a third rater.

The Cochrane Database of Systematic Reviews included 150 reviews of interventions for common mental disorders published between January 1, 2008 and June 24, 2025. Of those, 57 were excluded for various (overlapping) reasons (no GRADE rating: n=42; including only comparisons with active treatment(s): n=20; superseded by an updated version: n=1). Therefore, 93 Cochrane reviews met the inclusion criteria, encompassing 207 eligible interventions.

The included interventions were tested in adults (74/93 reports), in children and adolescents (13/93 reports), or in mixed samples of children, adolescents and adults (9/93 reports). In some reports, both adults and children/adolescents were studied separately (thus the sum exceeds 93).

The 207 interventions encompassed 50 treatments for depressive disorders, 46 for anxiety disorders (including obsessive-compulsive disorder), 27 for post-traumatic stress disorder, 46 for self-harm, 6 for pathological gambling, 5 for bipolar disorder or mania, 4 for somatoform disorders, 4 for eating disorders, 3 for insomnia, and the remaining for several other conditions.

Of the included 207 interventions, 11 (5.3%) were rated by the Cochrane authors as showing a high quality, 60 (29.0%) a moderate quality, 69 (33.0%) a low quality, and 66 (31.9%) a very low quality of evidence. Of these interventions, 8 (3.9%), 39 (18.8%), 20 (9.7%) and 20 (9.7%), respectively, were significantly superior to the control condition. In sum, 47 (22.7%) of all interventions were supported by a high or moderate quality of evidence and showed a significant superiority to the control condition (see also supplementary information).

Harms were reported for 62 of the 207 interventions (30.0%), with 12 (5.8%) yielding significantly more harms than the control conditions. Many of these comparisons (50.2%) were based on only one (75/207) or two (29/207) studies.

For pharmacotherapy (n=99 interventions) and psychotherapy (n=75 interventions), the proportions of interventions showing high or moderate quality of evidence and statistically significant results were 29.3% and 20.0%, respectively. Most pharmacological interventions showed low or very low quality of evidence (63.6%, 63/99), and the majority did not have statistically significant results (52.5%, 52/99). The same pattern was found for psychotherapy: the evidence was of low or very low quality in 66.7% (50/75) of interventions, and most of them (54.7%, 41/75) did not have statistically significant results. High or moderate quality of evidence plus statistically significant results was found in only 6.5% of all other interventions (see supplementary information).

In only 6 of 207 comparisons, the quality of evidence was high or moderate, the superiority over the control condition was statistically significant, and the Cochrane authors considered the intervention as effective. These included valproate for acute mania in mixed samples of inpatients and outpatients; eszopiclone for insomnia; cognitive behavior therapy (CBT) for adult self-harm; CBT for child and adolescent anxiety disorders; sildenafil for sexual dysfunction caused by antidepressants; and amitriptyline for depressive disorders.

For depressive disorders, anxiety disorders, post-traumatic stress disorder and self-harm, 32.0%, 28.3%, 14.8 and 10.9% of the interventions, respectively, showed high or moderate quality of evidence and statistically significant superiority over control conditions.

In sum, of all interventions evaluated for common mental disorders, less than a quarter (22.7%) were supported by high or moderate quality evidence and were statistically significantly superior to the comparator.

Our evaluation was based on the existing GRADE ratings of the Cochrane report authors, which may be considered a limitation. Errors from the Cochrane assessors cannot be excluded, but one can trust that these are probably quite accurate, as Cochrane reviews tended to have high quality in previous assessments[4].

Overall, our findings suggest that many often studied and clinically applied interventions for common mental disorders still lack robust, convincing evidence.

Falk Leichsenring[1,2], Christoph Flückiger[3], Nikolas Heim[4], Jürgen Hoyer[5], Despina Koletsi[6,7], Frank Leweke[1], Patrick Luyten[8,9], Thomas Munder[3], Christian Sell[4], Carsten Spitzer[2], Christiane Steinert[1,4], John P.A. Ioannidis[7,10-12]

[1]Department of Psychosomatics and Psychotherapy, University of Giessen, Giessen, Germany; [2]Department of Psychosomatics and Psychotherapy, University of Rostock, Rostock, Germany; [3]Department of Clinical Psychology II, University of Kassel, Kassel, Germany; [4]International Psychoanalytic University, Berlin, Germany; [5]Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany; [6]Clinic of Orthodontics and Pediatric Dentistry, University of Zurich, Zurich, Switzerland; [7]Meta-Research Innovation Center at Stanford, Stanford, CA, USA; [8]Faculty of Psychology and Educational Sciences, University of Leuven, Leuven, Belgium; [9]Research Department of Clinical, Educational and Health Psychology, University College London, London, UK; [10]Stanford Prevention Research Center, Department of Medicine, Stanford University, Stanford, CA, USA; [11]Department of Epidemiology and Population Health, Stanford University, Stanford, CA, USA; [12]Department of Biomedical Data Science, Stanford University, Stanford, CA, USA

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1. Howick J, Koletsi D, Ioannidis JPA et al. J Clin Epidemiol 2022;148:160-9.
2. Moher D, Liberati A, Tetzlaff J et al. BMJ 2009;339:b2535.
3. Howick J, Koletsi D, Pandis N et al. J Clin Epidemiol 2020;126:154-9.
4. Mustafa RA, Santesso N, Brozek J et al. J Clin Epidemiol 2013;66:736-42.

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Prevalence and predictors of sexual and physical violence during psychedelic use in a US population-based study

Psychedelics – such as psilocybin, lysergic acid diethylamide (LSD), ayahuasca, and 3,4-methylenedioxymethamphetamine (MDMA) – are psychoactive substances capable of creating profound mind-altering effects. They have gained significant public, media, research and clinical interest for their potential to enhance well-being and treat a range of physical and psychiatric conditions.

Within facilitated psychedelic services, several incidents and allegations of sexual abuse have emerged[1]. To date, only one empirical study has examined rates of violence experienced during psychedelic use. In an anonymous online convenience sample of adults who had used psychedelics, 8% reported ever experiencing or knowing someone who experienced inappropriate sexual contact by a psychedelic sitter, guide or practitioner[2].

In the US, in 2024, 9% of adults reported being followed or experiencing unwelcome physical touch or genital exposure, and 2% being forced into an unwanted sexual act in the past year[3]. However, no population-based study has examined the prevalence of sexual and physical violence during psychedelic use, or identified associated risk factors.

This study fills this critical gap by examining the prevalence of sexual and physical violence experienced during past 12-month psychedelic use in the National Survey Investigating Hallucinogenic Trends (NSIHT). Recruitment occurred between June 13 and July 28, 2025. Procedures avoided oversampling individuals who strongly advocate for or discourage psychedelic use[4].

Participants (N=1,964) were recruited from all states. Estimates were statistically adjusted to represent the US national population via calibration weighting. Demographic, health and substance use metrics were calibrated against benchmarks from probability-based federal surveys[5]. Questions on sexual and physical violence aligned with standard definitions. Further details on the questionnaire used and the statistical methods can be found in the supplementary information.

Among adults reporting any past 12-month psychedelic use, 9.8% (95% CI: 8.2-11.4) reported experiencing either physical or sexual violence while they were under the influence of a psychedelic, with 7.2% (95% CI: 5.7-8.6) reporting sexual assault, and 7.5% (95% CI: 6.0-8.9) physical violence. Some respondents declined to answer the sexual assault (6.4%, 95% CI: 5.1-7.8) or physical violence (4.9%, 95% CI: 3.7-6.0) questions. Among all participants that reported sexual assault during psychedelic use, 39.8% (95% CI: 29.7-50.0) classified their relationship with the perpetrator as "provider, facilitator, or guided leader", 36.4% (95% CI: 26.2-46.7) as "partner or someone close to me", and 33.1% (95% CI: 22.8-43.4) as "someone else" (unspecified).

For commonly used psychedelics, the percentage of adults experiencing sexual assault was 5.4% (95% CI: 2.4-8.4) during LSD use, 4.4% (95% CI: 2.2-6.6) during MDMA use, and 1.7% (95% CI: 0.7-2.7) during psilocybin use. Since the overall rate of sexual assault occurring during any psychedelic use was higher (see above), it is possible that some less commonly used psychedelics are associated with more elevated risk.

Of all potential risk factors examined, substance use disorder history was associated with the highest rates of sexual and physical violence. Participants indicating a history of cannabis, opioid or alcohol use disorder were more likely to report experiencing sexual or physical assault during past-year psychedelic use (40.9%, 35.6%, 29.7%, respectively) compared to people reporting no lifetime substance use disorder history (3.6%).

Several sociodemographic variables emerged as risk factors. Housing instability posed a notable risk: 21.9% participants with housing stability worries, and 28.3% of those with no steady place to live reported past-year sexual or physical violence during psychedelic use. Student status and younger age were also associated with heightened risk: 25.3% students and 18.8% young adults (aged 18-24 years) reported past-year physical or sexual violence, with risk of violence decreasing with age, and lowest for participants over the age of 55 years (1.7%). Race/ethnicity categories experienced differential risks: 17.3% Hispanic/Latino, 16.1% Black or African American, 15.9% Asian, 9.9% other race, and 7.5% White reported experiencing sexual assault or physical violence during past-year psychedelic use.

Adults reporting an eating disorder or attention-deficit/hyperactivity disorder (ADHD) diagnosis history also experienced high rates of sexual or physical violence during past-year psychedelic use: 20.7% of those reporting an eating disorder history and 16.3% of those reporting ADHD. Rates were lower for participants reporting a history of any anxiety disorder, major depressive disorder, or post-traumatic stress disorder: 10.1-12.5% of participants with a history of these diagnoses reported sexual or physical violence during past-year use.

Several risk factors for violence experienced during psychedelic use parallel well-known risk factors for violence more broadly: housing instability, student status, younger age, and racially minoritized groups. Results are consistent with prior research finding that psychiatric disorders increase victimization risk, but contrast patterns that link adult sexual assault most robustly with other conditions, such as post-traumatic stress disorder[6]. Instead, substance use disorders, eating disorders, and ADHD showed the strongest associations. Other findings were unexpected: socioeconomic status and gender did not emerge as risk factors in this study. Overall, these findings indicate that several known risk patterns for violence extend to psychedelic use, while also revealing certain departures from broader trends which suggest that unique precipitating factors may be present.

While media attention has highlighted risks of violence from healers/facilitators or within therapy contexts[1], our findings underscore the need for harm reduction support in recreational and unsupervised psychedelic use contexts, given that 87.4% in this general population sample endorsed recreational reasons for use, and many experienced victimization by close others or "someone else", not only by providers/facilitators/guides.

Future research with larger samples is needed, as sample sizes precluded investigation of several groups (less frequent racial categories, sexual and gender minorities, active-duty military) and intersections between factors. Future work should also examine contextual risk factors, including whether rates of violence differ across settings. Additionally, studies should examine perpetrator type with greater granularity: this study did not disaggregate provider/facilitator/guide, or separate partners from close others, and many participants reported the perpetrator falling outside these categories.

Overall, our findings suggest that a substantial proportion of people using psychedelics report experiencing sexual or physical violence while under the influence of the psychedelic, highlighting the need for further research, policy, harm reduction, and violence prevention efforts. Evidence-based prevention interventions (e.g., bystander training)[7] should be tested and implemented in high-risk psychedelic use contexts (e.g., colleges, shelters). The study also identified key sociodemographic factors (unstable housing, students, young adults, people of colour) and mental health risk factors (substance use disorders, eating disorders, ADHD) that could inform tailored harm reduction and support resources.

Documenting safety outcomes of psychedelics – which are rapidly growing in popularity in the US, Europe, Australia, and beyond[8] – in samples generalizable to the public is critical, and analogous studies should be conducted internationally. Risks with psychedelics are not exceptional, as sexual and physical violence victimization commonly involves substance use[9]. Whether psychedelics confer heightened or reduced risk relative to other substances, such as alcohol, cannabis or opioids, remains unknown. Nonetheless, the sizable proportion of participants reporting violence while under the effect of psychedelics underscores the need for safeguards and support across both supervised/therapeutic and recreational settings.

Christina Chwyl[1], Michael S. Ladka[2], Joshua C. Black[2], Karilynn M. Rockhill[2], Richard C. Dart[2,3], Jason B. Luoma[1], Andrew A. Monte[2,3]
[1]Portland Institute for Psychedelic Science, Portland, OR, USA; [2]Denver Health and Hospital Authority, Denver, CO, USA; [3]University of Colorado School of Medicine, Aurora, CO, USA

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1. Harrison TR, Faber SC, Zare M et al. Am J Bioeth 2025;25:40-55.
2. Kruger DJ, Aday JS, Fields CW et al. Psychedelic Med 2025;3:41-7.
3. Raj A, Rao N, Patel P et al. A national study of sexual harassment and assault in the United States. Newcomb Institute, Tulane University, 2024.
4. Black JC, Rockhill KM, Fox EJ et al. Ann Emerg Med 2025;86:456-62.
5. Black JC, Rockhill K, Forber A et al. J Med Internet Res 2019;21:e15830.
6. Tisseau D, Ngameni EG, Dubertret C et al. J Clin Psychiatry 2025;86:24m15631.
7. Mujal GN, Taylor ME, Fry JL et al. Trauma Violence Abuse 2021;22:381-96.
8. Lake S, Lucas P. Int J Drug Policy 2024;130:104507.
9. Basile KC, Smith SG, Liu Y et al. Drug Alcohol Depend 2021;226:108839.

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The causality problem in climate anxiety research

Research investigating negative emotional responses to climate and environmental change – referred to variably as climate anxiety, eco-anxiety, climate worry, eco-distress, and solastalgia (hereafter "climate distress") – is increasing rapidly[1]. Although these responses have been recognized as understandable reactions to real and escalating global threats, they are also frequently portrayed as risk factors for mental health problems, including clinically significant psychological distress, anxiety, depression, and post-traumatic stress disorder (PTSD)[2-4]. Several recent systematic reviews suggest that eco-anxiety is related to psychological burden[2] or that solastalgia may mediate the onset or worsening of mental health problems[4]. However, the available evidence does not support these implied causal interpretations. To understand why, I examine the methodological and conceptual challenges that currently limit causal inference in climate distress research.

The first challenge is methodological. Nearly all studies included in existing reviews are cross-sectional quantitative surveys or qualitative/mixed-methods case studies[2-4]. These designs cannot establish temporality and therefore the causal direction. What they show is between-person correlations, but they do not capture whether increases in climate distress within a person lead to subsequent changes in mental health. To evaluate the within-person change necessary for causal inference, longitudinal or experimental studies are needed, but these are scarce.

Among existing longitudinal studies, associations with later mental health are weak, often bidirectional, and highly sensitive to adjustment. For example, in New Zealand adults, higher climate concern was linked to slightly greater psychological distress one year later, but baseline distress also correlated with later concern, and the effects on life satisfaction were negligible once cross-lagged paths were modelled[5].

Similar patterns appear in youth cohorts, where associations between climate worry and later depression, anxiety or sleep largely disappear after adjustment for prior mental health and psychosocial vulnerabilities[6]. Large population panels, such as the UK Household Longitudinal Study, likewise report either weak bidirectional associations or no evidence that climate worry causes later mental health problems[7]. Several well-powered, higher-quality studies report no significant long-term associations[8].

The experimental evidence is even more limited. Existing studies typically examine short-term outcomes – such as state anxiety, hope or perceived agency – following brief informational manipulations, and none demonstrate sustained effects on generalized anxiety, depression, or other clinical outcomes.

Rather than climate distress causing mental health problems, the available evidence is more consistent with reverse causation. Individuals with pre-existing anxiety or depressive symptoms commonly exhibit heightened negative affectivity, attentional bias toward threats, and ruminative coping styles, making them more likely to respond with distress when confronted with a potential

stressor – whether a pandemic, nuclear war, or climate change.

This vulnerability pattern is well-documented in the broader research literature. Supporting this view, a recent large empirical study reports that "results point to prior distress possibly having a stronger impact on climate beliefs than beliefs have on distress"[7]. Furthermore, studies of dispositional factors, such as trait conscientiousness and antisocial behaviors, have been associated with stronger and weaker climate distress, respectively. These associations are more plausibly causal, since it is difficult to argue that low environmental concern itself produces antisocial behavior.

The second challenge that limits causal inference is conceptual. In much of the climate distress literature, the "exposure" is defined using indicators of emotional distress such as feelings of sadness, anxiety, or inability to cope – the same psychological concepts used to define mental health outcomes. When predictors and outcomes share this underlying cognitive or affective content, interpretation becomes circular, and distress appears to "cause" distress. Under these conditions, statistical mediation models are especially vulnerable to artefactual findings, because they cannot disentangle conceptually overlapping constructs.

This problem is evidenced empirically in a recent review on eco-anxiety and symptoms of major affective disorders, which notes that "stronger associations were observed where eco-anxiety was operationalized as 'anxiety' rather than 'worry'"[2]. More broadly, a synthesis of more than 200 studies shows that eco-anxiety is variably defined to encompass worry, fear, distress, anger, despair, and functional impairment, often without clear conceptual boundaries between these components[1]. This conceptual ambiguity and overlap with mental health outcomes makes it unclear whether observed associations reflect distinct processes or artefacts of measurement.

The above issues are compounded by measurement practices. Most available instruments were developed for descriptive purposes rather than causal inference, and the most widely used scales[9] – such as the Climate Change Anxiety Scale and the Hogg Eco-Anxiety Scale – combine cognitive worry (repetitive, future-oriented thought) with affective distress (fear, anxiety, sadness), behavioral responses, and, in some cases, functional impairment. Although this breadth helps reflect the complexity of climate-related emotions, it results in conceptual and empirical circularity.

Narrower measures, such as the Climate Change Worry Scale, avoid this problem by focusing on cognitive worry and affective intensity, which offers a cleaner definition of exposure. However, even these instruments lack adequate evidence of measurement invariance across age groups, cultural settings, and time, and few demonstrate sensitivity to within-person change, raising uncertainty about whether the observed differences reflect genuine psychological variation or scale artefacts.

Compounding these issues, many studies rely on single-item indicators (e.g., "How worried are you about climate change?"), use unvalidated measures, or apply them to populations for whom they have not been validated, such as children. Without clearer conceptual boundaries and measurement tools aligned with specific causal questions, observed associations between climate distress and mental health outcomes can only be interpreted as correlates or markers, not as evidence of a distinct or causally operative psychological response to perceived environmental change.

A related challenge, alluded to above, is state-trait conflation. Many studies do not distinguish transient reactions from stable dispositions in either climate worry or psychological distress. A single item such as "I am deeply concerned about climate change" can capture both short-term fluctuations (e.g., following distressing climate news) and enduring characteristics such as low emotional stability, intolerance of uncertainty, or a general tendency to worry. Likewise, symptom scales with short recall windows (e.g., "past week") may still reflect stable negative affectivity rather than situational mood. When measures of both climate distress and mental health contain substantial trait content, observed associations may primarily reflect shared vulnerability rather than a within-individual causal process in which climate distress drives later deterioration in mental health.

Taken together, current evidence does not support claims that climate distress causes mental health problems or worsens symptoms. Instead, the primary contribution of this work is documenting the extraordinary prevalence and heterogeneity of climate distress and related emotions, situating them as understandable and often morally grounded responses to profound and escalating global threats. It also helps identify a smaller subset of individuals for whom climate-related distress is persistent and functionally impairing, and who may benefit from targeted support, without treating their distress as a mental disorder or evidence of causal harm.

Given the public prominence of this topic, accurate framing matters. Even when authors caution that causality cannot be assumed, implied causal interpretations can move quickly from research literature into clinical and public discourse. In this sense, climate distress may be best understood as a signal of threat appraisal – sometimes adaptive, sometimes co-occurring with impairment – rather than evidence of harm in itself.

The central unresolved question is whether climate distress contributes to meaningful psychological harm. Addressing this issue requires research that aligns concepts, measurement, and causal design to within-person change; that clearly distinguishes cognitive concern, affective distress, and functional impairment; and that documents clinically meaningful outcomes. As climate and ecological challenges deepen, the call for clearer causal evidence will only grow.

Francis Vergunst
Department of Special Needs Education, University of Oslo, Oslo, Norway

1. Boivin M, Gousse-Lessard AS, Hamann Legris N. Cogent Ment Health 2025; 4:2490524.
2. Cosh SM, Ryan R, Fallander K et al. BMC Psychiatry 2024;24:833.
3. Boluda-Verdú I, Senent-Valero M, Casas-Escolano M et al. J Environ Psychol 2002;84:101904.
4. Sandquist AV, Biele L, Ehlert U et al. BMJ Ment Health 2025;28:e301639.
5. McBride SE, Hammond MD, Sibley CG et al. J Environ Psychol 2021;78:101713.
6. Collery A, Niedzwiedz CL. BMJ Ment Health 2025;28:e301318.
7. Helminen V, Jokela M, Elovainio M. https://doi.org/10.31235/osf.io/cn9gj_v1.
8. Major-Smith D, Halstead I, Major-Smith K. R Soc Open Sci 2025;12:251099.
9. Samarawickrama SK, Richmond S, Freeman NC et al. J Climate Change Health 2025;26:100595.

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Key aspects to consider in the design of prevention efforts for obsessive-compulsive disorder

Much has been written about the importance of targeted prevention work for obsessive-compulsive disorder (OCD), but little has been done in practice. At least two main factors are likely involved. First, we have had insufficient understanding of the risk and maintaining factors associated with OCD, and limited consideration of the ontogeny of the disorder. Second, designing (and funding) prevention studies is challenging. Here we summarize recent advances in the identification of risk factors for OCD, and discuss some key aspects to consider for the design of effective and scalable prevention strategies.

First, some progress has recently been made in the identification of risk factors for OCD. This knowledge is critical not only for the detection of individuals who are at increased risk and who may benefit from targeted prevention efforts, but also for identifying potentially modifiable factors. The most well-established risk factor is family history of OCD[1], particularly when the disorder co-occurs with tics. Other factors associated with increased risk include perinatal complications[2], high levels of repetitive behaviors in early childhood[3], subclinical obsessive-compulsive symptoms in childhood[4], childhood infections[5], bullying and violent victimization during adolescence, traumatic life events, and major life transitions such as becoming a parent. However, it is important to acknowledge that not all these risk factors are equally modifiable. For instance, genetic predisposition and perinatal events are not directly modifiable, but recognizing these factors can help identify individuals at risk and inform targeted secondary prevention efforts. On the other hand, bullying and victimization are potentially modifiable and may be more suitable for primary or early secondary prevention efforts.

Recent genetically informative studies suggest that many of the above risk factors are at least partially influenced by the genetic background of the individual. Potential mechanisms include genetic pleiotropy and evocative gene-by-environment correlations[5]. Regardless of the precise mechanisms, it is evident that early detection and, when feasible, mitigation of these risk factors in individuals with a familial risk of OCD would be desirable. To better inform prevention strategies, future studies should quantify the attributable risk or explained variance associated with these factors to gauge the potential impact of targeting each one.

It is important to differentiate among the three levels of prevention: primary (reducing risk before symptoms appear), secondary (early identification and intervention to halt progression), and tertiary (reducing the impact of established disorder). Current cognitive behavioral therapy (CBT)-based interventions that target maintaining factors – such as compulsions/safety behaviors, avoidance, family accommodation, and maladaptive appraisals of intrusive thoughts – may straddle the line between secondary and tertiary prevention. According to prevailing cognitive-behavioral models, such behaviors perpetuate OCD either by negatively reinforcing the obsessions or by preventing the disconfirmation of maladaptive beliefs. These maintaining factors are empirically supported and modifiable through evidence-based interventions[6], and represent promising targets for early intervention efforts.

A further, and perhaps most critical, component of prevention efforts is identifying optimal windows for intervention. Adopting a lifespan perspective is key. Evidence suggests at least two developmental periods during which the risk of OCD onset is particularly elevated.

The first critical period is during childhood. Repetitive behaviors and rituals are developmentally normal in young children, peaking around ages 2-4, and high levels of these behaviors are genetically linked with later OCD symptoms[3]. Subclinical OCD symptoms at age 11 have been shown to predict future OCD diagnoses in adulthood[4]. If the typical onset of childhood OCD is around age 14, a logical window for prevention or early intervention would be from ages 5 to 13. This period allows for targeting children at elevated risk before symptoms become impairing. Diagnostic delays in this group can lead to worse outcomes and increased chronicity. Therefore, increasing awareness among caregivers and primary care providers, and implementing low-intensity screening tools, may improve early detection.

A second critical period occurs in early to mid-adulthood, particularly the perinatal and postpartum periods. The incidence of OCD among new mothers has been estimated at up to 9%[7], with obsessive-compulsive symptoms also common in new fathers. The months preceding childbirth thus offer another window of opportunity. CBT-based interventions, including brief digital programs, have been shown to reduce postpartum obsessions and compulsions in at-risk individuals without full-blown OCD[8]. These results are encouraging, though larger randomized controlled trials with long-term follow-up are needed to confirm efficacy and scalability.

While most existing prevention strategies are nascent, lessons can be learned from research in other psychiatric disorders. For example, structured early intervention models developed for individuals at clinical high risk for psychosis have demonstrated promise. These models integrate symptom monitoring, psychoeducation, and low-intensity CBT, and may serve as a useful blueprint for OCD. Parallel approaches adapted to OCD risk profiles, perhaps combining digital screening and stepped-care CBT, could hold similar potential.

One final consideration concerns the design and implementation of effective prevention trials. Given the relatively low lifetime prevalence of OCD (approximately 1.3% in adults) and even lower rates in youth, prevention studies must recruit large cohorts of at-risk individuals and follow them longitudinally. The power requirements for such studies, particularly if the desired outcome is the prevention of incident OCD, rather than dimensionally measured symptom severity, are likely considerable. This presents important logistic and financial challenges. Therefore, identifying high-risk subgroups (e.g., first-degree relatives, individuals with subclinical symptoms, or those undergoing major life transitions) will be essen-

ial for enhancing statistical power.

Digital health technologies may offer a feasible, cost-effective platform for delivery. For example, brief self-guided or parent-guided online programs that target specific risk or maintaining factors could be developed[9]. These programs must be grounded in evidence, tailored to developmental stage, and designed for ease of dissemination. Involvement of people with lived experience in the design of these interventions will be critical to optimize engagement and effectiveness. Participation of health economists in early trial planning will be essential to ensure that the long-term cost savings from prevented cases can justify initial investments.

In conclusion, designing effective OCD prevention strategies will require a multifaceted approach: accurate identification of high-risk individuals; differentiation and targeting of modifiable risk and maintaining factors; attention to key developmental periods; and scalable implementation via digital technologies. Greater specificity in defining targets and methods is needed to move from theory to practice. With sustained investment and interdisciplinary collaboration, prevention of OCD may eventually shift from being a theoretical aspiration to representing a public health reality.

David Mataix-Cols[1,2], Kristina Aspvall[1], James F. Leckman[3]
[1]Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet and Stockholm Health Care Services, Stockholm, Sweden; [2]Department of Clinical Sciences, Lund University, Lund, Sweden; [3]Child Study Center, Yale University, New Haven, CT, USA

1. Mataix-Cols D, Boman M, Monzani B et al. JAMA Psychiatry 2013;70:709-17.
2. Brander G, Rydell M, Kuja-Halkola R et al. JAMA Psychiatry 2016;73:1135-44.
3. Bolton D, Rijsdijk F, Eley TC et al. J Child Psychol Psychiatry 2009;50:1139-46.
4. Fullana MA, Mataix-Cols D, Caspi A et al. Am J Psychiatry 2009;166:329-36.
5. Zhang T, Brander G, Isung J et al. Biol Psychiatry 2023;93:1023-30.
6. March JS, Mulle K. OCD in children and adolescents: a cognitive-behavioral treatment manual. New York: Guilford, 1998.
7. Fairbrother N, Collardeau F, Albert AYK et al. J Clin Psychiatry 2021;82:20m13398.
8. Timpano KR, Abramowitz JS, Mahaffey BL et al. J Psychiatr Res 2011;45:1511-7.
9. Olofsdotter Lauri K, Aspvall K, Mataix-Cols D et al. Cogn Behav Ther 2023;52:585-602.

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Towards a more inclusive psychiatry: diversity among presenters and participants in the 25th World Congress of Psychiatry

The WPA includes 147 psychiatric societies across 123 countries, and represents more than 250,000 psychiatrists globally. The WPA Action Plan 2023-2026[1-4] is grounded in the principles of the seventeen United Nations Sustainable Development Goals. Central to achieving better mental health is the promotion of equality, equity and justice across developmental stages, inclusivity, and transcultural awareness (EDIT), as well as maintaining excellence in mental health clinical practice, prevention and research.

A key step towards achieving these goals is the regular collection and analysis of data on participants and speakers at the World Congress of Psychiatry, which enables targeted initiatives and monitoring of progress over time. Data from the 24th World Congress of Psychiatry in Mexico already indicated some positive trends towards gender balance[5].

Promoting diversity in professional conferences is crucial for driving innovation, fostering inclusive discussions, and ensuring that voices from a wide range of backgrounds are represented. Conferences provide essential opportunities for sharing knowledge, collaborating across cultures, and building professional networks[6]. They also increase the visibility of clinicians and academics, supporting recognition and career development[7]. Previous research has reported that the number of conferences attended predicted post-conference publications, presentations, and research activity[8].

In this paper we contribute to these ongoing efforts by examining diversity among participants and presenters at the 25th World Congress of Psychiatry, held in Prague, Czech Republic, in 2025 with the motto "The Role of Psychiatry in the Changing World". The event was organized by the WPA with the Czech Psychiatric Association and the Slovak Psychiatric Association. Part of the scientific programme was the 21st Czech-Slovak Psychiatric Congress.

Among the 3,427 congress attendees, 54% were women, 45% men, and 0.3% identified as non-binary. Notably, 36% were below the age of 35, and 31% were early career psychiatrists, highlighting the growing engagement of younger professionals. Most attendees worked in health care settings (73%), with the remainder working in research and academia (19%), public sector (2.5%), media and industry (1%), or other settings (4.5%). Regarding caring responsibilities, 40% reported providing care – most commonly for children under the age of 18 (24%), followed by an elderly person (9%), or a person with a disability or long-term health condition (4%) – while 60% reported no caring responsibilities.

The Congress received 2,420 abstract submissions, surpassing the figures for 2024. The submitted abstracts resulted in 79 accepted symposia, 17 state-of-the-art symposia, 65 free communications, and 517 poster presentations. The program featured eight plenary sessions, eight distinguished lectures, and six specialist corner sessions.

Women were more represented than men as presenters in presidential panels (67%), panel discussions (67%), distinguished lectures (63%), original sessions (60%), and free communication sessions (56%). Men were the majority of presenters in the three meet-the-expert sessions (80%), followed by the inter-organizational session, in which each organization nominated its own representative (70%), continuing medical education (CME) courses (67%), specialist corner sessions (65%), state-of-the-art symposia (61%), accepted symposia (58%), and plenary/presidential sessions (56%). They were slightly more than half in the Czech/Slovak track sessions (53%).

Gendered patterns were observed in the thematic content of presentations. Women presenters were more common in sessions focusing on personality and behavioral disorders (64%), perinatal and gender-related topics (63%), and neurodevelopmental and childhood disorders (54%), while men presenters predominated in topics such as neurocognitive disorders and ageing (100%), clinical practice and treatment (71%), severe mental illness (63%), and research, neuroscience and genetics (60%). These patterns mirror broader trends observed in other disciplines, where women have been reported to deliver proportionally more non-biomedical presentations (57%), whereas men deliver more biomedical ones (61%)[9].

When considering speakers' countries of origin across session types, as classified by World Bank income groups, 77% of speakers were from high-income, 11% from upper-middle-income, 12% from lower-middle-income, and fewer than 1% from low-income countries, highlighting the ongoing need to address systemic barriers to global participation. A previous systematic review identified the main barriers faced by attendees from low- and middle-income countries, including high travel costs, visa restrictions, and lower acceptance rates for congress submissions[10]. Addressing these challenges is essential to achieving the WPA's vision of global collaboration.

Notably, a total of 42% of the speakers in the original sessions, specifically designed for early career psychiatrists, were from non-high-income countries. These sessions include a range of innovative and interactive formats, such as clinical case discussions, the WPA 3-min competition and the WPA quiz. This diversity of participants fosters inclusivity, cross-cultural learning, and the exchange of ideas across different contexts and health systems.

When analyzing country of origin by topic, speakers from high-income countries predominated in sessions addressing personality and behavioral disorders (78%); mood, anxiety and stress disorders (70%), society, culture and human rights (67%), severe mental illness (60%), and clinical practice and treatment (56%). In contrast, there was a greater representation from non-high-income countries in sessions on health systems and service delivery (83%), and on physical health and comorbidities (67%). Previous research has shown that mental health research priorities in low- and middle-income countries include health systems, social science, burden and risk factors[11].

The 25th World Congress of Psychiatry reflects the ongoing efforts and continued progress in the WPA's commitment to systematically collect, analyze and report diversity data, moving beyond gender to encompass socioeconomic and geographic inclusion. The WPA has taken a leading role in systematically collecting and reporting diversity data across congresses, contributing to transparency and actionable benchmarking in global psychiatry. Publishing this paper represents a further step in that process, contributing to the dissemination of evidence and good practice across the field.

Promoting representation across countries and professional stages enriches dialogue, improves cultural understanding, and strengthens the global mental health community. By continuing to systematically collect and report diversity data of participants and speakers, future WPA congresses can track progress, identify gaps, and guide policies that advance equity, justice, inclusivity, and transcultural collaboration in global psychiatry.

The 26th World Congress of Psychiatry will be held in Stockholm, Sweden on September 23-26, 2026, with the motto "Guided by Compassion, Grounded in Science: Psychiatry for our Time".

Mariana Pinto da Costa[1,2], Jozef Dragasek[3], Miriam Iosue[4], Tomas Kasparek[5], Pavel Mohr[6,7], Manase Nyametie[1,8], Harry Wiffen[1,9], Danuta Wasserman[4,10]

[1]Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [2]School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal; [3]First Department of Psychiatry, Faculty of Medicine, P. J. Safarik University and L. Pasteur University Hospital, Kosice, Slovakia; [4]Karolinska Institutet, Stockholm, Sweden; [5]Department of Psychiatry, Faculty of Medicine, Masaryk University and University Hospital Brno, Brno, Czech Republic; [6]National Institute of Mental Health, Klecany, Czech Republic; [7]Third Faculty of Medicine, Charles University, Prague, Czech Republic; [8]Royal Holloway, University of London, London, UK; [9]Sunshine Coast Hospital and Health Service, Birtinya, QLD, Australia; [10]President, World Psychiatric Association

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1. Wasserman D. World Psychiatry 2024;23:165-6.
2. Wasserman D. World Psychiatry 2024;23:302-3.
3. Wasserman D, Iosue M, Petros NG et al. World Psychiatry 2025;24:284-5.
4. Wasserman D, Iosue M, Avan A et al. World Psychiatry 2025;24:452-3.
5. Pinto da Costa M, Ng B, Sanchez T et al. World Psychiatry 2025;24:291-2.
6. Corona-Sobrino C, Garcia-Melon M, Poveda-Bautista R et al. PLoS One 2020; 15:e0243549.
7. Smiljanic J, Chatterjee A, Kauppinen T et al. PLoS One 2016;11:e0148528.
8. Katerndahl DA. Fam Med 2000;32:701-8.
9. Koop MA, Benson AC, Reneman MF et al. Scand J Pain 2023;23:767-73.
10. Velin L, Lartigue JW, Johnson SA et al. BMJ Glob Health 2021;6:e003455.
11. Sharan P, Gallo C, Gureje O et al. Br J Psychiatry 2009;195:354-63.

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Strengthening the global mental health workforce through collaborative education

Mental health needs are increasing globally, driven by demographic change, economic and social inequalities, climate-related stressors, conflict, and forced displacement[1]. These trends have highlighted a persistent mismatch between population mental health needs and the capacity of existing services, particularly for children, adolescents and other vulnerable groups. Meanwhile, positive developments such as greater connectivity and accessibility through improved information technology and effective adult education approaches, more accessible scientific publications and international collaboration, and an enhanced global presence of organizations such as the WPA and the World Health Organization (WHO) offer greater capacities for bridging the mismatch. Going forward, strengthening the mental health workforce requires sustained investment across the full range of mental health professionals, including psychiatrists and allied and non-specialist providers with core competencies in mental, neurological and substance use (MNS) care.

The *Blueprint for Advancing Psychiatric Education and Scientific Publications*, developed by the WPA through its Committee on Education and Scientific Publications, positions education and training as a central mechanism for sustaining mental health systems in an increasingly complex global context[2]. The *Blueprint* highlights the rising demand for care, as well as the limited resources, which necessitate renewed attention to how psychiatric knowledge, skills, and professional values are developed and maintained across disciplines and regions[2]. Education is presented not as a peripheral activity, but as a central, strategic function underpinning service quality, equity, and system resilience.

A core contribution of the *Blueprint* is its emphasis on coordinated, sustainable and inclusive approaches to psychiatric education. The document calls for a shift away from fragmented educational and training initiatives towards structured educational frameworks that align undergraduate, postgraduate, and continuing professional education with population needs. A key recommendation is for increased collaboration between professional associations, academic institutions, and global health organizations, to assure consistency, scalability, and long-term impact of these efforts.

In this broader context, the long-standing collaboration between the WPA and the WHO has played an important role in advancing education and training in mental health, particularly with respect to pre-service education. Since 2018, these organizations have worked jointly to strengthen pre-service education through a series of international consultations held in Prague, Mexico City, and Geneva. These consultations brought together educators, policy makers, clinicians and researchers to examine how evidence-based WHO tools and approaches, including the WHO Mental Health Gap Action Programme (mhGAP) resources and tools, can be systematically integrated into undergraduate medical and nursing curricula, around the world.

In the 2020, the WHO published *Enhancing Mental Health Pre-*

Service Training with the mhGAP Intervention Guide: Experiences and Lessons Learned[3]. The document included early international experience with integrating mhGAP principles into pre-service education. It demonstrated that such integration is feasible across diverse educational and health-system contexts. This experience has helped establish a shared conceptual and practical foundation for strengthening pre-service education as a sustainable approach to workforce development.

Drawing on this experience, as well as subsequent research, policy developments, and extensive global consultations, the WHO published in 2025 *Educating Medical and Nursing Students to Provide Mental Health, Neurological and Substance Use Care: A Practical Guide for Pre-Service Education*[4]. This guide represents a comprehensive, global framework for pre-service education in MNS care. It moves decisively beyond earlier guidance by offering a fully articulated, competency-based approach that defines twelve core competencies encompassing knowledge, clinical skills, and professional attitudes. The guide provides detailed, practical directions for curriculum design, teaching and learning methods, assessment strategies, and faculty development, as well as monitoring and evaluation. The *Guide* explicitly supports adaptation to national priorities, health-system capacities, and accreditation requirements. As such, it offers a robust, scalable, and action-oriented foundation for strengthening pre-service education[5].

WPA experts contributed throughout the development, consultation and review phases of the 2025 *Guide*, helping ensure broad, cross-region alignment with psychiatric education standards, ethical principles, and clinical training realities. The WPA aims to support dissemination and implementation of the *Guide* and its principles through its global network of Member Societies, academic partners, and educational platforms. The relevance of this collaborative work was further highlighted at the 2025 World Congress of Psychiatry in Prague, where the WPA and WHO jointly convened a Presidential Panel focused on advancing pre-service education for MNS care. The session offered an opportunity to discuss the new guide, share regional experiences, and reflect on practical challenges and opportunities for implementation.

Challenges in mental health care are unlikely to diminish. Workforce shortages, humanitarian crises, and rising demand for care represent enduring structural pressures rather than temporary disruptions. Addressing these challenges requires sustained alignment between global guidance, professional leadership, and local implementation. Continued collaboration between the WPA, the WHO, academic institutions, and national professional societies is essential. Joint efforts are needed to support contextual adaptation of global frameworks, strengthen educator capacity, share excellent training materials, and evaluate the impact of educational reforms on workforce readiness and service delivery[6].

Through coordinated and collaborative action, meaningful progress can be made in our shared commitment to strengthen global mental health by expanding a well-trained and well-prepared workforce.

Norbert Skokauskas[1,2], Brandon Gray[3], Gary Chaimowitz[4,5], Dina Aly El-Gabry[5-7], Andrea Fiorillo[5,8], Anusha Lachman[5,9], Angeles Lopez Geist[5,10], Paul Robertson[5,11], Hee Jeong Yoo[5,12], Bennett L. Leventhal[5,13]

[1]WPA Secretary for Education and Scientific Publications; [2]Norwegian University of Science and Technology, Trondheim, Norway; [3]World Health Organization, Geneva, Switzerland; [4]McMaster University, Hamilton, ON, Canada; [5]WPA Committee on Education and Scientific Publications; [6]Ain Shams University, Cairo, Egypt; [7]United Arab Emirates University, Al Ain, United Arab Emirates; [8]University of Campania "L.Vanvitelli", Naples, Italy; [9]Stellenbosch University, Stellenbosch, South Africa; [10]Association of Argentinian Psychiatrists, Buenos Aires, Argentina; [11]University of Melbourne, Melbourne, Australia; [12]Seoul National University, Seoul, South Korea; [13]University of Chicago, Chicago, IL, USA

1. Goto R, Pinchuk I, Okubo Y et al. World Psychiatry 2025;24:142-4.
2. Skokauskas N, Chaimowitz G, El-Gabry D et al. World Psychiatry 2024;23:304-6.
3. World Health Organization. Enhancing mental health pre-service training with the mhGAP Intervention Guide: experiences and lessons learned. Geneva: World Health Organization, 2020.
4. World Health Organization. Educating medical and nursing students to provide mental health, neurological and substance use care: a practical guide for pre-service education. Geneva: World Health Organization, 2025.
5. Kramer S, Gray B, Saxena S et al. World Psychiatry 2025;24:273-4.
6. Skokauskas N, Chaimowitz G, El-Gabry DA et al. World Psychiatry 2025;24: 453-4.

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WPA Scientific Sections: an update

This report provides an overview of the current status, significant achievements, and forward-looking strategic vision of the WPA Scientific Sections. The latest year has been marked by substantial progress, most visibly demonstrated during the highly productive sessions at the World Congress of Psychiatry held in Prague in October 2025.

The Sections firmly stand as the indispensable engine for global psychiatric collaboration, uniquely positioned to drive deep specialization, foster ground-breaking innovation, and facilitate critical knowledge exchange that reaches every corner of the world.

The momentum from our recent governance reforms[1,2] was powerfully evident at the Prague World Congress, where the network's vitality was on full display. Sections successfully organized and delivered 17 state-of-the-art symposia, showcasing cutting-edge research, and held 15 dedicated Section meetings to advance internal planning and collaboration.

A critical strategic dialogue was convened at the Congress on October 7, bringing together the WPA Scientific Sections Standing Committee with the Chairs, Co-Chairs and Secretaries of the Sections. This meeting served as a vital platform for organizational alignment, where 31 Sections presented reports on their activities, and constructive discussions were held on a range of operational and strategic issues essential for our collective advancement.

A paramount and defining strength of our network is its exceptional and truly global reach. We now have verified representation from over 70 countries, comprehensively spanning all continents.

This remarkable geographic diversity is fostering a richer, more dynamic intellectual environment, reflected in an increasingly international and younger membership base. Of particular note is the strong and growing participation by professionals in low- and middle-income countries, ensuring that the global discourse in psychiatry is inclusive and representative.

This diversity directly fuels our scientific excellence. The Sections collectively maintain an outstanding output of more than 135 peer-reviewed publications annually. Our contributions extend beyond volume, making significant contributions in high-impact journals, informing global treatment guidelines, and pioneering novel research in crucial areas such as refined risk assessment methodologies and next-generation therapeutic innovations. Papers recently published in *World Psychiatry*, the official WPA journal, are exemplary of this scientific input[3-15].

Educational leadership remains a cornerstone of our global impact. Our initiatives are designed for maximum reach and relevance: high-demand pre-congress courses consistently reach full capacity; our monthly global webinar series regularly engages over 400 participants worldwide, breaking down geographical barriers to learning; and we maintain a steadfast commitment through dedicated capacity-building programs aimed at strengthening psychiatric resources in underserved settings.

Our Section on Digital Mental Health exemplifies our forward-looking agenda, serving as a central hub for innovation. It is at the forefront of developing ethical frameworks for artificial intelligence in clinical practice, creating digital platforms for crisis intervention, and mastering the logistics of large-scale virtual engagement, thereby setting a standard for the future of psychiatric collaboration.

The character of our work is increasingly defined by purposeful and strategic partnerships. We have cultivated strong, productive alliances with leading international institutions and psychiatric bodies, amplifying our reach and influence. Our current innovation priorities are acutely focused on the most pressing contemporary global challenges: understanding and mitigating the mental health impacts of climate change; guiding the ethical integration of transformative technologies into patient care; developing concrete strategies to advance global health equity; and enhancing our collective capability to respond to trauma and conflicts worldwide.

Moving forward with the momentum generated in 2025, our immediate operational priorities are clear and actionable. We must collectively complete the optimization of our digital presence by ensuring that all Section profiles on the WPA website are updated to a high standard, and that all Sections fully implement the new governance protocols regarding leadership compliance, and develop a systematic, user-friendly framework to catalyze and support future inter-sectional collaboration.

Our long-term strategic vision is ambitious: to solidify the network's undisputed role as a global leader by leveraging technology as a central system for collaboration, significantly expanding practical support for our colleagues in developing regions, coordinating large-scale, cross-sectional research initiatives to tackle multifactorial challenges, and deepening our formal policy influence with paramount organizations such as the World Health Organization.

Our performance metrics consistently confirm a strong and positive trajectory, characterized by high-attendance events, a growing portfolio of influential publications, key international partnerships, and a responsible move towards more sustainable, self-financing operational models.

The WPA Scientific Sections have proven to be a model of professional and scientific excellence. By continuing to pursue our strategic priorities with focused determination and unified purpose, we are not merely adapting to the evolving landscape of global mental health – we are positioned to actively shape it. With continued focus and unity, we will ensure that this network remains at the forefront of advancing mental health worldwide for generations to come.

Armen Soghoyan
WPA Secretary for Scientific Sections

1. Soghoyan A. World Psychiatry 2024;23:306-7.
2. Soghoyan A. World Psychiatry 2025;24:454-5.
3. Keren M, Apter G. World Psychiatry 2024;23:168-9.
4. Fineberg NA, Stein DJ, Domschke K et al. World Psychiatry 2024;23:457-7.
5. Elkholy H, Bhad R, Ekhtiari H et al. World Psychiatry 2024;23:459-60.
6. Perna G, Caldirola D, Schatzberg AF et al. World Psychiatry 2024;23:460-1.
7. Wichniak A, Dikeos D, Mikoteit T et al. World Psychiatry 2025;24:148-9.
8. Mulder R, Kim Y-R, Tyrer P. World Psychiatry 2025;24:149-50.
9. Christodoulou N, Karpenko O. World Psychiatry 2025;24:150-1.
10. Karam EG, Keyes KM. World Psychiatry 2025;24:286-7.
11. Gaebel W, Salveridou-Hof E, Srinivasaraghavan J et al. World Psychiatry 2025; 24:288.
12. Baron D, Koh E, Ramalho R et al. World Psychiatry 2025;24:289-90.
13. Kato TA, Sartorius N, Volpe U et al. World Psychiatry 2025;24:290-1.
14. Heilbronner U, Rietschel M, Schulze TG et al. World Psychiatry 2025;24:455-6.
15. Abed R, Swanepoel A, O'Connell H. World Psychiatry 2025;24:456-7.

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Recent progress in the promotion and protection of human rights of older persons

The world's population over age 60 years, estimated to be 1 billion in the year 2020, is projected to reach 2.1 billion by 2050[1]. Of these, 20% are estimated to have a mental health condition, and 60% reside in low- and middle-income countries, where the challenging living circumstances elevate the risk of human rights violations[2].

Despite increasing awareness, older persons continue to face multiple barriers to mental health care: denial, fear, lack of knowl-

edge, normalization of symptoms, desire to maintain independence, and absence of support networks. Most critical among these is stigma, in the form of ageism, mentalism and ableism, three overlapping forces that constitute a profound violation of human rights.

The 1948 Universal Declaration of Human Rights[3], a landmark achievement, failed to anticipate today's demographic realities. When it was adopted, global life expectancy was only 43 years[4]. In 2024, it is nearly 74 years. This stark shift has made the lack of specific protections for older persons more pressing. To address this, the international community has made notable progress in recent years.

The Madrid International Plan of Action on Ageing called for comprehensive mental health care for older persons, spanning prevention to treatment. This led to the establishment of the Open-Ended Working Group on Ageing (OEWGA) by the United Nations (UN) General Assembly in 2010 to assess protection gaps in the human rights of older persons. In 2024, the OEWGA concluded its work and adopted the Decision 14/1, recommending the creation of an international legally binding instrument to promote and protect the rights of older persons[5]. On March 28, 2025, during the 58th session of the Human Rights Council, this recommendation was advanced with the establishment of an intergovernmental working group to draft a new UN Convention on the Rights of Older Persons.

Comparable progress has occurred in the mental health domain. In 2023, the UN Human Rights Council passed the Resolution 52/12, calling for a human rights-based approach to mental health[6]. The resulting report, published in January 2025, emphasized dignity, autonomy, and the need to end coercive practices in mental health systems. It called for coherence across global efforts and integration of human rights into mental health frameworks.

In April 2025, the World Health Organization published its Guidance on Mental Health Policy and Strategic Action Plans[7], articulating five reform areas aligned with international rights standards. The document recognizes the need for policies that are person-centred, recovery-oriented, and grounded in respect for autonomy and dignity. It also includes special considerations for diverse groups, including older adults.

In response to these global advances, national and civil society actors have begun operationalizing human rights principles in mental health care for older persons. One noteworthy example is from Canada, where the Canadian Coalition Against Ageism (CCAA) and the International Longevity Centre Canada (ILC Canada) have emerged as leaders in embedding dignity and rights into care systems. Their recent national forum called for systemic reforms to eliminate ageism through intergenerational strategies, policy change, and public education. This work explicitly positions older persons not as passive recipients of care, but as active rights-holders and contributors to society.

Building on these efforts, the CCAA and ILC Canada have proposed a Five-Pillar Framework for Dignity and Rights-Based Care[8]. This approach supports science- and evidence-based practices, a person-centred model of care, a Prism lens to address intersecting forms of discrimination, a human rights foundation, and accountability across all levels of care. This framework is both pragmatic and ethical, aiming to safeguard older persons' rights and promote holistic well-being. It also proposes the formation of a Global Alliance for Dignity and Rights-Based Care, bringing together stakeholders to promote international standards, knowledge sharing, and shared accountability.

These developments reaffirm that dignity must no longer be treated as an abstract principle, but as an actionable foundation for health and social care[9]. A growing body of literature has sought to define and operationalize dignity, including identity, autonomy, relational behavior, and structural inclusion. In mental health care, dignity is closely tied to ethical practice, quality of life, and legal protections, particularly in the context of reduced autonomy due to conditions such as dementia or psychosocial disabilities. Upholding dignity is essential to countering systemic exclusion and fostering positive clinical outcomes[10].

While the Convention on the Rights of Persons with Disabilities offers indirect protections, it does not address the full spectrum of mental health and aging-related concerns. A new UN Convention would fill this gap. However, progress depends on political will, sustained advocacy, and the active involvement of older persons and their representative organizations.

To advance this vision, national governments and multilateral institutions must prioritize mental health as a distinct and essential component of aging policy. Health systems must adapt to address older persons' unique needs through appropriate training, trauma-informed and culturally sensitive care, and integrated service delivery. Human rights protections must be expanded beyond legal declarations to everyday practices in mental health and long-term care systems. This is particularly urgent given the disproportionate impacts of the COVID-19 pandemic on older adults, where failures in rights protection became tragically visible.

The convergence of global momentum – the UN Decade of Healthy Ageing, the Madrid International Plan of Action on Ageing, the Resolution 52/12, and the OEWGA's final report – provides a critical opportunity. If seized, it could catalyze meaningful change. Dignity-centered, human rights-based care must become the new norm, not only to ensure ethical standards but to build inclusive societies where all people, regardless of age or ability, can thrive. As our global population continues to age, protecting the mental health and rights of older persons is not just a policy imperative. It is a moral one.

Carlos Augusto de Mendonça Lima[1], Kiran Rabheru[2,3]
[1]WPA Section of Old Age Psychiatry; [2]Bruyère Health Research Institute and Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada; [3]International Longevity Centre Canada, Ottawa, ON, Canada

1. United Nations Department of Economic and Social Affairs, Population Division. World population ageing 2020 highlights. www.un.org.
2. World Health Organization. Mental health of older adults. www.who.int.
3. United Nations. Universal declaration of human rights. www.un.org/en.
4. Worldometer. Life expectancy of the world population. www.worldometers.info.
5. United Nations. Political declaration and Madrid international plan of action on ageing. https://social.un.org.
6. United Nations Human Rights Council. Mental health and human rights, Reso-

lution 52/12. New York: United Nations, 2023.
7. World Health Organization. Guidance on mental health policy and strategic action plans. www.who.int.
8. de Mendonça Lima CA, Rabheru K. Acad Ment Health Well-Being 2025;2.
9. Banerjee D, Rabheru K, Ivbijaro G et al. Front Psychiatry 2021;12:774533.
10. Galderisi S, Appelbaum PS, Gill N et al. World Psychiatry 2024;23:364-86.

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The new German evidence- and consensus-based schizophrenia guideline

The German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN) has just published its revised guideline on schizophrenia. For the first time, this is a living guideline, included in MAGICapp (Making GRADE the Irresistible Choice)[1], a digital browser-based platform that allows to develop, publish and continuously update living guidelines.

Advantages of this platform include the consistency in evaluating evidence according to GRADE (Grading of Recommendations, Assessment, Development and Evaluation), the graphical depiction of the evidence, the possibility to develop shared decision-making tools, and the chance to make all steps of guideline development transparent[2,3]. We implemented a flexible evidence-to-decision framework focusing on the questions of interests, the quality of evidence, the risk-benefit ratios, values and preferences of patients, resource consumption, feasibility and barriers to implementation, and possible inequalities within the health care system.

Among the 444 guidelines published in MAGICapp, this is the first one addressing schizophrenia. The guideline group included members of 41 professional associations (including two associations of people with lived experience), six experts, and the four authors of this report, who led the process. A comprehensive evaluation of financial and non-financial conflicts of interests was performed, and they were rated by two independent experts. Delegates of the societies who had a conflict of interests for a given recommendation had to abstain from voting.

The transformation from a conventional to a digital living guideline was prepared from 2021 to 2023, funded by the German Federal Joint Committee[2]. The revision process started in 2023. After two years, the new guideline, that from now on will be updated in a living cycle at least every year, was ready. It includes 154 recommendations for the diagnosis and treatment of schizophrenia and four general statements. The document is freely available on the website of the Association of the Scientific Medical Societies in Germany (www.awmf.org), as a long (in German) and short (in German and English) version, and as a living guideline in MAGICapp (https://app.magicapp.org/#/guideline/jlYvkL).

The structure of the guideline is based on the 2019 published version, with Module 1 (General principles of the management of schizophrenia); Module 2 (Diagnostics, including ICD-11, and differential diagnoses, including autoimmune psychoses and rare diseases); Module 3 (Treatment in general); Module 4a (Pharmacotherapy, electroconvulsive therapy, transcranial magnetic stimulation, management of side effects); Module 4b (Psychotherapy and psychosocial care); Module 4c (Special circumstances, such as first episode, depression; post-traumatic stress disorder, PTSD; catatonia, aggression, at-risk stage, childhood and adolescence, the elderly, pregnancy and breast-feeding, gender aspects); Module 4d (Medical, social and occupational interventions, such as supported education or employment and rehabilitation); Module 5 (System-relevant interventions and integrated cooperation of all service providers); Module 6 (Cost-effectiveness); and Module 7 (Quality management)[4].

All recommendations of the 2019 published version were reviewed and updated, or replaced where necessary. As in 2019, the guideline recommends a comprehensive differential diagnostic process, and the monitoring and improvement of physical health of people with schizophrenia. Moreover, the guideline still highlights the combination of a continuous antipsychotic treatment with cognitive-behavioral therapy (CBT) as the gold standard. The following recommendations, highlighted in our 2020 report in this journal[4], remained unchanged or were adapted in some detail:

- to offer regular monitoring of physical health to all persons with schizophrenia;
- to evaluate and classify symptoms suggesting typical medical comorbidities in every patient with schizophrenia;
- to offer magnetic resonance imaging (MRI) to every person with first-episode schizophrenia, and to consider cerebrospinal fluid investigations if the course of disorder, the symptomatic presentation, or MRI or laboratory measures point towards a secondary psychosis;
- to offer acute and maintenance antipsychotic drug treatment using the lowest possible dosage to every person with schizophrenia;
- to select an antipsychotic drug mainly based on the side effect profile;
- to work out the duration of maintenance treatment on an individual basis, offering the possibility of an early discontinuation (e.g., to reduce side effect burden), but also of a long-lasting treatment in every disease stage (to reduce the relapse risk) (the guideline group decided that this issue will be further reviewed);
- to offer electroconvulsive therapy in cases of catatonia or ultra-treatment resistance;
- to offer psychosocial interventions, exercise interventions and/or metformin (for weight gain);
- to offer CBT, psychoeducation, cognitive remediation and family interventions to every person with schizophrenia;
- to develop crisis plans and advance treatment arrangements to avoid compulsory admissions;

- to offer primarily CBT rather than antipsychotic drugs to persons at risk for developing psychosis (the group decided to reduce the strength of this recommendation).

In Module 4a, the most important change was that we weakened the recommendation for antipsychotic monotherapy and we defined conditions for the use of combination treatment (e.g., when clozapine treatment is not feasible; to treat different symptom domains; to reduce prolactin levels). Moreover, the side effect chapter was significantly extended and includes now myocarditis screening and new blood-monitoring rules for clozapine.

Major changes were made to Module 4b, where four new recommendations were added:

- digital interventions such as avatar therapy (weak recommendation) as part of a holistic treatment approach;
- mindfulness-based interventions (strong recommendation) for the improvement of positive symptoms;
- acceptance and commitment therapy (consensus recommendation) as add-on treatment;
- eye movement desensitization and reprocessing (EMDR) or prolonged exposure (weak recommendation) for people with schizophrenia and PTSD.

Moreover, we increased the strength of recommendation for metacognitive training and systemic psychotherapy. We strengthened the recommendation for psychoeducation including families (strong recommendation) compared to bifocal psychoeducation (weak recommendation). Exercise interventions were also moved to a strong recommendation grade.

The chapter on schizophrenia in the elderly remained unchanged, as in this area still only limited evidence is available and new research reports could not be identified. The same applied for children and adolescence with schizophrenia. However, due to the clinical importance and the large body of evidence from adults, we decided to strengthen the clozapine recommendation for treatment resistance in people with schizophrenia <18 years (strong recommendation).

Compared to the UK National Institute for Health and Care Excellence (NICE) guidelines (2014, last reviewed in 2025 with no changes) and the American Psychiatric Association (APA) guidelines (2020), our new living guideline provides more clinically relevant details regarding the use of pharmacological, psychotherapeutic and other interventions, and is the first guideline in the field that has been fully developed within the evidence-ecosystem MAGICapp.

The latest version of this guideline has been the basis for the European Psychiatric Association guidance on pharmacological treatment of schizophrenia[5]. The English version of this guideline has the potential to be used by many other organizations which do not have the resources to produce a complete *de novo* guideline.

Alkomiet Hasan[1,2], Peter Falkai[2-5], Stefan Leucht[2,6], Wolfgang Gaebel[4,7,8]

[1]Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, University of Augsburg, Augsburg, Germany; [2]German Center for Mental Health, partner site Munich-Augsburg, Augsburg, Germany; [3]Department of Psychiatry and Psychotherapy, LMU University Hospital Munich, Munich, Germany; [4]WPA Section on Schizophrenia; [5]Max Planck Institute of Psychiatry, Munich, Germany; [6]Department of Psychiatry and Psychotherapy, School of Medicine and Health, Technical University of Munich, Munich, Germany; [7]LVR-Klinikum Düsseldorf, Heinrich-Heine-University, Medical Faculty, Düsseldorf, Germany; [8]WHO Collaborating Centre on Quality Assurance and Empowerment in Mental Health, Düsseldorf, Germany

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1. Association of the Scientific Medical Societies in Germany (AWMF). S3-Leitlinie Schizophrenie (living). https://register.awmf.org/de/leitlinien/detail/038-009.
2. Lorenz C, Gaigl G, Guler D et al. Trials 2022;23:807.
3. Pielenz C, Schneider M, Salveridou-Hof E et al. Z Evid Fortbild Qual Gesundhwes 2022;174:20-31.
4. Gaebel W, Falkai P, Hasan A. World Psychiatry 2020;19:117-9.
5. Falkai P, Wagner E, John M et al. Eur Psychiatry 2025;68:e26.

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