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World Psychiatry

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1. Cuijpers P, Sijbrandij M, Koole SL et al. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. World Psychiatry 2014;13: 56-67.
2. McRae TW. The impact of computers on accounting. London: Wiley, 1964.
3. Fraeijs de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). Stress analysis. London: Wiley, 1965:145-97.

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Understanding depression beyond the "mind-body" dichotomy

In both the ICD-11 and the DSM-5, the core symptoms of depression are reported to be depressed mood (e.g., feeling sad, down or hopeless) and markedly diminished interest or pleasure in activities. However, in the ICD-10 diagnostic guidelines, a third core symptom was also identified: "fatigue or low energy". In two regions of the world (Latin America and East Asia), "fatigue" is the most commonly experienced depressive symptom[1]. In a third region (Southeast Asia), "issues with the heart" are the most commonly reported depressive symptoms, along with depressed mood[1]. Do people in these regions just "somatize" what is primarily a "psychological" experience? Do "somatic" symptoms just represent a "mask", as implied some decades ago by the concept of "masked depression"[2]?

An alternative view may be that the core of the depressive syndrome, at least in part of the cases of this heterogeneous condition, is neither only "psychic" nor only "somatic", but consists of an actual "depression" of the individual's psychic/physical tone, energy, drive and/or response to rewarding stimuli (partially captured by the constructs of depressed mood, fatigue, and diminished interest or pleasure), along with an overwhelming feeling of psychic/physical pain (which has a complex and probably variable relationship to the cognitive component of the syndrome). The way these core phenomena are perceived, elaborated and verbalized by the affected person likely depends upon how that person generally functions and appraises her functioning (e.g., how rich and articulated her cognitive life is, or how much she is focused on her body and its functioning), upon the influence of the cultural environment in which she is immersed, and upon the pattern of predisposing and precipitating factors at work in that individual case.

Feelings involving the heart ("heavy heart", "heart pain"; chest tightness, weakness or excessive tension; palpitations) do not appear in textbook descriptions of depression, but are more frequently experienced by depressed individuals than we use to believe[1]. Ordinary people sometimes refer to depression as "broken heart", and we tend to regard this as a metaphor. But, the acute "broken heart syndrome" – which has the same precipitating factors as depression and, similarly to the heart involvement in depression, is ascribed to a sympathetic overactivation – is now a recognized clinical entity[3]. An intrinsic cardiac nervous system ("a brain in the heart") has been recently described[4], including a multitude of nervous ganglions consisting not only of neurons receiving sympathetic and parasympathetic input, but also of intracardiac interneurons which act as processors of information. Indeed, the heart conveys to the brain more information than the brain sends to the heart, and ascending fibres in the vagus nerve are more numerous than descending ones. Could the above dynamics be an under-recognized factor contributing to the frequent coexistence ("comorbidity") and complex interaction between depression and heart disease?

That many patients with a diagnosis of depression do not respond adequately to two subsequent antidepressant medications ("treatment resistance") is not surprising. Clinical trials of both medications and psychotherapies for depression have aimed during the past few decades to document the "equivalence" of any new experimental intervention to an already consolidated one, while "differences" in the profiles of action of those interventions have usually not been a focus of attention. Consequently, antidepressants and evidence-based psychotherapies for depression are regarded by treatment guidelines as essentially all "equivalent" to each other. It is only recently that secondary analyses of large trial databases, conducted using innovative methodologies, have started to focus again on the "differences" between the various antidepressants, and between antidepressants and evidence-based psychotherapies, with respect to their profiles of action[5,6]. On the other hand, it is not common in ordinary practice that a patient with a diagnosis of depression receives a detailed clinical characterization beyond that diagnosis, guiding the choice of treatment. It is therefore understandable that a person may receive two or more antidepressants that, although validated for depression *tout court*, are not among the most appropriate for her specific case, and consequently may not elicit an adequate response. Furthermore, medications do not work in a *vacuum*: a variety of "aspecific" factors (e.g., the therapeutic relationship, family dynamics, the socio-cultural context) may affect the outcome of an intrinsically efficacious intervention. The concept of "pseudo-resistance" does not adequately consider at the moment these factors (not to mention problems with the definition of what is an "adequate response" to an antidepressant, difficulties in ascertaining the adherence to the antidepressant regimens that have been used, and the basic incongruence of defining a case as "treatment-resistant" when one group of therapies currently regarded as first-line in the treatment of depression, i.e. psychotherapies, have not been tried).

In this issue of the journal, two papers and a Forum deal, respectively, with the lived experience of depression[7], with its multiple "physical comorbidities"[8], and (in a critical vein) with "treatment-resistant depression" and its management[9]. I think these contributions should be welcome by the scientific community, by people with depression and their families, and by the public at large.

A "depression" of the individual's psychic/physical tone, energy, drive and/or response to rewarding stimuli may be the outcome of repeated and inescapable adverse events, but also of a disruption of circadian rhythms, a non-psychiatric disease, or the use of certain medications. Or it may occur in the absence of any such evidence as far as the person is aware of, as often happens in bipolar disorder. Perhaps research should more actively focus on those core phenomena, building on the reports of experts by experience and exploring their biological correlates, without any prejudice about whether they are primarily or essentially psychic or physical in nature.

The effects of the various antidepressant medications could perhaps be explored – beyond current stereotypes – in the same

light (are they psychophysical "tonics"?; do they have energizing or disinhibiting properties?; do they affect reward responsiveness?; do they impact psychic/physical pain?), through a more in-depth and nuanced reconstruction of patients' experiences of "response" to those agents, and a more targeted investigation of their biological correlates. The same may apply to the effects of other interventions, from physical exercise and behavioural activation to neurostimulation techniques. Neuroscientific explorations of depression should probably look at the autonomic as well as the central nervous system (and at their interactions with the cardiovascular and gastrointestinal systems in addition to the immune and endocrine ones). Finally (or first of all), some more psychopathological sophistication should perhaps be added to the current conceptualization and description of "depression".

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8. Berk M, Köhler-Forsberg O, Turner M et al. World Psychiatry 2023;22:366-87.
9. McIntyre RS, Alsuwaidan M, Baune BT et al. World Psychiatry 2023;22:394-412.

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The challenges of defining and managing treatment-resistant depression in research and practice

McIntyre et al[1], in their excellent paper appearing in this issue of the journal, successfully tackle a critical issue in the field of depression: how should we define treatment-resistant depression (TRD) and how can we best manage it? They point out that a consensus definition of TRD with demonstrated predictive utility in terms of clinical decision-making and health outcomes does not currently exist, and that the definition adopted by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) – i.e., failure to respond to two or more antidepressant regimens despite adequate dose and duration and adherence to treatment – remains at the moment the reference one.

Although it makes perfect sense that regulatory agencies rely on a definition which can be easily adopted in clinical trials, as it captures a large population with unmet needs, should researchers and clinicians routinely use the same approach? The Massachusetts General Hospital Staging Model (MGH-S) provides an example of a definition of TRD which integrates the number of failed trials with the intensity/optimization of each trial, without assuming a hierarchy of antidepressant classes[2]. An observational study of patients receiving antidepressant therapy (N=78,477)[3] applied this model to claims data from the MarketScan Research Databases over a 24-month time period. Annual costs for patients with mild TRD (MGH-S score: 3.5-4) were 1,530$ higher than those for non-TRD patients, and annual costs for patients with complex TRD (MGH-S score ≥6.5) were 4,425$ higher than those for non-TRD patients (all $p<0.001$). A 1-point increase in the MGH-S score was associated with a 590$ increase in annual costs ($p<0.001$). There is, therefore, a clinical utility in adopting a staging method to evaluate the cost-effectiveness of new treatments for TRD.

The MGH-S model has been recently updated to reflect some of the new treatments for TRD, including ketamine/esketamine, transcranial magnetic stimulation (TMS) and vagus nerve stimulation. The new version of the model[4] provides a score for the characteristics of depression (including severity of the episode, presence or not of psychotic features, presence of suicidal ideation, and presence of anxious distress) (maximum score = 10), and a score for treatment history, considering the number of medication trials, the number of augmentation treatment trials, and the use of the above-mentioned new treatments as well as of electroconvulsive therapy (ECT) (maximum score = 25). We look forward to a wider adoption of this model in research and advanced clinical settings.

As pointed out by McIntyre et al, intravenous ketamine and intranasal esketamine (co-administered with an antidepressant) have an established efficacy in the management of TRD, while some second-generation antipsychotics are proven effective as adjunctive treatments to antidepressants in partial responders, but only the olanzapine-fluoxetine combination has established efficacy in FDA-defined TRD. However, despite the current FDA indication, the results of a pooled analysis[5] suggest that adjunctive aripiprazole can be an effective intervention for patients whose symptoms worsen during antidepressant monotherapy, challenging the view that its benefits are limited to partial responders to antidepressants. The same may be true for other second-generation antipsychotics, supporting the need for further investigations.

On the other hand, the authors highlight that ECT is regarded as an effective acute and maintenance intervention in TRD, with preliminary evidence suggesting its superiority over acute intravenous ketamine. The adoption of ECT in clinical practice, however, remains somewhat limited by the complexity of its administration and the possible adverse events.

The authors also argue that manual-based psychotherapies are not established as efficacious on their own in TRD, although offering significant symptomatic relief when added to conventional antidepressants. Nevertheless, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial compared the effectiveness of cognitive therapy and pharmacotherapy as second-step strategies for outpatients with major depressive disor-

der (MDD) who had received inadequate benefit from an initial trial of citalopram[6]. Among participants who were assigned to second-step treatment, those who received cognitive therapy had similar response and remission rates to those assigned to medication strategies, suggesting that there may be a role for cognitive therapy in TRD.

The recent approval for the treatment of MDD of the combination of dextromethorphan (an uncompetitive N-methyl-D-aspartate receptor antagonist and sigma-1 receptor agonist) and bupropion (a norepinephrine-dopamine reuptake inhibitor), as well as the recent FDA filing of a new drug application for the GABAergic modulator zuranolone, raise the possibility that the scenario concerning medications available for MDD will change significantly in the near future. A large number of other novel compounds developed with non-monoamine molecular targets are currently in phase 2 or 3, again questioning whether clinicians in the next few years will continue to routinely use monoamine-based therapies in the initial algorithm for the treatment of depression. The current construct of TRD, focusing on the lack of response to what have been considered the first- or second-line monoamine-based treatments for MDD, may consequently become obsolete.

Regardless of the methodology used to assess TRD patients, it is absolutely critical to carefully select subjects for randomization in clinical trials. "Professional patients" or duplicate subjects are a common problem in TRD trials, and may threaten the integrity of these studies. A number of digital platforms have been developed to identify duplicate subjects and allow investigators to exclude them from trials, as well as new methodologies to better document the treatment history of patients, including the measurement of blood levels of the ongoing therapies.

To avoid the issues of diagnostic misclassification and severity of illness grade inflation, it is essential to ensure that patients enrolled for TRD trials really fulfill the needed requirements. Patients recruited in these trials may present with a heterogeneous group of symptoms representing several syndromes or subtypes, subsumed under the same diagnosis in the DSM-5 classification system. The SAFER interview[7] has been developed to delineate a more symptom-specific and ecologically valid approach to the identification of the appropriate patients for MDD clinical trials through an independent assessment. It has been reported[8] that, overall, 15.3% of MDD patients who had been deemed eligible at research sites were not eligible after the structured interview, with the most common reason being that patients did not meet the study requirements for level of treatment resistance. In MDD trials utilizing the SAFER interview as a tool to confirm eligibility, placebo response rates ranged between 13.0% and 27.3%, below the 30% to 40% average in antidepressant clinical trials, suggesting a benefit of the quality assurance provided by this interview. This reminds us of the importance to make sure that the right patients get into our TRD trials.

In conclusion, there are currently several challenges in the definition and management of TRD, and the most significant feature of McIntyre et al's paper is probably its ability to reflect this evolving scenario.

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The lived experience of depression: a bottom-up review co-written by experts by experience and academics

Paolo Fusar-Poli[1-4], Andrés Estradé[1], Giovanni Stanghellini[5,6], Cecilia Maria Esposito[3,7], René Rosfort[8], Milena Mancini[9], Peter Norman[10,11], Julieann Cullen[12], Miracle Adesina[13,14], Gema Benavides Jimenez[15-17], Caroline da Cunha Lewin[18,19], Esenam A. Drah[20], Marc Julien[21], Muskan Lamba[22], Edwin M. Mutura[23-25], Benny Prawira[26,27], Agus Sugianto[26,28,29], Jaleta Teressa[30,31], Lawrence A. White[32-34], Stefano Damiani[3], Candida Vasconcelos[1], Ilaria Bonoldi[1,3], Pierluigi Politi[3], Eduard Vieta[35], Jennifer Radden[36], Thomas Fuchs[37], Matthew Ratcliffe[38], Mario Maj[39]

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We provide here the first bottom-up review of the lived experience of depression, co-written by experts by experience and academics. First-person accounts within and outside the medical field were screened and discussed in collaborative workshops involving numerous individuals with lived experience of depression, family members and carers, representing a global network of organizations. The material was enriched by phenomenologically informed perspectives and shared with all collaborators in a cloud-based system. The subjective world of depression was characterized by an altered experience of emotions and body (feeling overwhelmed by negative emotions, unable to experience positive emotions, stuck in a heavy aching body drained of energy, detached from the mind, the body and the world); an altered experience of the self (losing sense of purpose and existential hope, mismatch between the past and the depressed self, feeling painfully incarcerated, losing control over one's thoughts, losing the capacity to act on the world; feeling numb, empty, non-existent, dead, and dreaming of death as a possible escape route); and an altered experience of time (experiencing an alteration of vital biorhythms, an overwhelming past, a stagnation of the present, and the impossibility of the future). The experience of depression in the social and cultural context was characterized by altered interpersonal experiences (struggling with communication, feeling loneliness and estrangement, perceiving stigma and stereotypes), and varied across different cultures, ethnic or racial minorities, and genders. The subjective perception of recovery varied (feeling contrasting attitudes towards recovery, recognizing recovery as a journey, recognizing one's vulnerability and the need for professional help), as did the experience of receiving pharmacotherapy, psychotherapy, and social as well as physical health interventions. These findings can inform clinical practice, research and education. This journey in the lived experience of depression can also help us to understand the nature of our own emotions and feelings, what is to believe in something, what is to hope, and what is to be a living human being.

Key words: Depression, lived experience, first-person accounts, experience of the self, experience of time, social and cultural context, recovery, pharmacotherapies, psychotherapies

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Depressive disorders are common worldwide, affecting 3.8% of the general population, i.e., about 280 million people[1,2]. As depressive disorders often have a young age of onset (peak: 20.5 years)[3], their associated health care and societal burden is enormous[4].

Over the past decade, several psychopathological investigations of the essential depressive phenomena have been published[5-10]. However, these top-down (i.e., from theory to lived experience) publications are limited by a narrow academic focus and a language that may blur the understanding of the lived experience. On the other hand, several reports written by affected individuals describe the subjective experience of depression[11-22], but these analyses are limited by fragmented, particular and contextual narratives that do not fully advance the broader understandability of the experience[23]. To our best knowledge, no studies have adopted a bottom-up approach (from the lived experience to theory), whereby a global network of experts by experience and academics are mutually engaged in co-writing a joint narrative. Co-writing is essentially based on sharing perspectives and meanings about the individual's suffering whilst maintaining each subject's diction and narrative style without formatting them in pre-established conceptual frameworks or narratives[23-25].

This paper is a bottom-up, co-written review of what is like to be depressed. We present a detailed account of depression by drawing on real-world lived experiences and first-person perspective narratives, enriched by phenomenological insights. Numerous individuals with a lived experience of depression across different age groups, genders, ethnic and cultural backgrounds, as well as family members and carers, were involved, along with academics. The adopted co-writing methods refined an earlier method developed by our group to investigate the lived experience of psychosis[23].

In the first step, we established a collaborative core writing team of experts by experience (patients, their families and carers) and academics (psychiatrists, psychologists, philosophers, and social researchers). This team conducted a comprehensive systematic search of Web of Science, PubMed and EBSCO, from inception until August 17, 2022. The search terms were: ("depressive disorder" OR "major depression" OR depress*) AND (qualitative OR "focus group" OR "grounded theory" OR interviews OR "content analysis" OR ethnograph* OR phenomenol* OR "in depth interview" OR hermeneut* OR autobiography OR biograph*) AND ("lived experience" OR "first person" OR "user experience" OR "patient experience" OR meaning OR beliefs OR narrative OR self-narrative OR "illness experience"). We included qualitative studies providing first-person accounts and involving adult participants (≥18 years), published in English, Spanish or Portuguese.

We focused specifically on experiences consistent with the DSM/ICD diagnostic criteria/requirements for unipolar depression, without committing to specific diagnostic subcategories, but excluding postpartum depression due to its distinct psychopathology and pathophysiology[26-28]. We did not focus on psychotic features of unipolar depression, as these were already discussed in our previous work[23]. The DSM/ICD diagnoses were ascertained by a clinical interview conducted by a health care professional, a validated diagnostic instrument (e.g., the Mini-International Neuropsychiatric Interview[29]), or a validated clinical scale with an established cut-off translating into a categorical diagnosis. Studies investigating depressive symptoms, self-reported depressive features, bereavement or "understandable sadness"[30,31] were not included, to avoid the confusion between these conditions and the categorical diagnosis of depression which permeates the existing literature[32,33]. Overall, our focus on ICD/DSM unipolar depression has broad clinical relevance without being so broad in scope to render the analytic task unfeasible[34]. Two researchers screened titles and abstracts, and discrepancies were resolved in consultation with a senior researcher.

In the second step, all included papers were uploaded to NVivo software[35] for qualitative data analysis. Four independent researchers conducted a thematic synthesis of selected sources based on line-by-line coding of the text in the Results/Findings sections of the papers and generation of a preliminary list of descriptive themes and sub-themes of the lived experience of depression. Further complementary sources, such as autobiographical books written by experts by experience, were included to better characterize the lived experience of depression reported outside the medical field (see Table 1). The material was then shared across the core writing team and preliminarily classified across three overarching descriptive themes: "the subjective world of depression", "the experience of depression in the social and cultural context", and "the lived experience of recovering from depression", each of which included several sub-themes. These themes and sub-themes hold narrative value only, and are not assumed to represent entirely distinct categories, but are interconnected and frequently cross-referenced. For example, while we sought to distinguish between mental and physical experiences of depression, first-person narratives do not clearly differentiate between the bodily and the mental domains.

Table 1 Selection of complementary sources considered for the review

Anto SG, Colucci E. *Free from pasung: a story of chaining and freedom in Indonesia told through painting, poetry and narration*[19]
Burnard P. *Sisyphus happy: the experience of depression*[16]
Brampton S. *Shoot the damn dog. A memoir of depression*[17]
Lott T. *The scent of dried roses*[18]
Merkin D. *This close to happy: a reckoning with depression*[11]
Plath S. *The bell jar*[12]
Scialabba G. *How to be depressed*[21]
Solomon A. *The noonday demon. An anatomy of depression*[13]
Styron W. *Darkness visible: a memoir of madness*[15]
Tolstoj L. *A confession*[22]
White LA. *When the world leaves you behind*[20]
Wolpert L. *Malignant sadness: the anatomy of depression*[14]

In the third step, we promoted a collaborative and iterative sharing and analysis of the preliminary experiential themes and subthemes in virtual workshops involving a wider global network of experts by experience and their carers from the Global Mental Health Peer Network (https://www.gmhpn.org), which represents lived experience from over 40 countries; the Young Person's Mental Health Advisory Group (https://www.kcl.ac.uk/research/ypmhag), representing the perspective of young people; and the South London and Maudsley NHS Recovery College (https://www.slamrecoverycollege.co.uk), representing the lived experience of recovering from depression. Overall, we involved about 20 experts by experience of different gender and ethnicity from four continents and 11 countries, encompassing Europe (Spain and the UK), North America (Canada), Asia (India and Indonesia), and Africa (Cameroon, Ethiopia, Ghana, Kenya, Nigeria and Uganda).

The themes and sub-themes identified in the previous steps were presented to this wider group of experts by experience to collect their feedback and enrich them with their subjective perspectives, in order to ensure global representation, particularly for low-middle income countries and ethnic, sexual or social minorities.

In the fourth and final step, the selection of experiential themes and sub-themes was enriched by phenomenologically informed perspectives[10,34,36]. The broader group of experts by experience and academics collectively interacted to draft and review the manuscript via a shared Google Drive platform. All experts by experience who actively participated in the manuscript elaboration were invited to be co-authors. They were offered reimbursement for their time adhering to available guidelines for participatory research[37].

In this study, the words written or spoken by experts by experience are reproduced verbatim in italics. Commentaries from experts by experience participating in our collaborative workshops are anonymized as personal communications. Notably, although this paper outlines the most paradigmatic ways in which depression expresses itself across the majority of experts by experience on a global scale, it is neither assumed that the experiences reported are exhaustive nor that they are systematically applicable to all indi-

viduals with depression. We rather sought to appraise the kaleidoscopic coloring and phenomenological heterogeneity of the lived experience of depression by acknowledging individual variability and complementary, if not contrasting, types.

THE SUBJECTIVE WORLD OF DEPRESSION

In this section, we describe the subjective experience of depression across three overarching narrative themes: a) the experience of emotions and the body, b) the experience of the self, and c) the experience of time.

Depression and the experience of emotions and the body

Feeling overwhelmed by negative emotions

The most typical experience in depression is struggling with overwhelmingly negative emotions, such as guilt and despair, fear, anger and boredom. Life is frequently experienced as dominated by a deep sense of unchanging and inescapable guilt because one cannot contemplate the prospect of positive change in one's life. Such irrevocable guilt shapes any other experience[7].

This feeling is deep, not directed at anything in particular (objectless)[38], and thus cannot be described in terms of feeling guilty about something[7,38]: "*One awful thing about my depression was the tremendous sense of guilt that I was unable to attach to any memory, or action or any part of myself*"[39].

In many cases of severe depression, the pervasive experience of guilt is accompanied by fears of inescapable illness, and takes the form of an all-enveloping and seemingly unavoidable existential worthlessness and despair[34]: "*I shall not exist. Then why go on making any effort? And how go on living?*"[22]. Individuals may fear the outside world, other people, their own emotions and actions, or the future: "*I had a fear of change, fear of dying, fear of failure, fear of success, fear of being alone, which paralyzed me for years and years*"[40].

The interpersonal world is perceived as threatening, offering only suffering and disappointment: "*I am afraid of having relations with others, but I was not like this before*"[41]. Bonding with others may also be hampered by significant irritability[42], which impedes closeness: "*I get angry. I just hate noise. It disturbs and destroys me and I find myself arguing with others*"[41]. Familiar people can also be perceived as boring and unimportant, or as additional burdens: "*I just cannot deal with hearing all your troubles today. I've got enough to deal with on my own, just trying to keep myself afloat*"[43].

Feeling unable to experience positive emotions

In depression, positive emotions are overshadowed by negative ones. Individuals describe the inability to recognize and experience positive emotions such as pleasure: "*I tried to lick the honey which formerly consoled me, but the honey no longer gave me pleasure*"[22]. They also feel unable to experience happiness ("*I have of late lost all my mirth*"[34,44]), love ("*My husband expects me to express my love for him, but I do not know where I can find this love")*[45], or affection towards others ("*Because I was depressed last year, I became absorbed in my own self. I didn't care about others", personal communication).*

In the extreme variant, individuals may find it difficult to experience any emotions at all ("feeling of the loss of feelings"[46]). This experience leads to detachment from others and the world, coupled with emotional anesthesia and inability to establish relationships with others: "*A loss of feeling, a numbness, had infected all my human relations. I didn't care about love, my work, family, friends… or physical/emotional intimacy… I was losing myself, and that scared me*"[13].

Feeling stuck in a heavy aching body drained of energy

Individuals with depression frequently report low levels of vital energy: "*My vital energy is depleted*"[47]. This loss of energy, the driving force that pushes us to get involved in the world and directs our lives[48], can lead to a sense of exhaustion, or even paralysis: "*I am tired in the morning and tired at night and tired all day and never, never feel fresh*"[49]. People with depression tend to experience fatigue even when faced with mundane daily tasks involving bodily movement: "*Like you're swimming against a sea of something coming at you*"[50].

The body is so heavy that it impedes any movement: "*For me, it feels like gravity just starts working on my body harder than it works everywhere else in the world*"[51]. Physical heaviness is described as an intense sensation of oppression: "*It's like a pressure on my body, a pressure on my head*"[52], often associated with bodily pain: "*I get sort of like really sensitive… it's just pain that goes on and on*"[53]. Bodily pressure or pain can become so unbearable as to trigger extreme somatic delusions[54,55], such as the conviction that one's body is no longer functioning: "*I can't eat or drink because the bowel is blocked*"[56].

Feeling detached from the mind, the body and the world

Individuals living with depression often report experiences of detachment from their own mind, the body and the outside world. They also describe a reduced sense of both agency (experience of initiating and controlling) and ownership (feeling of mineness)[57] of thoughts, emotions, behaviors and bodily processes, which continue to occur on their own, leading to feelings of disconnectedness: "*I'm not in my body, I'm not in my mind, I'm just totally disconnected from myself*"[53]. While the body ordinarily operates as a medium through which the world is experienced, it becomes now uncomfortably alien and obtrusive, like an object external to oneself[58], working on its own and automatically: "*I do everything automatically, the signals from my body are shut down, I don't listen, I become like a machine, just doing what needs to be done*"[49].

Feelings of bodily detachment are often accompanied by a sense of distance and disconnectedness from the surrounding world, including others[5]: "*There was no real connection. You feel like you're*

talking and doing everything you should, but you're not really there. It's like you're removed from yourself… You weren't really connecting with other people"[43]. The surrounding world also appears immersed in an atmosphere of artificiality and unfamiliarity, devoid of its more usual emotional tone: "*I felt like in an artificial world that I didn't recognize*"[49].

Feelings of artificiality can become so pervasive to lead to depersonalization and derealization, characterized by the loss of bodily vitality and disconnectedness from the world. These experiences corrode the ordinary and "pre-reflective" (i.e., unconscious) sense of "belonging to a shared world"[34], which characterizes the human experience. The resulting overarching experience is a deep sense of estrangement and exclusion, which can lead to the struggling feeling of being cut off from an interpersonal world of possibilities that others continue to inhabit[34,59]: "*I feel completely cut off from the rest of humanity, the rest of the world, the rest of existence. I am a walking corpse*"[60]. This dramatic feeling of a lost world of possibilities can be experienced as the confirmation of one's inhumanity, further amplifying ruminations of guilt or even self-hate: "*I am not human… I hate myself*"[60].

Depression and the experience of the self

Losing sense of purpose and existential hope

A typical experience reported by people living with depression is that life has lost its purpose. This feeling is unchanging and irrevocable: "*All I seemed to be able to do was exist in the moment with no drive or purpose, no reason for being*"[20]. Individuals report existential despair, a loss not merely of many hopes but of the so-called "ground for hope"[61], the ability to hope for anything: "*Today or tomorrow sickness and death will come to those I love or to me; nothing will remain but stench and worms*"[22].

Individuals who despair withdraw from active involvement in the world: "*[Depression] comes with a loss of being fully engaged in the world around you*" *(personal communication)*. The drive of agency and motivation collapses[62]: "*I felt like my life was changed upside-down… I had become still and then driven down. I felt like nothing was important*"[63]. The outer world loses its importance, and the inner life becomes dominant, thus weakening the sense of practical connection with the world: "*At first you can still kind of function in the world – but then… you start living in your own mind*"[51].

Still, the person might feel an urgent and pressing need to act upon one's situation, to bring about some transformation. In a world deprived of meaningful change, the result is often a directionless psychomotor agitation ("*I just wandered, and wandered and wandered. Went about like a dog in a cage… I couldn't sit and eat… It was like a motor inside that you have no control of*"[64]), experienced both in the body and the mind[34].

Mismatch between the past and the depressed self

People with depression feel unable to recognize their usual self, feeling awkward: "*I guess I felt strange and alien*"[43]. They frequently describe the experience of not matching one's past self: "*I don't even know myself anymore*"[65]; "*I was losing… any sense of who I was*"[20]. Individuals struggle to recognize themselves as the person they used to be: "*I don't recognize, and I don't like the person I've become… It's almost like a slow erosion of the spirit*"[66]. This may amplify feelings of hopelessness, loss of purpose and lack of self-worth. Individuals may experience a self-alienation, observing themselves and their behavior from the outside as not fitting: "*You look in the mirror, and you still look the same, but you feel like you should be looking different. You feel like you've just gone*"[66].

Often the mismatch between the old and the depressed self is not noticed by others, leading to further isolation and incomprehension: "*Everybody else still thinks that this is me. But the person I knew myself to be, is gone. Just went away*"[49]. In this context, the past self is frequently idealized and desired in the face of the impotence of the depressed present self: "*I remember when I had a spark, high energy and the ability to motivate others. I desperately want that back*"[66]. However, it is also possible that people with depression are not able to relate to the past self: "*In my depression [the past self] disappeared, it was like it had never been that way… I could not relate to how I had been*" *(personal communication)*.

Feeling painfully incarcerated

Many people suffering from depression describe it as a prison they cannot escape: "*Depression is like a hole. You are stuck in the hole. You can't get out*" *(personal communication)*. The metaphors used (e.g., a hole, a fog, an endless tunnel) equally express the sense of violent constraint and impotence: "*Lost in a really thick fog, you can't find your way out, you have no direction or energy. It weighs you down, and you can't work it out*"[67]. The poet S. Plath metaphorized her depression as a bell jar: "*Wherever I sat – on the deck of a ship or at a street café in Paris or Bangkok – I would be sitting under the same glass bell jar, stewing in my own sour air*"[12].

The subjective feeling of incarceration is frequently described through physical symptoms, such as shortness of breath, feeling of suffocation, and fatigue, in particular in some cultural contexts: "*Living with depression is like walking in a dark tunnel with no end to… feelings of suffocation and shortness of breath*"[51]. The heavy, aching body is perceived so uncomfortably to become a prison itself: "*You feel like you are a prisoner in your own head*"[51]. To cope with this tension, individuals with depression unsuccessfully attempt to fight the feeling of oppression or passively accept being imprisoned: "*You give your power away, become immobilized and can't move through it*"[67].

Losing control over one's thoughts

People with depression often report the subjective experience of not being able to think or concentrate. They may perceive their thoughts as confusing and unclear, as if they were shrouded in fog: "*It's like a funky fogginess… I can't think, I can't concentrate. My*

words end up not even coming out the way that they should"[40]. A state of mental congestion is frequently experienced: "*Just hundreds of thoughts whirling around in my head, with no function or order. It's complete chaos*"[34].

The feeling of not being able to control one's thoughts may translate into the loss of agency with one's inner life. For example, people may feel at the mercy of ruminations of depressive thoughts: "*The thoughts just come… Sometimes I don't want to think but the thoughts just come. I try to stop them, but I can't*"[63]. Depressive ruminations typically focus on guilt, inadequacy or worry, and it is not possible to divert them, as if they had a life of their own. People feel overwhelmed because they don't have the strength to contain these negative thoughts and the anguish they cause: "*I'm trying to change the subject, but my brain is telling me to worry about this, worry about that, and the next thing, I couldn't concentrate on anything else except what was in my head*"[43].

Losing the capacity to act on the world

Based on the experiences described above, people living with depression may feel that they have lost the ability to act in effective or practically meaningful ways: "*I felt totally out of control, and there was no way to gain control, to take control of my life, or at least to have control of some of the events*"[52]. Even the simplest undemanding and ordinary daily activities and duties are perceived as an insurmountable difficulty[14]: "*You go to the wardrobe, and you look at your blouses, and you stand there in a state of indecision for ages before you can decide whether you'll wear the green one or the white one. Everything seems to assume momentous importance*"[68].

Depressed individuals may feel powerless and frustratingly unable to predict whether the next day they will be able to carry out ordinary tasks and therefore act on their life, feeling totally at the mercy of their mood: "*I never know whether I'm gonna be able to do what I planned that day until I get up that morning… Like I never have any control of my life*"[66].

Individuals with depression frequently describe indecisiveness, which impairs their ability to act on the world: "*I cannot decide even about the simplest things. Whenever I make a decision, I fail to do it*"[41]. Indecisiveness is closely associated with the sense of lacking immersion in the world: "*Every decision was segmented into a thousand tiny decisions. It came with a loss of being fully engaged in the world around you*" *(personal communication)*.

Feeling numb, empty, non-existent, dead

One of the most extreme experiences sometimes reported by people with depression is the loss of vitality of the self. The self is experienced as numb, empty, non-existent, as a walking shadow[69], or even dead[70-72]: "*I was feeling numb. All the things that used to make me happy felt like nothing*"[19]. An absence of thoughts and emotions is also described: "*You're just blank, there is no you, you just exist, you don't live… There are no emotions, no thoughts, no nothing… It's a state of numbness*"[53]. The feeling of emptiness is so strong as to be disabling, bringing with it an inability to properly function in the world: "*All of me got empty; my head, my body and the whole world*"[49].

The sense of numbness and emptiness leads people to conclude that they do not exist at all: "*I don't even exist anymore*"[69]. The givenness of being alive and existing, far from an immediate and pre-reflective certainty, becomes utterly doubtful and must be continuously and practically verified: "*My head is empty, so I keep marching about to know I'm alive*"[56]. In their most pronounced form, these experiences can amount to a feeling of total annihilation of the self; people describe having become like nothing, as if they have disappeared and died[69]: "*I feel dead. And [I have an] inarguable belief that I am nothing*"[60]. The feeling of non-existing and being dead can extend to the surrounding environment and even the world, whose existence is doubted: "*It feels like there's nothing outside of here*"[29]. The non-existence of one's own body and world may be firmly believed with delusional intensity (known as Cotard's syndrome)[73].

Dreaming of death as a possible escape route

Living with the experiences described above amounts to insurmountable mental and bodily pain and suffering, which the feeling of being emotionally dead cannot even alleviate: "*I feel dead. And yet, being 'dead' doesn't relieve the overwhelming, insurmountable pain inside me*"[60]. Therefore, people with depression often perceive their lives as meaningless and imagine death as the only way out of their existential pain and despair[34]. Death appears as an escape, given the lack of purpose for living and the impossibility of alternatives in the future: "*The only end I see for me is death really, quite honestly*"[53].

Suicide may be felt as the only possible escape from the apparent perspective of eternal incarceration and suffering[11]: "*Anyway, I felt that I must die… Everything would be over if I died. There would be no memory, painful memory, and no more real-world pressure. I felt that death could solve any problem*"[19]. Contemplating suicide may be experienced as a personal relief[17] as well as a relief for the loved ones: "*Now I think death is the best option for me… My death might hurt my family for a few hours, but now I hurt them every minute… Death is easier for me*"[17].

Depression and the experience of time

Experiencing an alteration of vital biorhythms

A common experience is the disruption of vital biorhythms that regulate one's daily life, affecting the basic biological functions of sleep-wake, hunger, and sex drive: "*I had sleep problems… I had poor appetite. I was constipated… I also had back pain and sexual problems*"[41]. Altered biorhythms in depression represent a disruption of the basic (pre-reflective) attunement between soma and psyche, and between the person and environment[74]. Biorhythms can be de-synchronized ("*I can't get to sleep, I lie awake and doze off a bit, sweating, chaotic*"[75]); inverted (*"My body just wanted to sleep. I would often sleep 20 or 22 hours a day", personal commu-*

nication); or flattened ("*I found myself eating only for subsistence: food, like everything else within the scope of sensation, was utterly without savor*"[15]). Sleep abnormalities are particularly perceived as disturbing. Despite feeling exhausted, individuals are often unable to conciliate a restorative sleep: "*Most distressing of all the instinctual disruptions was that of sleep… Exhaustion combined with sleeplessness is a rare torture*"[15].

Experiencing an overwhelming past

Depression stops the orientation and movement of life towards the future, which gives meaning to life[69], and ties affected individuals to the past[38], unable to move beyond its overwhelming grappling force and weight: "*I can't get away from my experience in the past*"[60]. The past becomes predominant, invading and erasing the possibilities of the present and the future[69,76,77].

Given that the world is devoid of future positive possibilities and changes, the significance of past events is no longer amenable to reinterpretation in the light of present events. The experience of the past is irrevocably fixed and determined once and for all[69]. Actions made in the past become irrevocable faults that cannot be expiated ("*You get what you deserve in life. And I don't deserve nothing*"[50]) or forgotten ("*I feel I am suffering more than a murderer is suffering. In the end, a murderer forgets, and everything goes away from him*"[7,39]).

Past faults thus reverberate in the present as guilt, shame and regret: "*Guilt about past life suffocates me*"[56]. As past faults cannot be changed, people feel that they deserve punishment and anticipate condemnation: "*I have to be punished for past misdeeds*"[56]. Depression itself could be subjectively perceived as a much-deserved punishment for past faults, potentially leading to self-harm behaviors.

Experiencing a stagnation of the present

Faced with the tyrannic dominance of the past, the present time in depression is subjectively perceived as suspended, totally stagnating: in the landscape of futility, nothing has significance, and everything just passes[69]. People with depression do not perceive the normal flow of time, which appears slowed down or stopped: "*I can't remember days because time has stopped*"[56]. The present drags on to what seems like an eternity in a world devoid of practically meaningful possibilities, where nothing new of significance occurs: "*Time seemed an eternity*"[56]. This lost sense of becoming leads to feelings of boredom, meaninglessness and worthlessness.

Sometimes, people feel that the world is coming to a complete stand-still: "*I look out of the window of my hospital room, it looks so overcast outside, the birds have stopped singing, the flowers blackened, silence, everything has stopped*" *(personal communication)*.

Experiencing the impossibility of the future

As time leads nowhere, several depressed individuals experience the future as an empty space which is no longer offering possibilities for positive changes: "*It just feels as though there's a big hole in the future, there's a big empty space somewhere that I'm going into, and there's just nothing in it*"[53]. The future contains nothing but never-ending pain and suffering: "*It was like existing in the dark, expecting a future in darkness as well*"[78]. The future can also be experienced as a mere repetition of the past[21] or an endless continuation of the dark present: "*The future was hopeless. I was convinced that I would never work again or recover*"[14].

The genuine possibility of an open future is negated, and several people with depression experience the impossibility of any future change or improvement[62], with a profound loss of hope and of all possible personal directions: "*I'm just dreading the future. There is nothing I look forward to, there is nothing… and I don't see it getting any better*"[53]. Some people describe the future itself as taking the form of an all-enveloping threat, more specifically, the threat of condemnation by others. This sometimes relates to guilt – all that one anticipates is punishment, something nasty is coming, and one awaits judgment[34]. Because of the impossibility of future positive change, depression is experienced as an eternal incarceration[69]: "*One thing about depression is that it feels like it's gonna go on forever… it's never gonna end*"[45]. And, if nothing can change, there is no escape other than death[34].

THE EXPERIENCE OF DEPRESSION IN THE SOCIAL AND CULTURAL CONTEXT

In this section, we explore the lived experience of depression across two overarching narrative themes: a) the experience of depression across different cultures, in ethnic and racial minorities, and across genders, and b) the interpersonal experience of depression.

The experience of depression across different cultures, in ethnic and racial minorities, and across genders

Experiencing depression across different cultures

The subjective experience of depression is deeply influenced by other people and by sociocultural contexts characterized by specific norms and values. For example, the biomedical model, which predominates in Western societies, posits that depression is primarily an "inner" and individual mood disorder[5]. This model is not universally accepted[79-81], coexisting and conflicting with other models of depression (e.g., religious), in particular (but not exclusively) in low- and middle-income countries: "*I've seen a psychiatrist and a bomoh [traditional Malay medicine practitioner]. I knew it was not right to see bomoh, but I do believe the bomoh will help me strengthen my faith… I do believe the power of will inside me will help me against my illness*"[60].

In these cultures, individuals may perceive depression as a "rich people problem": "*It's something that only white people have*" *(personal communication)*. The mental suffering of depression can be

experienced as personal incapacity and laziness, and "emotional needs" are considered much less important compared to the "basic material needs": *"I'm fine… I just feel sad, and I've a reason to be sad… Nothing to do with hypertension, cancer or heart attack… it is only a sad feeling, which occurs from my heart"*[60].

The lack of medical recognition of depression can lead to the belief that it is an experience that one should manage oneself, implying that individuals are responsible for their disorder[82-84]: "*It is not an illness… Depression is cured by oneself putting forth effort*"[85]. For example, among Australian First Nations, depression is primarily experienced as weakness or injury by spirits[86], which is not thought to require medical care: "*The [spirits] can cause you to be really sad or withdrawn or angry, or they can make you physically ill, like me, and then the doctors won't be able to find a cure for you*"[87].

In cultures whose members do not experience themselves as much as separate individuals but rather as parts of a social community, depression may be conceived not as an intra-psychic but rather as a bodily, interpersonal or even "atmospheric" process[5]. Bodily experiences of depression are themselves shaped by cultural variables, with "nerves" and "headaches" often featuring in Latino and Mediterranean cultures; "imbalance", "weakness" and "tiredness" in Chinese and Asian cultures; and "problems with the heart" in Middle Eastern cultures[34,88].

Experiencing depression in ethnic and racial minorities

Cultural differences in the experiences of depression are also a significant challenge for ethnic and racial minorities. Their suffering can be exacerbated by a mistrust of health care professionals because of a lack of reciprocal understanding: "*What do they understand about our ways? I wouldn't tell them – they would laugh at us and think we were strange, so I don't tell them" (South Asian in the UK)*[87]. Such mistrust is sometimes aggravated by perceived racist and discriminatory attitudes by health care workers: "*[Health care workers] are just more cold, like emotionally something happened to you that's traumatic, they're very cold" (African American in the US)*[89].

This feeling of not belonging to the main social group exacerbates a sense of isolation and difference that is already prominent in depression[90] and adds to the emotional burden: "*My depression might not be like Suzie Ann's depression?… They're going to treat her just a little bit more different than me" (African American in the US)*[89]. Discriminatory experiences of depression are also described: "*I'm part of an ethnic minority group in Indonesia, so there are systemic discriminations… there's a sense of mistrust" (personal communication).*

Experiencing depression across genders

While both male and female individuals with depression commonly report feelings of diminished self-worth ("*I've lost all my confidence*"[91]; "*The weakness within me has come out*"[63]), such feelings are differently tuned according to gender-specific stereotypes.

Male individuals tend to struggle with masculine stereotypes concerning a perceived need to be in control, successful, self-reliant, and not to show signs of weakness[18,52,92,93]: "*I think you grow up with it – men don't cry… it's the social group that does it… 'don't be a sissy'*"[94]. They often experience more difficulty expressing their emotional feelings and thoughts about their depressive disorder[41,95]: "*You have to be as macho as possible… perhaps makes it hard to express your feelings verbally*"[92].

On the other hand, women tend to be subjected to feminine stereotypes concerning emotions ("*I think girls more often, just like me, worry about a lot of things*"[6]) or motherhood ("*My kids are lonely… I have not taken care of their food or clothes in the past four years. I feel guilty*"[41]; "*a mother who is too much shade and too little sun*"[11]).

The interpersonal experience of depression

Struggling with communication

Individuals living with depression experience a profoundly altered world characterized by a deep loss of interpersonal connection, which is not shared and understood by others: "*[Depression] remains nearly incomprehensible to those who have not experienced it in its extreme mode*"[15]. Conveying and communicating such an all-enveloping alien reality becomes particularly problematic[34]: "*I'm hurting so badly, I don't even have the words to describe it… I'm a person of words, of descriptions, of communication. Now, I feel stripped of even that one small comfort: being able to express how I feel*"[60].

Individuals may feel alienated from others and unable to relate to them[34,96]. Isolation is exacerbated by the loss of physical connection that otherwise mediates the non-verbal communication of feelings and intentions. This deep communicative obstacle augments personal suffering by impeding interpersonal comprehension with family members and friends: "*I have had a hard time describing what it feels like to people. Especially when someone asks you what's wrong. You know what's bothering you, but you don't know what to tell*"[51].

In the attempt to re-establish meaningful communication, people may resort to metaphors, which help to mentalize and consequently communicate what would otherwise be difficult or impossible to express with non-figurative words[97]. The metaphors often describe restricted movements ("*I could not move; even picking up a cup required a serious attempt*"[41]); feelings of being in front of "*a wall*"[98] or finding oneself in "*the bottom of a pit*"[98] or "*in a dark place*"[98]; or an impaired perception of the environment or the self with ineffable feelings of isolation and hopelessness ("*The sun would shine, but it would be dark. So, I couldn't feel the sun; it really shines and brightens every day, but I couldn't feel the sun. As much as I could feel the rays hitting my body, I couldn't feel it. It was very deep, deep darkness. The light could not penetrate through", personal communication).*

Feeling loneliness and estrangement

Feelings of social and personal isolation, not being understood by others, and being cut off from the world, play a central role in the subjective experience of depression[34]. Interaction with other people becomes uncomfortable[99] ("*Part of what people say is upsetting, so I stay away from them*"[45]), meaningless ("*I feel like what people talk about is trivial and irrelevant*"[43]), or outright hurtful ("*The act of socializing seems like an act of self-harm, to expose myself to get hurt*", *personal communication*). The poet S. Plath, who struggled with depression, points out the emotional burden of being expected to keep up appearances: "*I also hate people to ask cheerfully how you are when they know you're feeling like hell and expect you to say 'fine'*"[12].

Lack of trust or, at times, an explicit sense of being unsafe or threatened by others are recurrent experiences that complicate interpersonal relations: "*I'm like a focus of attack, you know, it feels like all around me, you know*"[53]. This lack of trust is often accompanied by jealousy, resentment[43,75,100] and even paranoid interpretations: "*When people are talking to each other, I think they are talking about me*"[41].

Withdrawing from other people can be experienced as a relief from social pressure: "*Isolation can help me. That was my 'go-to' place*" (*personal communication*). Avoiding interaction allows the person to escape the otherwise unavoidable complications of interpersonal relationships: "*Living alone is fabulous. When you live on your own, you can get away from it all*"[101].

Although social isolation can function as a way of erecting a protective shield against other people ("*You just want to hide away from everything, that's all*"[68]), it is paradoxically also felt as extreme loneliness, generating a desperate cry for human contact: "*Why do I want to live in the world? Nobody loves me. None!*"[102]. This deep disconnection from others creates an agonizing longing towards intimacy and social relationships: "*I miss the interdependence in marriage and at work; when you lose that, everything falls apart*"[103].

Perceiving stigma and stereotypes

A deeply troubling dimension of depression is the pervasive experience of stigmatization, often eliciting internalized feelings of shame, guilt, and being worthless or weak[78,100,104] ("*Public stigma is internalized into the self-stigma… that we are lazy, worthless*", *personal communication)* or of being somewhat less capable than other people ("*Telling people is sort of showing your weakness, your underside, and they'll think less of you because you're weak and you can't cope with life*"[94]).

Hiding one's suffering is a common way of not having to deal with stigma: "*It's like there are two different yous*"[43]. It can be a strenuous task to constantly hide one's pain behind a surplus of energy or a mask of joy: "*I've always managed to put on this happy face*"[51]; "*I could no longer go to work, pretend to be well, and maintain a brave façade of happiness only to arrive home in tears*"[20].

Hurtful stereotypes often worsen the experience of suffering ("*People think you are making yourself out as the victim, or you are being silly… that it is just me wanting to feel bad*"[85]), or lack of understanding from the family ("*My parents still don't think that I'm sick*"[105]; "*I was not ready to accept the stigma of being called crazy by my own family*"[19]). Unhelpful comments such as "*Can't you just choose to be happy?*"[51] or "*Oh, we all get sad*"[94] are experienced as damaging because they turn the disorder into "*something that does not exist, something that you cause yourself*"[85]. Stigma and stereotypes can amplify the suffering by implying that the person is somehow responsible for the depressive disorder.

THE LIVED EXPERIENCE OF RECOVERING FROM DEPRESSION

In this section, we describe the lived experience of recovering from depression across four overarching narrative themes: a) the subjective nature of recovery in depression, b) the experience of receiving pharmacological treatments, c) the experience of receiving psychotherapy, and d) the experience of receiving social and physical health interventions.

The subjective nature of recovery in depression

Feeling contrasting attitudes towards recovery

Individuals often describe contrasting experiences of recovery from depression, reflecting an ambivalent attitude concerning different components of the process. Even the very meaning of "recovery" can be variably understood as the simple disappearance of symptoms, as a return to "who I was", as the future starting to open up, as a profound existential maturation, or as a middle ground between these experiences. As the healing processes seem to involve something unpredictable, some patients may prefer to speak about "discovery" rather than "recovery": "*I think rather than the word 'recovery', it's more 'discovery'… it's a journey of discovery that does not necessarily have an end*" *(personal communication)*.

The recovery process implies acknowledging that depression is not simply a disorder in the biomedical sense but, more broadly, a human experience[106-108], although not an unavoidable aspect of all human lives. The human experience of depression is a different way of being in the world, a different life-world experience[109]. Thus, the life-world experience of depression may also include an existential change in a positive sense: "*What has changed? I think my outlook on life, I love life, I really do*"[110].

By some individuals, recovery is described as restoring personal stability and functioning: "*I really have to put so much effort to stay stable, to function normally*"[111]. However, rather than accepting that one is somehow stuck with depression for life, recovery has to do with regaining a sense of at least partial agency of one's existence and a renewed appreciation of life[74]. Changes and possibilities reappear after having been out of reach for a long time.

This rediscovery of well-being does not imply a denial of depression, but a greater awareness of one's own limits: "*It gives me hope that you can still have life even though you have to change it around a little bit*"[105].

Recognizing recovery as a journey

Most individuals describe recovering from depression as a journey; one goes through something horrible to reach a peaceful destination, a condition of enhanced strength. This is achieved through self-understanding, often involving a change of perspective regarding oneself and, therefore, personal growth, accepting that sometimes healing depends upon factors outside one's control (e.g., medications and other people): "*Many times, I have said coping with depression enriched me… I live a more conscious and a grateful life*"[112].

On the other hand, recovery is not always experienced as a process of personal growth. Some people are so distressed that they just want to erase the illness from their memory and return to their lives and past selves as if nothing had happened: "*Doctor, when will I become my old self again?*" *(personal communication)*. The idealization of the experience of depression and of recovering from it can even be criticized: "*There is, for me, little to be 'learned' from being depressed. It is certainly not a spiritual journey or one that is likely to lead to 'finding oneself'*"[16].

Actually, the trajectory of the journey is seldom so neat, and its endpoint seldom so clear: "*Recovery is not a straight-line process, there will be a lot of ups and down. It's a long way process. It's a life learning*" *(personal communication)*. Furthermore, the process of recovery can be experienced very differently by the same individual in different moments – it is not a black-or-white crystallized picture: "*It's more of a cyclical journey rather than a start-middle-end*" *(personal communication)*.

Recognizing one's vulnerability and the need for professional help

People with depression frequently report that they couldn't have gotten out of it without someone's help and support: "*If it weren't for them, I don't know what would have happened*"[113]. Although some people reject professional help altogether, most express a need for professional support to accompany them through the recovery process: "*There was always that net underneath me to catch me if I was falling and I couldn't stop it*"[110].

Recognizing one's vulnerability and seeking professional assistance is complex. People with depression are often in desperate need of help: "*You're going there to ask for help because you can't deal with it anymore*"[114]. This makes them particularly vulnerable to feelings of rejection and abandonment: "*What can be worse for someone with depression than to be abandoned?*"[114]. Some people express the underlying belief that mental health professionals do not really know in depth what they are treating because they have not personally experienced depression: "*I have experienced depression, for anyone who treats or writes about depression and who has not themselves been depressed is rather like a dentist who has had no experience of toothache*"[14].

The experience of receiving pharmacological treatments

Feeling ambivalent about antidepressants

A variety of experiences and a certain ambivalence have emerged in narratives about receiving pharmacological treatments: "*Depression cannot be cured despite medicine. However, I feel uncomfortable without medicine. I have to take it every day as long as I live, even if the fear of side effects bothers me*"[115]. Although subjective experiences vary across different cultures, most individuals think that antidepressants are needed to improve their symptoms and recover: "*I think they help me, they give me a sort of baseline to work from*"[116]. Even if they may not fully eliminate depression, they are perceived as helpful: "*[My antidepressant] does not eradicate the depression, but it makes me worry about it far less*"[16]. At the same time, they may be feared because of subjectively perceived dependence: "*One becomes dependent on the medication to be well and able to do things*"[85].

The experience of receiving antidepressants is poorer when they are prescribed without consideration for the individual person[117,118]. This may also explain why sometimes individuals feel that antidepressants are not targeting their core problems: "*I thought that medication was not dealing with the reasons why I was getting depressed*" *(personal communication)*. When psychiatrists explain in detail the functioning and the risks of the prescribed drugs, individuals with depression feel recognized as human beings and, therefore, adherence to treatment increases: *"There is stuff I don't know and stuff I don't understand, and he (the clinician) will explain it to me… and I like just being able to understand, it makes me feel a lot better; he helps me to have some objective view of myself"*[119]. However, at the same time, people may feel overwhelmed by the amount of technical information to digest and paralyzed to reach any decision: "*I don't know what the different pills do for me. It's difficult to cooperate and suggest changes when you don't have the necessary insight*"[120].

The experience of receiving psychotherapy

Feeling listened to and supported

People with depression generally experience psychotherapy as a safe space in which to feel welcomed and understood, and where they can speak freely about their sufferings and problems. Feelings of unprecedented relief and liberation ("*It was the first time I was able to talk about my feelings, and it was a big release*"[52]), and of freedom to be themselves and authentic without the need to hide their weaknesses, are sometimes reported.

One aspect frequently mentioned is the importance of sharing expert knowledge to improve self-management and self-efficacy. Involvement is important in restoring a sense of agency: "*It made me feel empowered*"[121].

Feeling improved through change

Individuals receiving psychotherapy describe several improvements in various aspects of their lives, both interpersonal and intrapersonal: "*My psychotherapy has improved my life… Everything has changed in my life… my relationships, everything*" *(personal communication)*. Psychotherapeutic benefits are often reported as increased self-awareness and improved confidence in the future: "*I feel that I'm armed now, that I can handle misfortune better because I've gained more insight into myself*"[111].

Self-improvement achieved through psychotherapy allows people to engage in relationships with other persons with better focus: "*That's my motto for the moment: I'm not investing in things that will gain me nothing. I do not think that's selfish, but more like healthy selfishness. It means considering yourself as well*"[111]. Psychotherapy can help them understand what they want in life, offering new insights and new perspectives: "*Psychotherapy made me reflect upon things and gave me some different ideas about situations that… needed to be looked at from a different perspective*"[122].

People may feel better because they know how to cope with their emotions and recognize their condition: "*I didn't even know I was getting depressed. [Now] if things are difficult, I can do something about it*"[110]. The success of psychotherapy also entails becoming aware of one's vulnerability: "*I remain fragile… which is where the skill of therapy comes in*"[123].

Feeling that psychotherapy threatens the self and is ineffective

Despite the above positive experiences, psychotherapy can sometimes be experienced as a threat to one's self and identity, and a challenge to values, beliefs and self-views: "*Giving up part of myself*" or "*Blowing my cover*"[52]. People may be afraid to start psychotherapy because it will expose them and show their weakness: "*I didn't want to be labeled as weak or mentally ill*"[52].

Some people with depression are dissatisfied with the purpose or efficacy of their psychotherapy: "*I still don't understand the purpose of talking about all these things; I often felt worse after the session*"[122]. They report that something was missing and that psychotherapy did not fully match their needs or expectations, and did not lead to recovery through change: "*A lot got untied in therapy, and some of those things are still loose ends, like not all pieces of the puzzle are put together yet*"[111].

Sometimes, the perceived ineffectiveness of psychotherapy is taken as evidence of the impossibility of future changes and of completely recovering: "*So, psychotherapy has ended now and once again I'm nowhere, it did not help, and it only cost me money, a lot of time and energy, and why? For nothing*"[122].

The experience of receiving social and physical health interventions

Empowering the self

People recovering from depression report that occupational therapy provides a space for them to feel empowered in their thoughts and feelings, and improves self-efficacy, self-confidence and self-esteem: "*It reminded me of the achievements in my life and gave me hope that I can do it again*"[124]. Sometimes, people are excited to discover new skills, of which they were unaware: "*I feel like I've done something, that I've achieved something even though it was so hard*"[125]. This discovery of one's abilities can lead to new insights into one's life challenges and the desire to solve them, nurturing hope in the future: "*If you want to achieve goals in your life, you must start with the old matters and deal with them, then focus on the new ones, then you will see progress*"[124].

People with depression generally feel that social interventions also helped to focus on practical matters: "*I did not know my creativity until I did beads necklace. It was relaxing, and I never had time to think about my problems*"[124]. Occupational therapy is also perceived as useful to distract them from their negative thoughts: "*I was very down, very emotional that day, but being in the fingerboard released my mind where I was, and I ended up being happy and laughing*"[124].

However, not all experiences are positive, and people with depression may feel discomfort in relating to others or being confronted with operational difficulties.

Sharing mutual peer support

Peer support is frequently experienced as a moment of sharing in which individuals can feel accepted and understood. Treating everyone's experiences equally allows individuals to feel less alone and strange: "*Everybody knows each other, and we all have our pains and problems, but we laugh about it, and you don't have to feel as if you're being tedious*"[49].

Sometimes people with depression who are engaged in peer support can make new friends that they cultivate with great care: "*God put somebody in my life at that time, she was like my angel…, and she pulled me up out of that dark hole*"[126]. Yet, others may feel uncomfortable attending peer support groups and discussing their challenges: "*I don't like to see people with obvious mental illness… It reminds me so much of me… I wish I had never joined the group*"[105].

Restoring bodily experience

Individuals living with depression report that exercise sets in motion their abilities to participate in life and engage with others: "*When I exercise, I'm not in the bubble, it feels like I know what everybody is up to, and I'm just like them working out*"[125]. Exercise can be about structuring, doing household tasks, or taking the initiative for more social contacts. It may provide a sense of relief from de-

pression: "*It kind of helps to rip open the cocoon you're in. It helps me to get the strength to crawl out of it, in a way*"[125].

People often talk about physical exercise as a way to re-become the person they used to be. Sometimes, they report a new vitality flowing through the body: "*I notice that my body softens and that I feel more alive, more in contact with my body*"[125]. Their narratives highlight how the bodily experience can be restored via physical exercise: "*It feels like I'm coming back to myself again, both body and mind. I'm taking them back*"[125]. Because of the improved bodily experience, people can report an improvement in their sense of self, since body and self together form an "embodied self" structured in a relationship of mutual interdependence[59,127].

However, other individuals report needing external motivation to engage in physical exercise: "*You need someone to practically drag you there. How could I make myself go if no one waits for me there?*"[125]. For many, lack of motivation has kept them inactive for a long time: *"I've never felt motivated enough to start a physical activity" (personal communication)*. Some people also express disappointment because physical workouts do not correspond to their expectations or are perceived as meaningless: *"I was hoping to feel some moments of euphoria, but there was nothing like that"*[125].

DISCUSSION

This paper follows and transcribes the lived words of individuals who have faced the experience of unipolar depression. We have given voice to these individuals' inner suffering, emotions, loneliness, and desperate need for help. The paper, as our previous one published in this journal[23], ultimately belongs to all the individuals with a lived experience of depression, their families and carers.

Our co-writing approach delivers a fresh integrated perspective on the experience of depression. The vividness of the subjective experience of suffering can only be captured by allowing personal insights to emerge, minimizing exclusion and misrepresentation of the affected individuals' perspectives[128]. Notably, we are not investigating whether narratives of depression adequately represent the condition: the main purpose of this study is to "give the word" to experts by experience and then integrate phenomenological insights rather than primarily testing researchers' hypotheses. In this context, this study outlines some essential (paradigmatic) ways by which depression expresses itself. However, it is evident that there is no such thing as a unique experience of depression, which "appears in various different clinical forms"[129], but rather a plurality of individual experiences. This evidence aligns with current clinical research efforts aiming at the clinical characterization of depressive disorders at the individual subject level[118].

Despite such heterogeneity, we found that most depressive experiences have broader themes in common, which express a radical change in the overall structure of one's overall relationship with emotions and the body, the self and time. Changes in the experience of emotions and the body include sub-themes such as feeling overwhelmed by negative emotions, feeling unable to experience positive emotions, feeling stuck in a heavy aching body drained of energy, and feeling detached from the mind, the body and the world. Changes in the experience of the self are described as losing sense of purpose and existential hope, mismatch between the past and the depressed self, feeling painfully incarcerated, losing control over one's thoughts, losing the capacity to act on the world; feeling numb, empty, non-existent, dead, and dreaming of death as a possible escape route. Individuals also report changes in their perception of time (experiencing an alteration of vital biorhythms, an overwhelming past, a stagnation of the present, and the impossibility of the future). These structural changes are inextricable aspects of an altered unitary experience, some kind of overarching existential change, an all-enveloping shift in one's sense of belonging to a shared world[34,130].

The world is seldom an explicit object of experience; rather, it is something that we are already practically, unreflectively immersed in, something that goes unnoticed when intact[131,132]. The experiences described confirm that depression disturbs something fundamental to our lives: this sense of being comfortably immersed in a familiar world[34]. Indeed, individuals often remark on the profundity of what happened to them[34]. According to our analysis, depression is, therefore, essentially a disturbance of world-experience[130].

The existential shift in how one finds oneself in the world can be expressed not only in terms of emotions, body, self or time. In addition, there are changes in the structure of interpersonal experience, resulting in an overarching feeling of being disconnected from other people. Individuals report struggling with communication, experiencing loneliness and estrangement, and perceiving stigma and stereotypes; these features lead to an overall loss of dynamism and openness to life. Individuals with depression find themselves in a different world, in an isolated, alien realm that is indifferent to others, painfully cut off from them or experienced only in terms of threat[34].

We also found that these experiences are highly variable across different cultures, ethnic or racial minorities, and genders. For example, in cultures whose members experience themselves as integral parts of a social community, depression is conceived less as an intra-psychic disorder and more as a bodily and interpersonal experience[5]. The loss of bodily vitality is, at the same time, a privation of emotions and self. The feeling of constriction of a trapped body cuts across the distinction between bodily and mental. This suggests that, in order to fully understand experiences of depression, we should avoid imposing dualistic distinctions upon them. The traditional dualism of mind and body is derived from the Cartesian dichotomy of positive sciences[133]; it locates the mind and affects exclusively inside the brain, a container contemplated in abstraction from the rest of the living, moving, environmentally situated unity of the organism[5]. On the other hand, psychological reductionism tends to attribute depression to intrapsychic mechanisms (e.g., faulty information processing[134,135]). In both cases, depressive experiences are disconnected from the body and put into an inner container[5]. As a result, the real embodied experience of individuals with depression is at best regarded as a secondary "somatization" process[5]. In contrast, the bodily experience of depression is the crucial dimension of a non-reductionist view. We should not understand depressive disorders as just an intra-individual state, localizable within the psyche or the brain, but as a detunement in

the literal sense – a failure of bodily attunement to the shared world of emotions[5].

We observed an individual variability of attitudes towards the recovery process. Recovery was described by some people as a journey based on their ability to recognize their vulnerability and the need for professional help, but other people just wanted to erase the illness from their memory, or experienced the recovery process very differently in different moments. Similarly, individuals were ambivalent about the experience of receiving pharmacological treatments (felt as needed but at the same time feared because of side effects and subjectively perceived dependence) and psychotherapy (some individuals felt listened to and supported, and improved through change, but others experienced threats to the self and concerns about its effectiveness). Social and physical health interventions were overall experienced as supportive, allowing self-empowerment, sharing mutual peer support, and restoring bodily experience. Good care and phenomenologically informed practices for persons with depression should be first and foremost based on understanding what it is like to receive these treatments, starting from the inner realities described in this study.

In conclusion, this study brings dialogue with experts by experience into psychiatric clinical practice and research. While biologically-oriented approaches tend to sideline and marginalize the personal perspective, we argue that depression cannot be understood if one neglects or trivializes that experience. In clinical practice, our phenomenologically-enriched study can complement biological approaches by allowing clinicians to empathize with persons with depression, because "the science of persons… begins from a relationship with the other as person and proceeds to an account of the other still as person"[136]. From the research viewpoint, our work can accomplish the purpose of moving away from the academic complexities of traditional phenomenological and philosophical studies, speaking in terms that everyone can understand.

We thus hope that our work will be useful to people who suffer from depression and those in supporting roles. By comprehensively improving the understanding of what it is like to live with depression, this study holds an educational potential to train health care professionals, and can be widely disseminated to experts by experience and family organizations to improve their mental health literacy. Health care providers and research funders may also access this co-developed source of lived experiences of depression to inform their agenda and strategic priorities[137].

Finally, this co-written journey in the lived experience of depression can also help us to understand the nature of our own emotions and feelings, what is to believe in something, what is to hope, and what is to be a living human being.

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Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management

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Populations with common physical diseases – such as cardiovascular diseases, cancer and neurodegenerative disorders – experience substantially higher rates of major depressive disorder (MDD) than the general population. On the other hand, people living with MDD have a greater risk for many physical diseases. This high level of comorbidity is associated with worse outcomes, reduced adherence to treatment, increased mortality, and greater health care utilization and costs. Comorbidity can also result in a range of clinical challenges, such as a more complicated therapeutic alliance, issues pertaining to adaptive health behaviors, drug-drug interactions and adverse events induced by medications used for physical and mental disorders. Potential explanations for the high prevalence of the above comorbidity involve shared genetic and biological pathways. These latter include inflammation, the gut microbiome, mitochondrial function and energy metabolism, hypothalamic-pituitary-adrenal axis dysregulation, and brain structure and function. Furthermore, MDD and physical diseases have in common several antecedents related to social factors (e.g., socioeconomic status), lifestyle variables (e.g., physical activity, diet, sleep), and stressful live events (e.g., childhood trauma). Pharmacotherapies and psychotherapies are effective treatments for comorbid MDD, and the introduction of lifestyle interventions as well as collaborative care models and digital technologies provide promising strategies for improving management. This paper aims to provide a detailed overview of the epidemiology of the comorbidity of MDD and specific physical diseases, including prevalence and bidirectional risk; of shared biological pathways potentially implicated in the pathogenesis of MDD and common physical diseases; of socio-environmental factors that serve as both shared risk and protective factors; and of management of MDD and physical diseases, including prevention and treatment. We conclude with future directions and emerging research related to optimal care of people with comorbid MDD and physical diseases.

Key words: Depression, physical diseases, comorbidity, cardiovascular diseases, cancer, inflammation, lifestyle factors, childhood trauma, collaborative care, digital technologies

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Major depressive disorder (MDD) is prevalent within the general population, with an approximate global point prevalence of 4.7%[1]. In populations with common physical diseases – such as cardiovascular diseases[2,3], cancer[4] and neurodegenerative disorders[5-8] – this prevalence is much higher, with several meta-analyses reporting MDD rates of up to 41% in selected physical diseases[2-8]. This relationship is often bidirectional, with both observational and some Mendelian randomization studies demonstrating that MDD and physical diseases can be predictors and outcomes of each other[9-14].

There are a range of potential explanations for the high level of comorbidity between MDD and physical diseases[15-18]. Shared genetic and biological pathways suggest that there are numerous pathological mechanisms implicated in both MDD and physical diseases that may increase risk or exacerbate comorbidity[15,16]. Furthermore, there are several shared antecedent social, lifestyle and life event risk factors for MDD and physical diseases[17,18]. In addition, factors precipitated by one disease can increase the risk of another. For example, motivational impairments present in MDD may affect the ability to exercise and maintain a healthy diet, resulting in an increased risk of physical diseases.

The consequences of this high level of comorbidity are far reaching, with evidence supporting worse outcomes[19], reduced adherence to treatment[20], increased mortality[21], and increased health care utilization and costs[22-26]. MDD poses a substantial disease burden, ranking second among leading causes of years lived with disability according to the Global Burden of Disease Study[27]. Using data from the Danish registry and previously published methods[28], more than one third of the total nonfatal burden (34.4%) in people with MDD was due to comorbid physical diseases, such as respiratory diseases (e.g., asthma and chronic obstructive pulmonary disorder), pain-related conditions, cardiovascular diseases, and gastrointestinal disorders.

Comorbidity of MDD and physical diseases also introduces several clinical challenges that are often not apparent within the published literature, in which clinical populations can be highly selected. These include a higher prevalence of other mediating or moderating disorders such as substance abuse and personality dis-

orders, a more complicated therapeutic alliance, issues pertaining to adaptive health behaviors[29], drug-drug interactions and adverse events induced by medications used for physical and mental diseases.

This paper draws on meta-analyses and Mendelian randomization studies, as well as on randomized controlled trials (RCTs) where appropriate, to provide a detailed, up-to-date overview of: a) the epidemiology of the comorbidity of MDD and physical diseases, including prevalence and bidirectional risk; b) shared biological pathways implicated in the pathogenesis of MDD and physical diseases, c) socio-environmental factors that serve as shared risk and protective factors; d) clinical management of MDD and physical diseases, including considerations regarding prevention and treatment; and e) future directions and emerging research related to optimal care of people with comorbid MDD and physical diseases.

While this review focuses on, and primarily refers to, MDD and its relation to physical diseases, it is also informed by evidence concerning closely related constructs, such as elevated depressive symptoms, as well as by studies that investigate depression but have not used formalized DSM-5/ICD-11 diagnoses of MDD. Furthermore, we use the term "physical diseases" throughout to refer to non-psychiatric and non-communicable diseases discussed in the review. We do, however, acknowledge that this is an imperfect definition, as MDD itself can also be considered a physical disease with well-observed physical mechanisms (as discussed in the paper) and clinical manifestations.

EPIDEMIOLOGY OF THE COMORBIDITY OF MAJOR DEPRESSIVE DISORDER AND SPECIFIC PHYSICAL DISEASES

In this section, we provide an overview of the association between MDD and specific physical diseases as emerging from meta-analytic data.

MDD has been identified as a risk factor for several physical diseases (see Figure 1), with much evidence suggesting a bidirectional relationship. We explore this further using results from Mendelian randomization studies, which use genetic variation as a natural experiment to investigate the causal relations between potentially modifiable risk factors and health outcomes[30]. This method is arguably less susceptible to known limitations of observational studies such as confounding or reverse causation[30], thus complementing

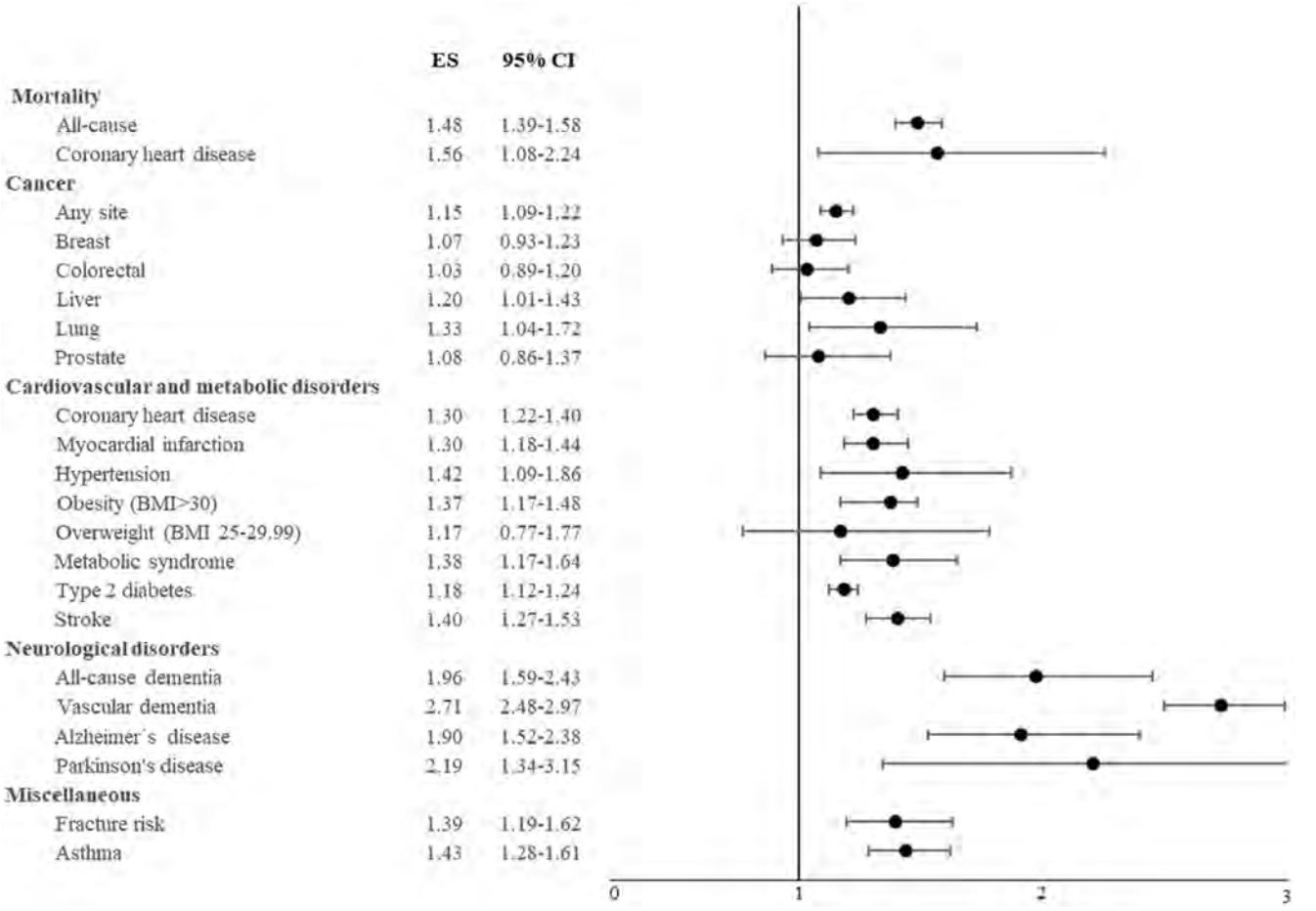

Figure 1 Meta-analytic data on the risk for mortality and physical diseases among individuals with major depressive disorder compared to people without this condition. ES – effect size (risk ratio or odds ratio), BMI – body mass index (see also supplementary information).

the extensive observational literature in this area.

MDD is also highly prevalent in a range of physical diseases (see Figure 2), with an approximate mean aggregate point prevalence of 25%. While this is higher than the general population[1,31], meta-analyses that have synthesized prevalence estimates often report high heterogeneity (with I^2 typically higher than 90%)[32-34], suggesting that prevalence is highly variable. The influence of factors such as disease stage, severity, setting (e.g., hospital vs. community), tim-

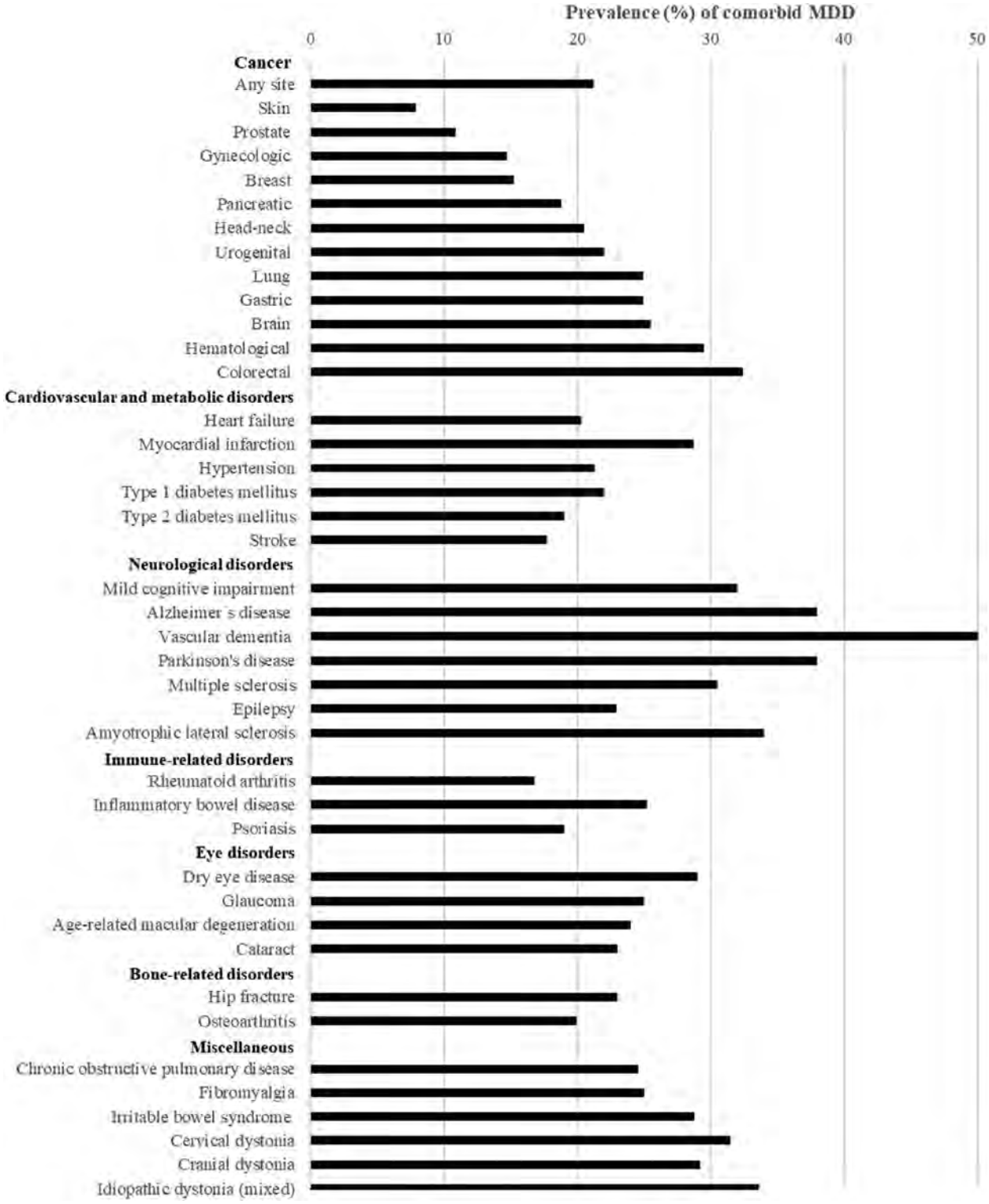

Figure 2 Point prevalence of comorbid major depressive disorder (MDD) in physical diseases, using estimates from published meta-analyses (see also supplementary information).

ing (e.g., immediate vs. years after disease onset), measurement methods (e.g., self-report, clinical diagnosis, clinician rating), and definition of MDD used (e.g., clinical cut-offs vs. elevated symptoms) in determining these estimates should be considered. Such factors are explored in the following disease-specific sections.

Cardiovascular diseases

The point prevalence of MDD after myocardial infarction is reported to be 28.7%, while it is 17.7% after stroke[33,35]. Prevalence rates of MDD are influenced by the severity of the comorbid disease[36]. For example, in people with heart failure, MDD rates range from 11% in people with less functional impairment (class 1 according to the New York Heart Association) to 42% in those with severe impairment (class 4)[36].

Many guidelines and position statements, such as those of the American Heart Association and the European Society of Cardiology[2,37], consider MDD a potentially modifiable risk factor for cardiovascular diseases. Indeed, several meta-analyses of prospective cohort studies have reported that baseline MDD increases the risk of future cardiovascular events[38-41]. While previous meta-analyses have raised concerns regarding a variety of potential confounders[39], a recent meta-analysis of Danish registry cohorts that accounted for these confounders reported that MDD diagnosis was associated with higher risk of subsequent ischemic heart disease (hazard ratio, HR: 1.63, 95% CI: 1.36-1.95) and stroke (HR: 1.94, 95% CI: 1.63-2.30)[11]. On the other hand, baseline ischemic heart disease (HR: 1.79, 95% CI: 1.43-2.23) and stroke (HR: 2.62, 95% CI: 2.09-3.29) were associated with subsequent MDD, demonstrating a bidirectional relationship[11].

Recent Mendelian randomization studies have indicated that the genetic liability for MDD is associated with an increased risk for coronary artery disease (odds ratio, OR: 1.26, 95% CI: 1.10-1.43)[42], small vessel stroke (OR: 1.33, 95% CI: 1.08-1.65)[43], and myocardial infarction (OR: 1.15, 95% CI: 1.07-1.23)[44], while there is a null association between genetic liability for cardiovascular diseases and subsequent increased MDD risk (see Figure 3)[42-44].

In people with cardiovascular diseases and stroke survivors, MDD is associated with increased health care costs and unplanned rehospitalizations[23,25], an increased risk of atrial fibrillation and chest pain[2], and a significant decrease in quality of life[45,46]. Furthermore, MDD occurring after a cardiovascular event is associated with poorer adherence to treatments and adaptive lifestyle changes[20],

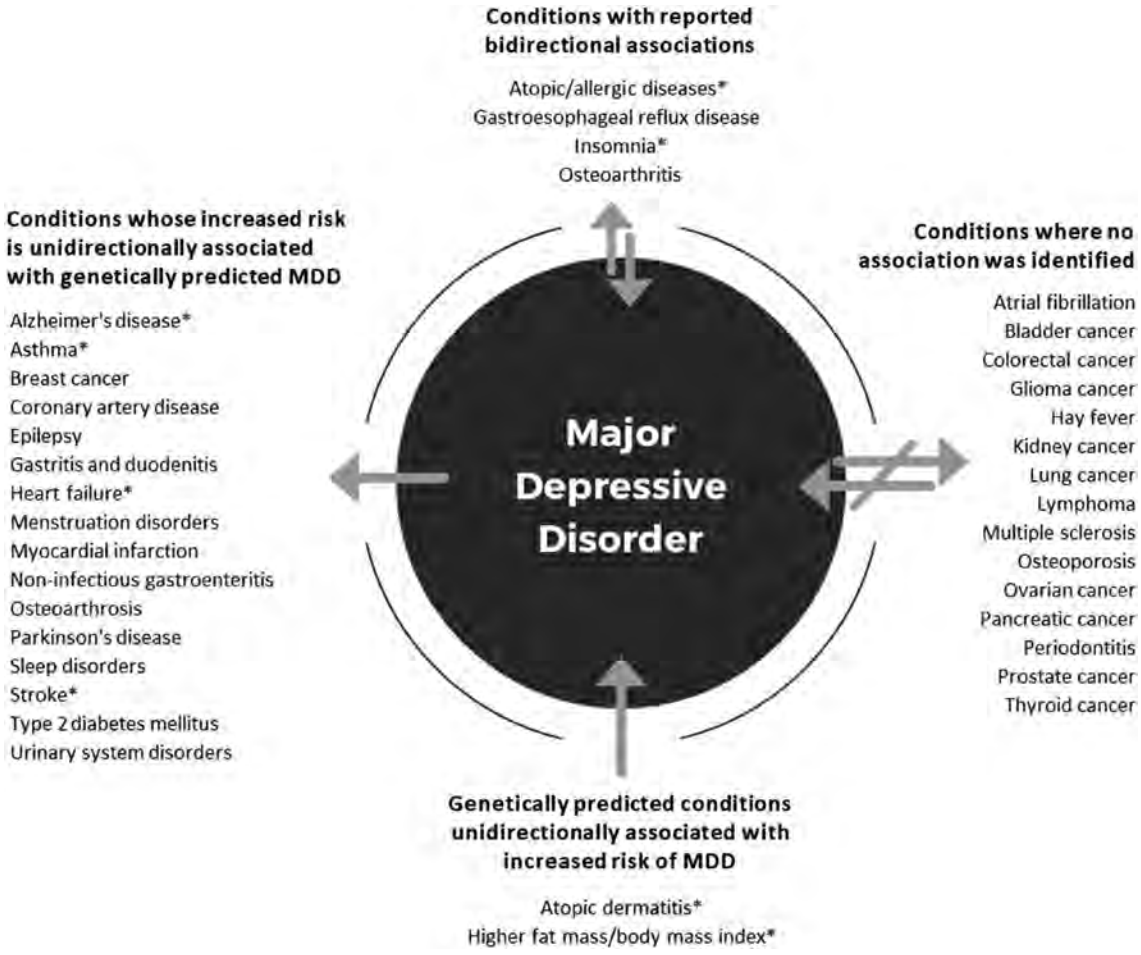

Figure 3 Association between major depressive disorder (MDD) and physical diseases according to Mendelian randomization studies. Asterisks indicate conditions where the evidence is mixed (see also supplementary information).

including attendance and completion of rehabilitation[47], which improves after resolution of depressive symptoms[48].

Diabetes mellitus

The point prevalence of MDD is high in both type 1 (22%) and type 2 (19%) diabetes mellitus[32]. People with MDD have a higher risk of type 2 diabetes (risk ratio, RR: 1.18, 95% CI: 1.12-1.24)[49] and people with type 2 diabetes have a higher risk of MDD (RR: 1.15, 95% CI: 1.02-1.30)[50]. Previous meta-analyses of prospective cohort studies suggest a bidirectional association between MDD and type 2 diabetes. However, recent Mendelian randomization studies suggest a unidirectional relationship, with genetic liability for MDD associated with increased risk of type 2 diabetes[42,51].

Comorbid MDD in people with type 2 diabetes is associated with poorer adherence to diabetes treatment[52] and self-care activities (e.g., exercise, healthy eating)[53,54], increased health care costs[22,54], reduced glycemic control[55,56], and increased hospital admissions and complications[57-60]. A recent meta-analysis reported that baseline MDD is associated with an increased risk of incident diabetes-related complications (HR: 1.14, 95% CI: 1.07-1.21)[57]. The risk of functional disability is also substantially increased in people with comorbid MDD and diabetes compared to individuals with one disease[58].

Furthermore, comorbid MDD and diabetes may increase the risk of other physical diseases[59]. For example, a prospective study reported that individuals with diabetes and comorbid MDD had an increased risk of dementia (HR: 2.69, 95% CI: 1.77-4.07) compared to individuals with diabetes only[41,59].

Metabolic syndrome

The metabolic syndrome includes insulin resistance, central obesity, impaired glucose tolerance, raised triglycerides, reduced high density lipoprotein (HDL) cholesterol, non-alcoholic fatty liver disease, and hypertension[61]. It is a major risk factor for developing both type 2 diabetes and cardiovascular diseases, as well as for premature mortality[62].

There is a bidirectional association between MDD and the metabolic syndrome. People with MDD are 1.38 (95% CI: 1.17-1.64) times more likely than the general population to develop the metabolic syndrome[63], while people with the metabolic syndrome are 1.49 (95% CI: 1.20-1.87) times more likely to develop MDD[10]. This association exists in both adults and older people[64]. However, a Mendelian randomization study suggests that genetically predicted MDD is positively associated with the risk of the metabolic syndrome, but that genetically predicted metabolic syndrome is not associated with the risk of MDD[65].

Individual components of the metabolic syndrome, such as obesity, may also have a bidirectional association with MDD. Meta-analyses of prospective observational studies report that baseline MDD increases the risk of developing obesity (RR: 1.37, 95% CI: 1.17-1.48), and baseline obesity increases the risk of onset of future MDD (RR: 1.18, 95% CI: 1.04-1.35)[66]. However, several recent Mendelian randomization studies have shown that genetically predicted increased body mass index and fat mass are associated with an increased risk of MDD, while the reverse is not true[67-70].

Emerging studies also suggest that the metabolic profile can influence the association between obesity and MDD, with a recent meta-analysis of cross-sectional studies reporting that metabolically unhealthy obesity was associated with a 30% to 83% increased risk of MDD, whereas obesity with a favorable metabolic profile was not associated with an increase of that risk[71]. Furthermore, one cohort study found that, while the metabolic syndrome overall was not associated with the resolution of MDD symptoms, abnormal circulating triglycerides and cholesterol were associated with a lower likelihood of symptom resolution[72]. This is in keeping with another small case-control study which found an association between low HDL cholesterol and poorer MDD prognosis[73].

Cancer

Large meta-analyses have estimated the point prevalence of MDD in people with cancer to be around 21%[4,74,75]. However, this estimate is highly variable depending on a range of factors related to disease course (e.g., early vs. advanced stages), treatment time point (acute treatment vs. survivorship), and assessment method (self-reported or clinical diagnosis)[4,74,75].

A previous meta-analysis demonstrated that prevalence rates of MDD are generally highest during the acute phases of the disease and during treatment (estimates between 14% and 27%)[4]. Prevalence rates at 2- and 5-year post-treatment generally return to similar estimates as the general population or healthy controls[76,77].

Previous meta-analyses and large cohort studies have also identified that the prevalence of MDD can substantially vary based on cancer type[78-80]. While there is some inconsistency between studies, hematological, gastrointestinal, lung and gynecological cancers are often identified as having a higher MDD prevalence compared to other types of cancer[78-80].

A large number of factors have been associated with a greater risk of MDD in people with cancer[81]. A recent systematic review identified a range of somatic (e.g., advanced cancer stage, comorbidities, pain), sociodemographic (e.g., female gender), social (e.g., low socioeconomic status, impaired social support), and psychiatric (e.g., previous history of MDD) factors that were commonly associated with increased MDD risk. Pre-existing MDD and personality factors such as neuroticism were the most consistently associated[81].

MDD may modestly increase the risk of cancer onset and mortality. A recent meta-analysis reported that MDD and anxiety were associated with a significantly increased risk of cancer incidence (RR: 1.13, 95% CI: 1.06-1.19) and cancer-specific mortality (RR: 1.21, 95% CI: 1.16-1.26)[82]. These estimates are similar to a previous meta-analysis that examined MDD separately from anxiety[83,84].

Mendelian randomization studies suggest that genetically predicted MDD is associated with a slightly increased risk of breast cancer (OR: 1.09, 95% CI: 1.02-1.17), but not of a range of other can-

cer types[85,86]. Some studies have also reported that MDD may predict lower T-cell cytokine expression and reduce treatment adherence or initiation[87,88], while improvement in depressive symptoms has been associated with increased survival in people with cancer[89].

Neurological diseases

MDD is associated with multiple neurological diseases. Meta-analytic evidence from longitudinal studies indicates that MDD is a meaningful risk factor for future Alzheimer's disease (RR: 1.90, 95% CI: 1.52-2.38)[90], all-cause dementia (RR: 1.96, 95% CI: 1.59-2.43)[90], vascular dementia (RR: 2.71, 95% CI: 2.48-2.97)[90], and Parkinson's disease (RR: 2.20, 95% CI: 1.87-2.58)[91]. Some authors suggest that MDD may be considered a prodrome of these neurological diseases[92].

Mendelian randomization studies provide further support to a unidirectional association for some neurological diseases, but not all. Genetically predicted MDD is a risk factor for Parkinson's disease and epilepsy, while there is no evidence for genetically predicted neurological diseases being a risk factor for MDD[93,94]. Two Mendelian randomization studies provided contrasting results for MDD and Alzheimer's disease[95,96], and two studies found no association between genetically predicted MDD and multiple sclerosis[97,98].

Meta-analyses and reviews indicate an overall high point prevalence of MDD in Parkinson's disease (38%)[34], epilepsy (22.9%)[5], migraine (up to 47.9%)[99], multiple sclerosis (30.5%)[6], mild cognitive impairment (32%)[7], and Alzheimer's disease (41%)[8]. MDD is consistently associated with reduced quality of life across several neurological diseases[100], as well as with increased disability and poorer functioning. For example, MDD is associated with increased seizure frequency in people with epilepsy and excessive daytime sleepiness in Parkinson's disease[101,102].

Furthermore, MDD increases the risk for progression and chronicity[103-105]. For example, the presence of depressive symptoms is associated with faster progression from mild cognitive impairment to Alzheimer's disease[104]. A separate study reported similar results for migraine, where depressive symptoms dose-dependently increased the risk of progression from episodic to chronic disease[105].

Osteoporosis

A growing body of evidence shows that MDD is associated with poor bone health[106-109]. A meta-analysis pooling the results of 21 cross-sectional studies involving 1,842 participants with MDD and 17,401 controls found that MDD was associated with lower bone mineral density at the lumbar spine, femur and total hip, with small to medium effect sizes[110].

A separate meta-analysis also reported that MDD was prospectively associated with an increased annual bone loss rate of 0.35% (95% CI: 0.18-0.53), and a 39% increased risk of fracture (RR: 1.39, 95% CI: 1.19-1.62)[106]. Complicating this, the use of selective serotonin reuptake inhibitors (SSRIs) is independently associated with osteoporosis[107].

A recent Mendelian randomization analysis failed to substantiate these findings, reporting that a genetic predisposition towards MDD showed no effect on bone mineral density or fracture risk, concluding that reverse causality or residual confounding may be at play[108]. In support to these latter data, there is some evidence that the prevalence of MDD is increased in those with osteoporosis, with a recent meta-analysis reporting that 23% of older adults with osteoporosis also reported MDD[109]. MDD is also common following fractures, likely due to associated pain and reduced functional status[111].

Mortality

While both MDD and several physical diseases are associated with independent increases in mortality, their coexistence compounds this risk. For example, a prospective analysis using the UK Biobank (N=499,830) reported that both MDD (HR: 1.26, 95% CI: 1.19-1.33) and diabetes mellitus (HR: 1.62, 95% CI: 1.52-1.72) independently increased the risk of mortality; however, the presence of both conditions amplified that risk (HR: 2.16, 95% CI: 1.94-2.42)[112]. Furthermore, a recent umbrella review found that MDD increased all-cause or cardiovascular-related mortality in patients with several physical diseases (i.e., heart failure, coronary heart disease, stroke, cancer, chronic kidney disease, diabetes mellitus)[113]. The associations between MDD and all-cause mortality among populations with cancer, post-acute myocardial infarction, and heart failure showed the strongest level of evidence[113]. There is also evidence that increasing levels of psychological distress can confer greater risk of premature death owing to cardiovascular diseases [114].

Research using Danish registers and the recently introduced life-years lost metric[115] examined the overall reduction in life expectancy associated with MDD, and explored how different types of physical diseases contribute to this premature mortality[21]. Overall, men and women with MDD lost 8.27 (95% CI: 8.10-8.47) and 6.40 (95% CI: 6.25-6.55) years of life respectively, compared to age- and sex-matched controls from the general population. The co-occurrence of a mood disorder such as MDD and substance use disorders (e.g., alcohol use disorder) had a substantial further impact on premature mortality, with an additional ~6 years lost[116]. The contribution of comorbid cardiovascular disease to premature mortality in those with MDD was comparable in men and women (~1 year), while respiratory diseases accounted for further 0.71 and 0.99 years lost in men and in women respectively.

COVID-19 and neuropsychiatric sequalae

A global 27.6% (95% CI: 25.1-30.3) increase in MDD prevalence due to the COVID-19 pandemic has been estimated[117], although this finding remains controversial[118]. The long-term psychiatric and physical disease consequences of the infection or "Long COVID" are currently unclear and an area of emerging research[119,120].

Long COVID has been associated with new onset of a range of physical diseases (e.g., cardiovascular disease, type 2 diabetes)[120].

There also appears to be an increased risk of MDD as well as other mental disorders[121]. However, this risk may be transient and similar to non-COVID severe respiratory infections[122].

Furthermore, COVID-19 infection has also been implicated in several biological processes relevant to MDD and associated physical diseases, such as immune activation, particularly in those with severe acute infection[120,123]. Neuroimaging studies in people who have recovered from the infection have also identified numerous small brain changes, including structural and functional alterations within the hippocampus[124]. Continued research is required to elucidate the potential neuropsychiatric sequelae of COVID-19 infection.

SHARED RISK FACTORS

Lifestyle and behavioral risk factors

To fully understand the comorbidity between MDD and physical diseases, it is crucial to consider the role of health behaviors. In the general population, there is broad acceptance that adverse health behaviors, such as alcohol consumption, tobacco smoking, or illicit drug use can increase the risk of physical diseases and associated mortality[125,126]. Additionally, there is strong evidence that low physical activity, poor diet, and poor sleeping patterns are key drivers of subsequent physical diseases.

For instance, the World Health Organization's 2020 Physical Activity Guidelines presented moderate-certainty evidence of a curvilinear dose-response relationship between physical activity and risk of all-cause mortality and multiple life-threatening physical diseases, including cardiovascular diseases, diabetes mellitus and even cancers[127]. Similarly, striking data on the impact of eating patterns was provided by the 2016 Global Burden of Disease Study[128], which identified "poor dietary habits" as one of the leading risk factors for mortality worldwide, with almost one fifth of all deaths attributable to it.

While the relationship between sleep and disease is non-linear, there is a strong indication from large-scale studies that sleeping problems are a risk factor for common physical diseases[129], with either too short or too long sleep durations associated with increased mortality risk[130].

These lifestyle factors are also likely to be a central driver of the heightened rates of physical diseases (and associated mortality) observed in MDD, especially when considering the extensive evidence that people with MDD are affected by the same lifestyle and behavioral health risks[131,132]. For instance, systematic reviews have found that people with MDD are significantly more likely to engage in excessive alcohol and tobacco use[131,132], and have a higher total food intake and reduced diet quality[133], higher levels of sedentary behavior[134], and poorer sleep continuity and quality[135], compared to non-depressed people.

Despite the observed trends, the causality of the relationships between health behaviors and MDD is unclear and likely bidirectional. On the one hand, multiple independent meta-analyses of prospective data have shown that physical inactivity, tobacco smoking, excessive alcohol consumption, impaired sleep, and poor diet at baseline are all associated with a subsequently increased risk of developing MDD[136,137]. On the other hand, developing MDD can have a pronounced detrimental impact on an individual's health behaviors, including sleep impairment, low motivation for physical activity, over/under-eating, and a propensity to self-medicate with tobacco, alcohol or substance use[138,139].

MDD is also associated with reduced adherence to treatment for chronic diseases, which may further exacerbate disease outcomes[140]. Furthermore, certain medications used to treat MDD may induce behavioral risks. For instance, the appetite-increasing effects of medications such as mirtazapine and quetiapine may partially account for the increased risk of obesity and cardiometabolic diseases among people treated with these medications[141,142], while the sedative effects of agents such as mirtazapine and tricyclic antidepressants (e.g., amitriptyline, clomipramine)[138] could inhibit individuals from engaging in regular physical activity.

Stressful life events

Life stressors can have negative consequences on both mental and physical health across the lifespan. Research on early life stress – often referred to as childhood adversity or adverse childhood experiences – primarily focuses on experiences of maltreatment (e.g., abuse or neglect) and household dysfunction (e.g., domestic violence or parental mental illness)[143,144]. For instance, accumulating evidence from several meta-analyses of both retrospective and prospective studies suggests that adverse childhood experiences are related to a more than two-fold increase in the risk of developing MDD in adulthood[143,145].

In parallel, a recent meta-review of 16 meta-analyses indicated moderate associations between adverse childhood experiences and respiratory diseases (d=0.44), gastrointestinal diseases (d=0.38), neurological diseases and pain (d=0.34), and cardiovascular diseases (d=0.32), as well as weak associations with cancer (d=0.24), diseases of the musculoskeletal system (d=0.21), and endocrine and metabolic diseases (d=0.17) in adulthood[144].

Adverse childhood experiences are additionally associated with a higher likelihood of experiencing further severe stressful life events later in life (e.g., losing one's job or divorce)[146-149]. Notably, severe stressful life events frequently precede the onset of a first episode of MDD[150]. Furthermore, a meta-analysis of six RCTs[151] suggests that, although severe stressful life events affect the prognosis of individuals seeking treatment for MDD, these effects are largely shared with environmental factors (e.g., social support or employment status) that may be a consequence of the experience of trauma.

Severe stressful life events are also associated with an increased risk of physical diseases, particularly cardiovascular diseases[152]. Adults from the general population who experienced a stressful life event had a 1.1 to 1.6-fold elevated risk of incident coronary heart disease and stroke[152]. Stressful life events can also act as a disease trigger among individuals at risk for cardiovascular diseases, and as a factor aggravating the prognosis of these diseases[152]. A further consideration is that physical diseases and their related symptoms

(e.g., pain, fatigue), as well as treatment-related factors (e.g., surgery, medication side effects), can be a stressful life event accompanied by feelings of grief, stress, shame, and other negative psychological states that can exacerbate or increase the risk of MDD.

It is important to note that not all individuals who experience life stress develop MDD and/or a physical disease[153,154]. Indeed, a meta-analysis of cross-sectional studies showed that resilience (i.e., the ability to successfully adapt to difficult, challenging or disruptive life events) significantly mediated the association between adverse childhood experiences and symptoms of MDD[155]. Likewise, social connection and belongingness, adaptive lifestyle behaviors, positive parenting, and supportive relationships from carers, friends and within the community are all resilience-promoting factors that may have a protective effect on an individual's risk for MDD following adverse childhood experiences[156,157].

Social risk factors

Reducing the burden of disease related to MDD and poor physical health requires the focus to move beyond individual risk and protective factors to consider the social determinants of health, i.e., "the conditions in which people are born, grow, live, work and age"[158]. In this context, risk and protective factors cluster and are interwoven at multiple levels. Some occur at different times, while others persist across the life course[159].

There is clear evidence that both MDD and physical diseases are more common in people from disadvantaged backgrounds[160,161]. Both absolute poverty (i.e., level of income necessary to maintain basic living standards) and relative poverty or deprivation (i.e., level of income necessary to maintain minimum living standards relative to those of a society or country) have independent, adverse impacts on mental and physical health. Indigenous people, those from cultural or linguistic minorities, migrants or refugees, and people with a disability are more likely to experience socioeconomic disadvantage than other individuals in the community[162]. Intergenerational poverty and trauma are also common and confer an additional risk to family members of parents who live in poverty.

Other common social determinants that intersect with the aforementioned variables include gender inequality and restrictive gender norms, which, in many settings, privilege the male or masculine over the female or feminine[163]. Discrimination, marginalization and victimization linked to gender are associated with a greater risk of experiencing poor mental and physical health. This appears to be mediated through exposure to stress-related experiences, but may be also driven by gender-specific disparities in access to education, home ownership, and safety in the home and employment (women and girls), or an over-representation in the criminal justice system and reduced access to health care (men and boys)[164].

Racial, ethnic or sexual minority status is associated with higher rates of health problems, through experiences of discrimination and systemic biases[165]. Structural racism, cultural racism[166] and intergenerational trauma can also impact on mental and physical health. As with gender norms, norms related to race become embedded in later childhood and adolescence, and the effects persist across the life course[167].

The above social determinants exert their impacts on mental and physical health through multiple inter-related mechanisms. Effects on health may be direct (e.g., through restricted access to quality nutrition) or mediated through individual (e.g., security provided by safe housing and/or neighborhoods), relational (e.g., exposure to parental stress in childhood; presence of positive peer relationships in adolescence), psychological (e.g., effects on self-efficacy), or institutional (e.g., neighborhood disadvantage, access to health care) factors[168]. These factors interact in complex ways with other social determinants (e.g., gender inequality, exposure to hazardous work, child labor). For example, low social status because of poverty may be associated with discrimination and other disadvantages (e.g., exposure to violence, social isolation or loneliness), all of which are associated with poor mental and physical health[169-172].

Such processes also have a developmental and transgenerational aspect[161]. The impacts of exposure to adversity may differ according to developmental periods, and health impacts may also vary by type of adversity. Children and adolescents raised in poverty may be less likely to accumulate the "health capital" that contributes to educational attainment, health literacy, a healthy parent-child attachment style, positive peer relationships, the development of social and emotional skills, and the ability to parent later in their own life[173]. As a consequence, early life poverty contributes to intergenerational cycles of poverty and transmission of mental and physical health risks[173]. In contrast, protective factors such as access to resources (e.g., education), consistent relationships (i.e., supportive and stable families), and social and policy factors (e.g., access to affordable health care, social welfare) may assist individuals to overcome the impacts of adversity[174].

SHARED BIOLOGICAL MECHANISMS

Several biological pathways are implicated in the pathogenesis of both MDD and physical diseases (see Figure 4). Here, we first provide a conceptual overview of how these shared pathways contribute to disease outcomes, and then discuss several prominently investigated biological mechanisms. Pathogenesis is unlikely to be driven by any singular pathway alone, but rather by the interaction of multiple pathways affecting both mental and physical health.

Neuroprogression and somatoprogression

The term "neuroprogression" refers to the process of psychiatric disease acceleration and its underlying operative factors, including reduced neurogenesis and increased apoptosis as well as hypothalamic-pituitary-adrenal (HPA) axis dysfunction, immune and oxidative stress, and mitochondrial dysfunction. Its manifestations, such as impaired cognitive function and structural neuroimaging changes, and consequent deteriorating function and declining treatment response, tend to increase with stage[175,176].

The same pathways (e.g., inflammation, oxidative stress, mitochondrial dysfunction) that are involved in neuroprogression of MDD

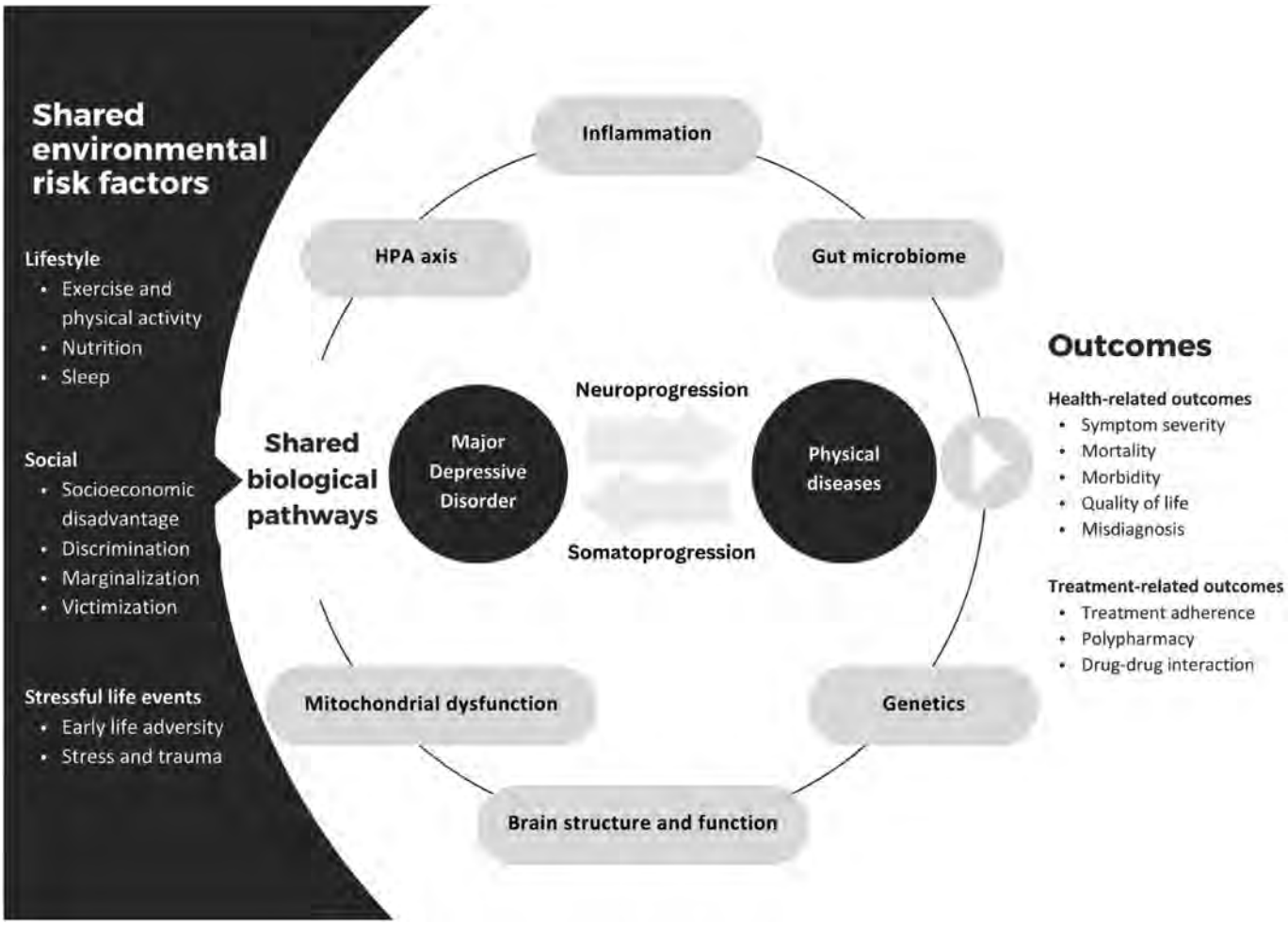

Figure 4 Environmental and biological factors influencing the comorbidity between major depressive disorder and physical diseases. HPA – hypothalamic-pituitary-adrenal.

have a parallel role in the genesis and progression of many physical comorbidities, including cardiovascular diseases and the metabolic syndrome. The term "somatoprogression" refers to these pathways and the accumulation of a physical comorbidity that often occurs in parallel to neuroprogression. This construct overlaps with that of allostatic load, which encompasses biological effects secondary to the aggregate burden of stress and wear and tear on the body[177].

The above two parallel processes provide a theoretical foundation for the comorbidity across MDD and physical diseases. Understanding these processes also provides a mechanistic foundation for the construct of clinical staging[178]. Many of the individual elements of progression – such as inflammation[179], oxidative stress[180], and neurogenesis[181] – are also individually targetable and potentially plastic.

Genetics

Both MDD and several physical diseases have a substantial genetic component. For example, family and twin studies suggest that the genetic contribution to MDD accounts for approximately 37% of the variation in susceptibility[182]. Similar rates are estimated for physical diseases such as coronary artery disease (~43%)[183] and stroke (~38%)[184]. Furthermore, several large meta-analyses of genome-wide association studies (GWAS) have identified genetic loci associated with MDD[185] as well as with many physical diseases, such as obesity[186], type 2 diabetes mellitus[187], and heart disease[188].

There are several shared genetic factors between MDD and physical diseases. For example, in a large UK study, significant genetic correlations were identified between MDD and body mass index, coronary artery disease, and type 2 diabetes mellitus[189]. The significant genetic overlap between MDD and cardiometabolic conditions, in particular coronary artery disease and obesity, has been confirmed in other studies[190]. In contrast, a large study by the Brainstorm Consortium reported little genetic overlap between common neurological diseases (such as Alzheimer's disease, epilepsy, multiple sclerosis, and Parkinson's disease) and psychiatric diseases including MDD[191].

A recent systematic review identified 24 pleiotropic genes that are shared between mood disorders and cardiometabolic condi-

tions[192]. Shared genetic pathways were detected between type 2 diabetes mellitus, cardiovascular disease, obesity and MDD, relating to axonal guidance (e.g., glycogen synthase kinase-3 beta, insulin-like growth factor-1), corticotropin releasing hormone, and 5′adenosine monophosphate-activated protein kinase signaling[192].

Hypothalamic-pituitary-adrenal axis

Stress is a major precipitating factor for the onset and progression of psychiatric disorders, including MDD. HPA axis dysregulation has been implicated in the onset, symptom profile, severity, chronicity, treatment response, and treatment resistance in MDD[193-196]. A large meta-analysis reported that individuals with MDD tend to display elevated cortisol (d=0.33, 95% CI: 0.21-0.45) and adrenocorticotropic hormone (ACTH) (d=0.27, 95% CI: 0.00-0.54) levels[195].

HPA axis dysregulation in MDD becomes more pervasive with age. For example, basal cortisol is elevated during all phases of the diurnal cycle in older adults with MDD (g=0.88, 95% CI: 0.60-1.15) [197]. This is noteworthy, as late-life MDD is associated with immune dysregulation and high rates of comorbid physical diseases[197] and consequent polypharmacy.

Mechanistically, the signal transduction of glucocorticoids is involved in an array of behavioral, cardiovascular, cognitive, immunological, metabolic and reproductive processes[198,199]. According to longitudinal data from a large cohort study[200], increased levels of hair cortisol were predictive of MDD somatic symptoms. Furthermore, the results of a meta-analysis[195] support the notion that HPA axis hyperactivity is a link between MDD and comorbid physical diseases, such as diabetes mellitus, dementia, coronary heart disease, and osteoporosis. This link seems to be particularly pronounced in people who present with melancholic or psychotic features[195]. It is, however, worth noting that there are several other pathways involved in the stress response that may be relevant to the comorbidity between MDD and some physical diseases, including the renin-angiotensin system[201].

Unfortunately, despite the apparently common co-occurrence of HPA axis dysregulation, MDD and comorbid physical diseases, few clinical studies have specifically investigated their interplay. Exclusion criteria have been often applied to people with both MDD and a comorbid physical disease in clinical trials.

There is some indication that sex-specific differences in HPA axis dysregulation exist in humans. However, the relevant evidence is somewhat contradictory (possibly due to variability in menstrual cycle stage, health, age, or stress modality)[202]. This area is still largely under-researched.

Inflammation

It is generally appreciated that MDD is associated with inflammation[203], at least in a proportion of individuals (~30-50%)[204]. In large meta-analyses, MDD has been related to the up- or down-regulation of acute-phase reactants[205], cytokines[206] and chemokines[207]. Low-grade inflammation – as indexed by a concentration of C-reactive protein (CRP) higher than 3 mg/L – is more likely in individuals with depression than in matched controls, occurring in around a quarter of the former according to a large meta-analysis (OR: 1.46, 95% CI: 1.22-1.75)[205].

Chronic low-grade inflammation is also a feature of a variety of physical diseases (e.g., cardiovascular, metabolic and respiratory diseases; cancer, osteoporosis, arthritis) as well as of other serious mental disorders[208-211]. In both atherosclerotic conditions and depressive episodes, a pro-inflammatory state can be induced by hypercortisolemia, reduced paraoxonase-1 levels, as well as reduced HDL and elevated low-density lipoprotein (LDL) cholesterol, leading to endothelial injury and the downstream release of interleukin-6 (IL-6), CRP, tumor necrosis factor-alpha (TNFα), and soluble endothelial adhesion molecules[211]. Activated immune cells release IL-1β, stimulating the production of interferon gamma and TNFα, which are commonly elevated in MDD, cardiovascular diseases, metabolic diseases such as diabetes mellitus, and autoimmune conditions such as rheumatoid arthritis[212].

Data-driven GWAS analysis supports the association between MDD and immune disorder liability. A recent study (N=500,199) found that MDD was positively correlated with Crohn's disease, ulcerative colitis, hyperthyroidism and asthma (Z-scores: 0.09-0.19, $q<0.05$)[213]. The most robust association was observed for asthma (OR: 1.25, 95% CI: 1.13-1.37)[213]. IL-4 is a major cytokine involved in asthma, and is associated with a T helper (Th)-2 cell response[212]. In MDD, the induction of M1 macrophage cells may lead to IL-4 production via the compensatory immune-regulatory system (CIRS) Th-2 response[212]. Another point of possible overlap is in elevation of highly pro-inflammatory Th-17 cells, which are implicated in autoimmune disorders[212]. Emerging evidence supports a role for Th-17 cells in the genesis and progression of MDD[214,215]. This suggests that there may be a subgroup of MDD people with a "lymphoid immunophenotype" (adaptive immune response), contrasting with the innate-immune response myeloid immunophenotype[204].

Mitochondrial function and energy metabolism

Mitochondrial function is widely recognized as a factor in the pathophysiology of several psychiatric disorders, including MDD[216], and a variety of physical conditions, such as metabolic diseases[217], cardiovascular diseases[218], and neurodegenerative disorders[219].

Mitochondria are dynamic organelles that generate adenosine triphosphate (ATP) and are involved in calcium homeostasis, as well as playing key roles in the redox state of the cell and apoptosis. For example, mitochondrial dynamics substantially affect cardiomyocyte health, with multiple rodent studies showing that alterations to processes such as fusion and fission can lead to cardiomyopathy, hypertension, atherosclerosis and heart failure[220]. ATP production is also impaired in people with MDD compared with healthy controls[221,222]. Preclinical models of MDD suppress mitochondrial function[223]. In humans, there is evidence of reduced mitochondrial respiration[221] and neuroimaging evidence of decreased energy generation[224] in MDD.

Oxidative stress occurs when there is an excess of reactive oxy-

gen species, which are predominantly produced by mitochondria during the process of respiration, and especially when respiration is inefficient. While reactive oxygen species are required by cells and play a role in processes such as cell signaling, a sustained excess of these species can cause damage to DNA and various cellular structures[225]. There is a wealth of evidence that oxidative stress is associated with both MDD[227] and several physical conditions, such as insulin resistance[217] and cardiovascular diseases[218,227].

Mitophagy is the selective degradation of dysfunctional/damaged mitochondria, and is a crucial process for optimal cellular function and in the adaptation to cellular stress. Adequate mitophagy is not only required for optimal ATP production, but also to reduce oxidative stress, and impairments to mitophagy have been associated with both MDD and physical diseases such as cardiovascular diseases[228,229] and neurodegenerative disorders[230]. For example, insufficient mitophagy has been shown to have a role in the development of atherosclerosis, which is partly mitigated by inflammatory processes, and could contribute to cardiomyopathy, heart failure, and myocardial infarction[231].

Gut microbiome

The gut microbiome, increasingly implicated in MDD and other psychiatric disorders[232], as well as in several physical diseases, may potentially underpin their interactions. The microbiome affects the gut-brain axis through several of the aforementioned shared mechanisms, i.e. regulating physiological homeostasis via the autonomic nervous system and the HPA axis, and signaling within and between the enteric and central nervous systems via neuromodulatory metabolites and immunomodulatory responses[233].

There is overlap in the relevant mechanistic pathways across MDD and physical diseases. Prime amongst these is the physical maintenance of the tight-junction integrity of the intestinal epithelium, which contains immune signaling pathways and is mediated by the microbiome and its metabolites[234]. Disruptions to the gut epithelial cell wall and transfer of microorganism-associated molecular patterns, such as lipopolysaccharides (LPS), cause an immune cascade through the activation of toll-like receptors (TLRs) and inflammatory responses, with flow-on effects to blood-brain barrier function and neuroinflammation[235,236]. In addition to a compelling body of pre-clinical evidence[237], plasma biomarkers of increased gut permeability, including LPS and zonulin, have been found in greater abundance in people with depressive disorders compared to healthy controls[238].

Evidence of bacterial translocation from the gastrointestinal tract to systemic circulation has been observed within several organs and tissues and is considered contributory to a range of physical diseases. For example, atherosclerotic plaques have microbial communities resembling the gut and oral microbiomes. The resulting immune activation may contribute to the pathophysiology of plaques in the context of cardiovascular disease[239]. In the metabolic syndrome, systemic LPS activates a TLR4-mediated inflammatory response and alters insulin signaling within white adipose tissue[240]. Increased osteoclastic activity and reduced bone mineral density have been observed following increased intestinal permeability in the context of osteoporosis[241]. Evidence of serum and plasma IgG against periodontal bacteria in human and animal studies of Alzheimer's disease has also supported the systemic and neurological relevance of the oral microbiome[242].

Microbial metabolites – most notably, short-chain fatty acids, trimethylamine N-oxide and bile acids – have cell-specific effects on the central nervous system as well as on peripheral organs involved in MDD comorbidities[233]. The strength of evidence for microbial causation varies across conditions, being relatively stronger in the metabolic syndrome. For example, germ-free mice are resistant to the obesogenic effects of high-fat diets[243], whilst wild type and germ-free mice experience metabolic alterations from microbiota-modulating antibiotic and fecal microbiota transplant interventions[244-247]. However, this link is less established in osteoporosis and cancers outside of colorectal cancer[241,248]. Larger longitudinal cohort and intervention studies are required to translate pre-clinical observations across all diseases.

Brain structure and function

Severe emotional distress can directly or indirectly (e.g., through functional reorganization of associated neural networks) affect neural substrates that are key in modulating depressive symptoms[249], including hippocampus, amygdala, hypothalamus, insula, striatum, and medial and orbitofrontal as well as anterior cingulate cortices[250-252]. Physical diseases (e.g., stroke, brain tumors, multiple sclerosis, Alzheimer's disease and Parkinson's disease), as well as lesions or neurodegeneration induced by such diseases, can similarly affect these neural substrates via disease-specific pathology or indirectly via elevated emotional distress (e.g., at time of diagnosis and adjustment).

Common neural circuitries can also emerge from shared underlying biological mechanisms. These constitute either common underlying mechanisms influencing the liability to both MDD and physical diseases, or mediating mechanisms in causal relationships between MDD and physical diseases. Autonomic, immunoinflammatory and neuroendocrine dysregulations influence the brain's homeostatic, cognitive, reward and emotional circuitries[253]. The insula, the hypothalamus (particularly the paraventricular nucleus) and the anterior cingulate cortex play a critical role in monitoring the body's homeostatic state. Deficiencies in immunological, glucocorticoid and metabolic (e.g., leptin, insulin) signaling affect the activity of these interoceptive regions and their connectivity with core emotional, cognitive and motivational brain regions[254].

Alterations in interoceptive regions are associated with "sickness behavior", characterized by lack of energy, weakness, hyperalgesia, loss of appetite and insomnia, commonly associated with both MDD and physical diseases such as cancer[255,256], as well as symptoms of increased appetite, energy balance disturbances and hypersomnia, which are shared between atypical MDD and metabolic diseases including obesity, the metabolic syndrome and diabetes mellitus[15,257]. Deficiencies in endocrine and immunological signaling via interoceptive pathways can also lead to interrup-

tions in dopamine signaling in the brain's reward and motivation circuitries[258], most notably in the orbitofrontal and ventromedial prefrontal cortex, ventral tegmental area and ventral striatum[259,260]. An extensive literature implicates shared alterations in the reward circuitry in MDD, neurodegenerative disorders, and obesity[261-263].

The interoceptive network receives afferent projections from the vagus nerve via the nucleus tractus solitarius and the thalamus[264], thereby receiving information from respiratory, cardiac and gastric sources. A frontal-vagal brain network – including the medulla of brainstem, hypothalamus, amygdala, insula, as well as dorsolateral prefrontal, anterior cingulate and orbitofrontal cortex – has been proposed to link cardiovascular diseases, metabolic diseases and MDD, because of its influence on the cardiovascular system, mood, appetite and sleep[265].

Finally, hippocampal atrophy is shared across MDD and many physical diseases. Impairment of hippocampal neurogenesis, neuroplasticity and dendritic remodeling is critically linked to several physical conditions[266-268]. On the other hand, lower hippocampal volume is one of the most consistently reported structural brain abnormalities in MDD[250,269]. The hippocampus is part of the brain's default mode network. Grey matter and functional connectivity of this network are commonly affected in MDD and neurological diseases[270,271].

CLINICAL MANAGEMENT

Diagnosis of comorbid MDD and physical diseases

Diagnosing comorbid MDD in people with physical diseases can be challenging, as several depressive symptoms overlap with symptoms of these diseases (e.g., fatigue, aching, sleep disturbances, appetite and weight changes), thus showing poorer sensitivity and specificity in this context. Furthermore, grief and distress due to physical diseases are frequent, particularly in severe disease states (e.g., terminal cancer), and can result in clinical difficulties to distinguish between adjustment reactions or "appropriate sadness" and MDD[272]. For example, a study reported that only half of individuals with MDD and diabetes mellitus were recognized as having depression during standard care and, out of those correctly identified, few received adequate treatment[273].

Similar complexities are present for the appropriate diagnosis of physical diseases in people with MDD. This has been termed "diagnostic overshadowing", describing the tendency for clinicians to misattribute physical symptoms (e.g., pain) to a person's mental disorder rather to a potential comorbid physical disease[274].

Prevention of comorbid MDD

Interventions aimed to prevent MDD have been explored in people with at-risk physical diseases. A Cochrane review[275] found very low-certainty evidence from ten RCTs supporting the use of antidepressant medications in the prevention of MDD. Similar results have been reported by systematic reviews of trials exploring antidepressant medications as a means for preventing MDD related to administration of interferon alpha. However, due to the limited evidence base, tolerability and acceptability of preventive antidepressant use has not been rigorously assessed. Further research is required to ensure that the benefits of prophylactic interventions outweigh potential medical (e.g., side effects) and financial considerations.

Preventive psychotherapy interventions have been similarly understudied. The previously cited Cochrane review[275] identified only one trial (N=193), which examined problem-solving therapy in age-related macular degeneration, and found lower odds for developing MDD compared with treatment-as-usual (OR: 0.43, 95% CI: 0.20-0.95). A recent meta-analysis of RCTs of psychotherapy – mostly cognitive-behavioral therapy (CBT) – as a preventive intervention for MDD found positive results, including for a sub-sample of people with physical diseases (n=11; RR: 0.71)[276]. A systematic review of five RCTs evaluating the effectiveness of psychotherapy in preventing MDD in adults with cancer found that it was superior to usual care (standardized mean difference, SMD: –0.23). In a cohort of people with breast cancer, findings were similarly favorable (SMD: –0.32)[277].

However, a large RCT in people with cardiovascular disease and/or diabetes showed that there was no significant effect of a CBT-based preventive program. Four risk factors predicted MDD at follow-up: baseline anxiety and MDD symptoms, stressful life events, and the presence of three or more chronic diseases[278]. It may be that preventive programs will be more effective if targeted at high-risk cohorts such as those with high subclinical depressive symptoms (indicated prevention) or other MDD risk factors (selective prevention).

In summary, proactive treatment to prevent MDD in at-risk individuals with physical diseases may be a viable approach, but large high-quality RCTs are needed.

Treatment of comorbid MDD

Among individuals with MDD and a physical disease, systematic reviews of RCTs have shown that antidepressants, compared to placebo, show effect sizes similar to or even larger (i.e., SMDs higher than 0.50)[279-286] than those for MDD without physical comorbidity, where SMDs range between 0.17 and 0.49[287]. Such effect sizes have been reported for MDD comorbid with cardiovascular diseases (e.g., coronary artery disease[281], ischemic heart disease[282], myocardial infaction[288]), neurological diseases (e.g., multiple sclerosis[279], Parkinson's disease[289], stroke[290,291]), diabetes mellitus[292], cancer[286,293], rheumatoid arthritis[280] and human immunodeficiency virus (HIV) infection[294]. Whether these larger effect sizes are due to differing biological processes, smaller placebo effects, or other reasons such as small-study inflation, needs further study. Indeed, most meta-analyses were based on a few small RCTs.

In other diseases – such as epilepsy, inflammatory bowel disease, traumatic brain injury, asthma and chronic obstructive pulmonary disease – few or no RCTs of antidepressant treatment for comorbid MDD have been conducted[295-301], resulting in a sparse evidence base

for treatment recommendations.

Many studies have demonstrated that psychotherapies[302] – including CBT[303-305], mindfulness-based interventions[306-308], compassion-focused therapies[309,310] and problem-solving therapy[311] – effectively treat MDD in people with diseases such as cancer[307,308], diabetes mellitus[312,313], cardiovascular diseases[314-318], HIV infection[319], psoriasis[320], multiple sclerosis[279,321,322], inflammatory bowel disease[305], chronic obstructive pulmonary disease[323-325], and kidney failure[326-328].

Regardless of intervention type, effect sizes are generally low to moderate[309], and many individual studies are at risk of bias[309], have low sample sizes, and use heterogenous research designs[310]. Findings concerning cardiovascular diseases are more robust, particularly in people with heart failure. An umbrella review concluded that there is sound evidence that psychotherapy can treat MDD in people with ischemic heart disease, based on the findings of four systematic reviews[318]. Similarly, in a scoping review of nine psychotherapy trials, seven showed significant reductions in MDD symptoms, although two did not maintain benefit at longer-term follow-up[314].

Psychotherapy can also be delivered online or via telephone to people with physical diseases, with comparable outcomes to face-to-face delivery[303,304,322,329], particularly if clinician-guided[303]. These modalities have also been shown to be acceptable to individuals[330,331], which is particularly important for those who may have mobility or accessibility difficulties[322].

Effect of MDD treatments on physical disease outcomes

In addition to improving depressive symptoms, antidepressant medication may have positive effects on physical disease outcomes. For example, a recent umbrella review found that SSRIs may improve fasting glucose/HbA1c and pain[332], and may reduce hospitalization rates in coronary artery disease[281]. Among individuals with diabetes mellitus, antidepressant treatment is reported by RCTs to improve glycemic control[292], and is associated with lower mortality[333] and a lower risk for myocardial infarction[334]. Furthermore, antidepressants improve motor function and disability after stroke[290], and motor symptoms in Parkinson's disease[289].

There is also tentative evidence that psychotherapies may improve physical health-related quality of life and fasting glucose/HbA1C[332], and have a positive impact on physical outcomes in people with ischemic heart disease[318]. However, results are limited by the low quality of trials, and recent advances in medical care may have outweighed previously demonstrated benefits of psychotherapy[318]. A systematic review found that the effect of psychotherapy on disease activity in people with inflammatory bowel disease was not clear[305].

A systematic review focusing on people with rheumatic conditions reported that CBT led to reduction of pain severity in four of seven studies, and to significant reduction of fatigue in one of four studies[329]. Psychotherapy may also lead to increased engagement in lifestyle behaviors that positively influence physical health[327,335]. For example, CBT has been found to improve medication adherence in people undergoing dialysis[327]. However, it is not yet known whether these changes translate into improved physical outcomes [327].

Effect of physical disease treatments on MDD outcomes

Medications such as non-steroidal anti-inflammatory drugs (NSAIDs), statins, angiotensin-converting enzyme (ACE) inhibitors, drugs acting on the renin-angiotensin system, and cytokine inhibitors may yield additional positive effects when added to an antidepressant[179,336-339], reducing depressive symptoms among individuals with a physical disease[338,339]. As a prominent example, a recent meta-analysis found that anti-inflammatory drugs improved depressive symptoms with a SMD of 0.64 (95% CI: 0.40-0.88) when used as add-on to antidepressants in MDD, and of 0.41 (95% CI: 0.22-0.60) when used as monotherapy among people with a physical disease[338]. Furthermore, anti-inflammatory add-on to antidepressants in MDD improved response and remission rates[338].

The most frequently studied anti-inflammatory drugs are NSAIDs, cytokine inhibitors and statins. Several of these drugs (e.g., statins) target physical diseases that are disproportionally common in people with MDD (e.g., cardiovascular diseases and diabetes mellitus)[340]. The antidepressant effects of these drugs provide further support to the previously discussed shared biological mechanisms of MDD and physical diseases (e.g., inflammation, HPA axis activation, and mitochondrial dysfunction)[341].

On the other hand, many commonly used treatments for physical diseases can induce depressive symptoms as a side effect[342]. A well-known example is interferon or IL-2 treatment, in which up to 80% of individuals develop depressive symptoms, often dominated by somatic/neurovegetative manifestations within the first weeks, and 25% develop a major depressive episode within 48 weeks[343]. The proposed mechanism is pro-inflammatory and immune-activating[344], with administration of pro-inflammatory cytokines representing one of the most robust human models of MDD[345].

Adverse events and clinical considerations of management

Among individuals with physical diseases, it is important to balance the potential antidepressant effects of pharmacotherapy with possible side effects. The adverse event profile of any antidepressant must be tailored to the symptomatic and risk profile of the comorbid physical disease and the specific individual. Potential adverse events include weight gain and the related risk of developing or exacerbating diabetes mellitus (particularly relevant to tricyclic antidepressants and mirtazapine)[346]; cardiac toxicity and QTc prolongation (highest risk with tricyclic antidepressants and lowest with sertraline)[347,348]; impact on bone metabolism, increasing the risk for osteoporosis and fractures (especially with SSRIs)[349]; and bleeding, which is further increased when combining multiple classes of medications (e.g., SSRIs and NSAIDs[350]). Furthermore, clinicians need to consider potential drug-drug interactions, which are divided

into pharmacodynamic (more frequent with older antidepressants) and pharmacokinetic (e.g., affecting hepatic metabolism, with antidepressants often being dependent on cytochrome P450 metabolism)[351].

Overall, the antidepressant treatment of MDD that is comorbid with a physical disease will benefit from interdisciplinary care (e.g., frequent discussions with the clinician responsible for the treatment of the physical disease), consideration of patient-related factors (e.g., age, pain, polypharmacy, and previous antidepressant trials all affect choice of antidepressant drug), and ongoing management. Finally, psychotherapy trials have not systematically assessed adverse events or contraindications[352-354]. Therefore, psychotherapy intervention trials in individuals with physical diseases have thus far reported very few adverse events, but clinical monitoring is indicated[310,324].

FUTURE DIRECTIONS AND CONCLUSIONS

This paper reviews the substantial evidence base documenting that MDD is highly prevalent in populations with a range of common physical diseases, and vice versa. This high level of comorbidity translates into poorer economic and treatment outcomes.

A range of mechanisms have been implicated in both MDD and comorbid physical diseases, suggesting shared pathophysiology. We have discussed prominent pathways, such as inflammation, the gut microbiome, mitochondrial function, brain structure and function, and the HPA axis. Additional pathways requiring further investigation are endothelial and autonomic dysfunction, leptin and insulin signaling, and biological aging[2,15].

Shared mechanisms provide opportunities for treatment that may benefit both MDD and comorbid physical diseases, but may also inform the investigation of potential off-label interventions and drug-repurposing strategies. For example, statin therapy, commonly prescribed for cardiovascular diseases, is being trialed for MDD[355,356]. Metformin (a medication typically prescribed for type 2 diabetes mellitus) and candesartan (an angiotensin II receptor blocker) are also being trialed for depression[357].

Similarly, there are a range of lifestyle, physiological, social and genetic risk factors that are shared by MDD and physical diseases[358]. Interventions that address these factors may improve both psychiatric and physical outcomes. An example is the developing evidence base to support the use of lifestyle approaches to mental health care. Clinical guidelines[359] increasingly suggest that lifestyle interventions should be a major component of MDD management. Of the lifestyle domains reviewed in one of these guidelines[360], the strongest recommendations when treating MDD were for exercise, relaxation, and work-directed, sleep and mindfulness-based interventions. There was further evidence to support dietary and green space interventions, but fewer data from RCTs to support interventions targeting smoking, loneliness or social support.

Further to the need for additional intervention and prevention strategies is the need for new models addressing challenges to accessible care and integrating psychiatric and physical considerations[361]. Having MDD, as well as subthreshold depressive symptoms, that are comorbid with a physical health condition amplifies barriers to accessing and engaging in potentially helpful treatments and self-management strategies[16]. Treatment needs are often multiplied, diverse and chronic, placing strain on health services and families, especially in low- and middle-income countries, cultural and linguistic minorities, and First Nations people, and those in rural areas with scarce resources[362]. Innovative strategies to overcome these barriers, incorporating integrated care for physical health conditions (particularly cardiometabolic diseases) in MDD, are required [363].

One example is the collaborative care model, usually involving a physician and at least one other health professional (and sometimes peer or carer supports) who communicate with each other and the individual with MDD in a structured and planned way, to optimize treatment and care[16,61]. Contact and follow-up appointments are organized by a central coordinator (e.g., a case manager) who promotes self-management strategies (e.g., symptom and treatment monitoring and management, goal setting, problem solving, healthy lifestyle habits, and stress management)[364]. There can also be emphasis on enhancing patient-centered decision making, and consideration of patients' broader recovery goals[16,365]. Including lived experience input may also strengthen and support the broader aims of person-centered management.

Collaborative care interventions have shown positive effects for people with depressive symptoms and coronary heart disease[366], breast cancer[367], and diabetes mellitus[292,364]. Such interventions appear to be equally effective in delivering MDD care for people with and without physical diseases[368]. Their effect on physical health, however, varies depending on the specific condition[292,369]. Implementing collaborative care interventions also requires careful consideration of leadership and delivery resources, costs for ongoing care, and cultural context[370].

A further potential way to extend the reach and scope of effective treatment and care is provided by digital technologies. eHealth and mHealth interventions range from multicomponent intensive psychosocial programs to briefer specific self-management interventions (e.g., targeting exercise)[16,371-373]. They can be adapted to suit context and resource capabilities, although the majority of RCTs are being conducted in high-income countries[372].

A meta-analysis of RCTs of digital interventions reported a significant moderate effect on depressive outcomes (g=–0.37, 95% CI: –0.60 to –0.14)[371]. Key predictors of significant effects were a two-way "clinician-patient communication loop", coupled with progress monitoring and adjustment of treatment as well as self-management strategies over time[362,371]. Successful interventions ranged from those delivered via phone to more complex ones delivered via web platforms, highlighting the adaptability of digital approaches[371]. At this stage, however, the number of trials on each comorbid physical disease varies, and results are inconsistent[371,372]. More attention also needs to be paid to the scalability and validation of digital interventions and how they can be better integrated into health services[362,372].

In summary, there is now a substantial body of evidence documenting a shared biological and environmental pathogenesis between MDD and several physical diseases. Further efforts are

required to develop prevention and intervention strategies that target these shared pathways. These include investigation of therapeutics that target overlapping biological mechanisms (e.g., statins, metformin, interventions on gut microbiome) and the integration of strategies that address risk factors such as lifestyle behavior (e.g., exercise, diet). Furthermore, research and implementation efforts are now required to accelerate the development and translation of transdiagnostic, interdisciplinary models of care that consider both psychiatric and somatic presentations.

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Community care for people with mental illness: challenges emerging in the 2020s and consequent recommendations

The later years of the 20th and the beginning of the 21st century – coinciding with deinstitutionalization and shift to managing mental health problems outside of hospitals – have been characterized by several socioeconomic trends which are of major importance for the strategies of community mental health care[1,2].

The rampant urbanization is one of these trends. All the predictions are in agreement that at least 60% of the world's population will live in towns by the year 2050. Urbanization has many positive effects, but it also affects the notion of community. The increasing population density, combined with the lack of links or relations between neighbours, reduces their tolerance for behaviour which was previously not seen as disturbing.

Another trend which is relevant to community psychiatry is commoditification, i.e., the tendency to measure everything in financial terms of losses and gains. The conversion of health care from being society's ethical obligation to being an economic opportunity has led to an increase of privately owned health care institutions and other services. It is also leading to a neglect of care for those who are poor and unemployed. Private health care facilities attract the best specialists by offering high salaries, which leaves government health services with lesser chances to employ the best of staff. It also makes it more difficult to organize health care in the community.

The tremendous development of social media is also contributing to the obsolescence of the concept of geographically defined communities. At the same time, the poor, the elderly and other people who do not use social media are becoming even more separated from those who do, although they live in the same locality or close to those who have access to the tools of the Internet age and the skills to use them.

The developments in low- and middle-income countries should be an even greater reason for concern. In many countries, rich people have withdrawn into gated settings, sometimes protected by barbed wire fences from the rest of the population. The fact that they live in the same geographical area rarely makes them interested or ready to help others. Those making up the middle class and the poor live more and more often in high rise dwellings making contact and mutual help less likely or impossible. The poor in favelas and other forms of slum have more contact and often help one another – conditions in which they live make this necessary, not necessarily desired.

The disappearance of the community defined as a group of people knowing and helping one another has led to the replacement of the notion of *community care* by that of *care in the community*, meaning that the care is provided outside of a hospital or other inpatient facility rather than in collaboration with people living next to the person who is suffering from a disease. The only persons in the "community" are members of the family of the person who is not well, and more rarely friends of that person.

Most of the people with more severe forms of mental illness (unless they are rich and make use of private institutions) are left in the setting in which they lived before the illness broke out. They are usually looked after by their families, for whom the responsibility to provide care can be a huge burden and an obstacle to provide education to children or live a life of acceptable quality. So, it has become necessary to re-examine the principles of care defined in the late years of the 20th century[3], and produce plans which will help people who have mental illness and their families or others who provide care.

In my opinion, the following measures – partly recommended by health care authorities and experts and by representatives of families and other carers – will have to be introduced without further delay:

- The practicing psychiatrist, in collaboration with family members (and other carers), social workers and persons who have experienced mental illness, should define: a) what are the basic needs of a person who has experienced mental illness and is about to be discharged from a treatment facility, and b) what is the minimum of resources that a family or other carer should have if the person who is experiencing a mental illness or its aftermath should be given care at home.
- The family or other carer should be given financial and other support (for example, regular home visits by a nurse) which is necessary to make the continuing treatment and care at home possible and successful.
- Social workers or nurse-visitors should be given the responsibility for a certain number of families (how many will depend on geography and possibility of transport) whom they should regularly visit. During their visit to these families, they should offer help in tasks which may surpass the capacities of the carers, as well as monitor and support the person with mental illness.
- The staff of teams which will provide outpatient care to persons who have experienced or experience mental illness should be given training focussed on work with mentally unwell people at their home. This training should be provided by psychiatrists and by carers and people who experienced mental illness.
- The facility which coordinates mental health care should establish links with other social services in the area which it will cover, and staff from these services should be invited to participate in the training of the field workers.
- The peers willing to help people who are experiencing a mental disorder or did so in the past should be offered training in matters relevant to their provision of support to people in distress. They should also be offered financial reward for their work.
- Psychiatrists who will participate in the mental health care network should, in addition to their training in clinical psychiatry, also spend a defined period of time working in the facility which organizes care for a geographical area and in the services established outside that facility. This should allow them to decide whether they would be willing to work in this type of services.
- The team managing services in a geographically defined area should carefully monitor signs of staff burn-out and foresee

measures which can be taken to reduce it.
- It is possible that some of the persons who were discharged from a facility providing mental health care will experience another episode of illness. The management of this new bout of illness should be done in the same facility which provided care in the first instance, taking into account advance directives which all persons who had treatment in the facility will have to produce on discharge.
- It is expected that the treatment in the facility and subsequently will abide by the rules ensuring the protection of human rights of the individual in treatment and of his/her carers.

The suggestions made here may require a significant reorganization of services, and an investment into the training of personnel who will provide care, of persons experiencing mental illness, and of their carers. It is also clear that it is necessary to provide services with financial resources which are at present lacking in most parts of the world. This may be seen as or declared as impossible at present – if such is the case, it will be necessary to realize that it is extremely unlikely that fiddling with arrangements without the provision of additional resources will produce solution to the current crisis of community care for people with mental illness, their families and other carers.

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Family psychoeducation in the early stages of mood and psychotic disorders

When combined with pharmacotherapy, family psychoeducation and skills training are key strategies for preventing, delaying or minimizing the severity of illness episodes in major psychiatric disorders[1-3]. High levels of expressed emotion – as indicated by critical comments, hostility and/or emotional overinvolvement from caregivers – are associated with high rates of recurrence in patients with schizophrenia, bipolar disorder and major depressive disorder. These familial attitudes can become more negative and fixed as the disorders progress[4].

Early on in the illness trajectory, there is a window of opportunity for prevention or mitigation of disability in young persons. During this interval, patients and parents are usually most open to the collaborative approach of psychoeducation, in which they examine their thinking and behavior in relation to one another. Family psychoeducational interventions, however, have never completely "made it out of the shop". Few practitioners have been trained in these methods. When psychoeducation is offered at all, it is usually in the form of unstructured support groups or canned didactic lectures. Moreover, support groups have limited reach: in a 2017 survey of 2,395 patient and caregiver respondents from the Depressive and Bipolar Support Alliance, a US-based support organization, 87% of persons with bipolar disorder were taking medications but only 10% attended support groups[5].

When adolescents or young adults first experience symptoms of mood or psychotic disorders, both they and their families are understandably confused as to what is happening. Parents have basic questions about the diagnosis, the likely course of symptoms over time, and what treatments are likely to be successful. Unfortunately, many clinicians simply provide didactic information in rote fashion, instead of assisting the family and the patient in negotiating the complex challenges of a new illness.

What psychoeducational strategies help engage families and patients at these stages of illness development? Consider an 18-year old male, Zak, who has had an acute manic episode requiring hospitalization. Zak's father is able to describe the prodromal symptoms prior to his admission (e.g., rapid speech, irritable mood), but believes that his son has schizophrenia. His mother thinks that he is depressed. Zak thinks that there is nothing wrong with him. A psychoeducational family clinician will start with the provision of factual material: the key symptoms of mania and how they are different from those of a psychotic episode or normal teenage behavior. The clinician will personalize this information by encouraging Zak to describe the development of his symptoms and parents to chime in with their observations. The patient is identified as the "expert in the illness", because "you can educate us as to what you've gone through and what might help you recover". When their position in the family is elevated in this way, young people are more able to cope with the well-intended but often intrusive or critical comments of their relatives.

Moving a step further, the clinician will encourage the parents and offspring to explore the practical application of Zak's diagnosis: what might be the early warning signs of new manic or depressive episodes? A paper or online mood chart[6], completed daily by Zak and his parents, will help the family to become familiar with his patterns of mood shifts. The parents' attributions about the causes of these fluctuations (e.g., "He has a biologically-based mood disorder" versus "He's lazy") will be addressed. The clinician will gently challenge parents as to the usefulness of certain beliefs, especially those that lead them to become harsher or expect an unrealistically high level of functioning in their offspring.

In a similar vein, families need help locating and evaluating the advantages and disadvantages of treatment options. They may be confused about how to decide on the intensity (e.g., weekly individual therapy vs. partial hospitalization) or type of care (e.g.,

pharmacotherapy, psychotherapy, or support groups). The parents may not agree on the need for medications or, if they do, they may not agree on what type or dosage is needed. They may need guidance in advocating for the child within the school system. Siblings may be confused as to their role in helping their ill brother or sister (or, at minimum, how not to trigger symptoms further).

A different set of questions may haunt young affected people during this period. These issues surround how the illness will impact their peer and school relationships or activities, or even how their identity has been changed by the illness. They may express considerable resentment toward their parents for seemingly overreacting to minor symptoms or for insisting on a regimented lifestyle. These issues can become intertwined with the young persons' struggle for autonomy. Psychiatric treatment may come to symbolize the last bastion of their parents' control over them, with the psychiatrist seen as an agent of the parents.

A key component of psychoeducation is the relapse prevention plan. The patient and the parents make a list of early warning signs of episodes and past stressors – major or minor – that appear to have triggered those episodes (e.g., the start of a new school year). Then, clinicians coach the family to make a list of potential coping strategies (e.g., try to regulate sleep and wake times) and potential obstacles to their implementation (e.g., foregoing late-night parties). The plan is modified over time as more data are collected on warning signs, eliciting stressors and effective coping strategies.

In later segments of psychoeducation, clinicians attempt to modify levels of expressed emotion by guiding families in effective communication and problem-solving. Clinicians elicit role-play interchanges between parents and offspring with practice of skills such as active listening, making requests for changes in each other's behaviors, and balancing positive and negative feedback. To reduce parent/offspring criticisms (e.g., "I resent the hours you keep"), clinicians can take several steps: a) reframe the criticism as coming out of positive intentions (e.g., "I am worried about you not getting enough sleep and getting ill again"); b) point out that the parent's manner of delivery is inadvertently alienating the offspring; and c) model for the parent how he/she might make a request for behavior changes (e.g., "I'd appreciate your helping me manage my own anxiety by keeping to a regular bedtime"). These exchanges can be followed by problem-solving exercises in which family members offer practical input about how to keep consistent nightly routines.

Severe family conflict often grows out of parents' disappointments over failed expectations of the child. Input from the offspring about what they can or cannot accomplish while still symptomatic is essential. The offspring can be coached to make decisions that will enhance their chances of recovery (e.g., avoiding enrolling themselves in too many courses; discontinuing use of cannabis or psychostimulants). Recovery can be framed as an objective that must be achieved by the family as a whole, not only by the patient.

Randomized clinical trials indicate that, among youth in the early stages of bipolar disorder, a 12-session, 4-month protocol of family-focused therapy (psychoeducation, communication training and problem-solving) is associated with shorter depressive episodes, longer periods of wellness between episodes, and less suicidal ideation and behavior than briefer forms of education[1,7]. The broader availability of psychoeducational therapy may do much to reduce the long-term personal, familial and societal burdens imposed by severe psychiatric disorders.

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Putting psychological interventions first in primary health care

Task-sharing – in which specialists train, supervise and support non-specialist health care providers – is proven to be acceptable, feasible and effective in scaling up mental health care for depressive and anxiety disorders[1]. In this perspective, we focus on reasons for and barriers to task-sharing of psychological interventions in primary health care. We also cover what the World Health Organization (WHO) does to address these barriers.

Task-sharing in primary health care is vital to increase treatment coverage for people in need, but it rarely includes providing evidence-based psychological interventions. Yet research shows that cognitive-behavioral therapy (CBT), on its own or combined with antidepressants, is the first-line treatment for adult depressive disorders[2]. CBT is also first-line treatment for other conditions, including anxiety disorders. Several other psychological therapies – such as interpersonal, problem solving and behavioral activation therapies – are likely equally effective[3].

Many evidence-based psychological interventions are well suited to task-sharing. They can be designed to be safely delivered by supervised non-specialists. They can be adjusted to be briefer and less resource-intensive than conventional psychotherapy, without being less effective[1]. And they can be adapted for remote or group delivery or provided through guided or unguided self-help man-

uals, websites and applications. WHO's Problem Management Plus, for example, comprises just five weekly sessions, can be delivered to individuals or groups, and is suitable for many contexts, types of adversity and types of helpers[4].

Despite their potential, psychological interventions are rarely provided at scale[5]. Yet scale up is possible. The National Mental Health Programme in Lebanon is showing that implementing a nationwide self-help intervention for depression is feasible, even amid multiple crises[1,6].

There are many barriers to including psychological interventions in task-sharing:

- *Lack of political support*. Despite the evidence, decision-makers in many countries remain unaware of the effectiveness of psychological interventions and so exclude them from universal health coverage packages of essential services and financial protection schemes.
- *Resistance to change*. Still some psychologists today – including some national psychological associations – are against sharing responsibility for delivering psychological treatments with non-specialists. The reality though is that no society, however rich, will ever have enough specialists to offer more than a fraction of the volume of care required to help the large numbers of people who need mental health interventions.
- *Little commercial incentive*. Despite their cost-effectiveness, there is little commercial incentive to make psychological interventions widely available. By comparison, pharmacological interventions are heavily promoted by pharmaceutical companies, which may influence decision-makers and medical staff to focus on drug treatments[6].
- *Lack of human resources*. Task-sharing for psychological interventions in primary health care typically means recruiting and retaining additional (non-specialist, community-based) staff to deliver those interventions. This is needed since medical staff in primary health care typically have heavy workloads and, while they can refer people for psychological interventions, they rarely have time to deliver lengthy therapeutic sessions themselves.
- *Lack of financial resources*. Funding a national workforce of providers, trainers and supervisors demands larger mental health budgets than are currently available. This means that more funds must be allocated within health budgets or, importantly, from the state treasury.
- *Lack of access to relevant tools*. Too few proven psychological intervention manuals for non-specialists are freely available (open access)[7].
- *Lack of operational guidance*. Apart from the Design, Implementation, Monitoring and Evaluation (DIME) manuals[8], there is little international guidance on how to integrate psychological interventions in primary health care. Even if service planners want to add those interventions to their services, they may not know what steps, service models and resources they need.

Building on the work of many others, the WHO is addressing a range of these barriers. We recommend psychological interventions and promote task-sharing through our *Comprehensive Mental Health Action Plan 2013-2030*, our mhGAP programme, our Universal Health Coverage (UHC) compendium and our *World Mental Health Report*[1]. We develop, test and publish open access diverse psychological interventions that are scalable and suit different delivery models. And we support training and supervision tools to help assure a competent non-specialist workforce through our Ensuring Quality in Psychological Support (EQUIP) initiative[9].

We are also finalizing a new, operational guide – a *Psychological Interventions Implementation Manual* – to help service planners and programmers add psychological interventions to their services. Written for managers and others responsible for planning and implementing services, this manual provides practical guidance on how to plan, prepare and provide psychological interventions within existing services, such as health, social or education services.

This new WHO manual advises service planners on how to: a) choose and adapt psychological interventions to be relevant for their specific settings; b) decide a setting and system for delivery, including linking to associated services; c) develop a competent workforce by selecting, training, assessing and supervising providers; d) identify potential service users, assess their support needs and ensure people get the care they need; and e) use monitoring and evaluation to evaluate and improve the service provided.

The manual marks the latest addition to our toolbox for psychological interventions. After publication, it will be field-tested and refined.

Service planners can now freely access all the resources they need to implement psychological interventions: intervention manuals, tools to support competence, and operational guidance for implementation. The next big step is to get these resources into use. Ultimately, this work is intended to help improve the quality and local availability of evidence-based mental health care, so that millions more people with depression and anxiety will be effectively helped.

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Challenges in improving mental health literacy at population level

The expression "mental health literacy" was introduced in 1997 by Jorm et al[1], referring to "knowledge and beliefs about mental disorders which aid their recognition, management or prevention". Compared to contemporaneous programmes aiming to reduce stigma and discrimination related to mental illness, this construct reflected a broader and positively framed public mental health goal. However, the concept of mental health literacy does not ignore stigma as a public mental health problem. A more recent definition[2] explicitly includes reduced stigma as a component of mental health literacy.

One approach to improving mental health literacy has been provided by Mental Health First Aid trainings, mostly conducted in Australia and targeted towards specific professional groups, population subgroups, or disorders. However, while training 1% of the Australian population[3] may be an important milestone, given positive evidence for its effectiveness, this coverage is far lower than that achieved by mental health social marketing campaigns in many countries and regions.

The cost of mass media once limited the use of social marketing, such that mental health campaigns tended to be brief and showed either limited or no effectiveness[4]. The advent of social media has allowed organizations to increase their reach and duration for a given spend, and to cover also low- and middle-income countries. Campaigns can deliver more content and drive people towards Internet resources with further content.

The clearest example of a public mental health programme which effectively delivered a variety of contents over a long period is Time to Change[5], whose social marketing campaign ran in the UK from 2009 to 2021. Although a stigma reduction campaign, this is worth discussing in relation to mental health literacy because of its promotion of supportive behaviors towards people with mental health problems. Market research showed that solely asking people not to stigmatize or discriminate is unsatisfactory; they want to know how they should behave instead.

The focus on recognition of signs of common mental disorders, coupled with supportive responses, demonstrates some convergence with the stated objectives of mental health literacy definitions besides stigma reduction. Nevertheless, Time to Change did not cover details about specific disorders. While the campaign included people discussing a variety of disorders, its messaging and evaluation were in relation to "mental illness" or "mental health problems".

The evaluation of the outcomes of this campaign focused mainly on stigma and discrimination, but the results illuminate a major challenge in improving population mental health literacy, which is the expansion of the concept of mental illness to include experiences that are not considered as such by professionals. Population survey respondents were asked whether they considered stress and grief to be mental illnesses[5]. Between 2009 and 2019, the proportion endorsing stress as a mental illness increased from 57.5% to 67.5%; similarly for grief, from 49.3% to 57.9%. This raises the question of whether population mental health campaigns, either targeting stigma or mental health literacy, should try to prevent the medicalization of some experiences as an unintended consequence.

The reverse of this issue is the failure to recognize signs and symptoms of common mental disorders due to their normalization. Evidence for this challenge comes from the evaluation of England's first mental health literacy programme, Every Mind Matters. Developed and delivered by Public Health England, Every Mind Matters was launched in October 2019. Its target was to encourage adults in England to take positive action regarding their mental health and thus reduce development of common mental disorders, through a social media marketing campaign promoting digital support resources. The digital resources comprise National Health Service-assured content covering sleep, stress, anxiety, and low mood. There were two bursts of social marketing to drive people to the digital resources before the first national COVID-19 lockdown, while subsequent bursts occurred during the pandemic. The content was therefore further developed to address the mental health challenges created by the pandemic.

Web analytics showed that, between October 2019 and February 2021, the Mind Plan for supporting one's mental health was completed over three million times, against a target of one million for the first year. However, in contrast to this high level of usage – and despite small improvements from September 2019 to March 2020 in knowledge of management for stress, depression and anxiety, mental health vigilance, sleep literacy, psychological wellbeing and self-efficacy – by March 2022 there was a deterioration in all outcomes compared to the September 2019 baseline, except for sleep literacy which was unchanged[6].

This dramatic example of reduced ability to recognize and act on signs and symptoms of common mental disorders should not be taken as an isolated event. People in difficult social circumstances are more likely to attribute mental distress to these circumstances than to something amenable to professional help-seeking, and responses to medication and psychological therapies are weaker in the presence of such circumstances[7]. Public mental health organizations must acknowledge the impact of these circumstances and work to address them.

The development of Every Mind Matters highlighted two further challenges in improving population mental health literacy. One is differential demand for literacy components. Following a pilot study, revisions were made to the digital resources and campaign before the launch, shifting from promoting recognition of signs and symptoms to evidence-based actions to protect and improve mental health. The feedback indicated that people wanted easier access to information on actions, and did not want to first read content promoting recognition.

The other challenge is avoidance in relation to severe illness. Content in addition to the initial four problems (sleep, stress, anxiety, and low mood) was planned, including on obsessive-compulsive disorder, panic, social anxiety and the impacts of trauma, but was not added due to funding decisions. Psychosis was not

considered in scope for Every Mind Matters, as the National Health Service recommendation emphasizes the need to seek help from health professionals for this condition. The immediate issue arising is that excluding disorders from a campaign named Every Mind Matters risks alienating some. However, market research also indicated that fear of psychosis is such that inclusion of content about it might reduce use of the site. This would be problematic for future programmes wishing to include information on psychosis, given the severity of the disorder and its raised incidence in communities experiencing high levels of adversity[8].

It seems that Time to Change has been insufficiently effective in relation to the stigma towards psychosis, to the extent that a literacy campaign cannot include it without negative consequences. There is evidence from newspaper content analysis of a differential outcome of Time to Change with respect to diagnosis[9]. The probability of an article on schizophrenia being rated as stigmatizing was not different for 2008 and 2019, whereas for depression the probability fell between these years. Thus, while stigma reduction may be considered a component of mental health literacy, stigma presents a barrier to its improvement. A specific focus on psychosis may be needed, following the WPA's Open the Doors programme.

Improving mental health literacy thus faces several challenges, which may be amenable to the careful development, over several years, of a programme which is inclusive while paying attention to the need to reduce the risk of avoidance due to fear; acknowledges the impact of social problems such as lack of economic opportunities and discrimination on mental health; and avoids medicalization without discouraging help-seeking.

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Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions

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Treatment-resistant depression (TRD) is common and associated with multiple serious public health implications. A consensus definition of TRD with demonstrated predictive utility in terms of clinical decision-making and health outcomes does not currently exist. Instead, a plethora of definitions have been proposed, which vary significantly in their conceptual framework. The absence of a consensus definition hampers precise estimates of the prevalence of TRD, and also belies efforts to identify risk factors, prevention opportunities, and effective interventions. In addition, it results in heterogeneity in clinical practice decision-making, adversely affecting quality of care. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have adopted the most used definition of TRD (i.e., inadequate response to a minimum of two antidepressants despite adequacy of the treatment trial and adherence to treatment). It is currently estimated that at least 30% of persons with depression meet this definition. A significant percentage of persons with TRD are actually pseudo-resistant (e.g., due to inadequacy of treatment trials or non-adherence to treatment). Although multiple sociodemographic, clinical, treatment and contextual factors are known to negatively moderate response in persons with depression, very few factors are regarded as predictive of non-response across multiple modalities of treatment. Intravenous ketamine and intranasal esketamine (co-administered with an antidepressant) are established as efficacious in the management of TRD. Some second-generation antipsychotics (e.g., aripiprazole, brexpiprazole, cariprazine, quetiapine XR) are proven effective as adjunctive treatments to antidepressants in partial responders, but only the olanzapine-fluoxetine combination has been studied in FDA-defined TRD. Repetitive transcranial magnetic stimulation (TMS) is established as effective and FDA-approved for individuals with TRD, with accelerated theta-burst TMS also recently showing efficacy. Electroconvulsive therapy is regarded as an effective acute and maintenance intervention in TRD, with preliminary evidence suggesting non-inferiority to acute intravenous ketamine. Evidence for extending antidepressant trial, medication switching and combining antidepressants is mixed. Manual-based psychotherapies are not established as efficacious on their own in TRD, but offer significant symptomatic relief when added to conventional antidepressants. Digital therapeutics are under study and represent a potential future clinical vista in this population.

Key words: Depression, treatment-resistant depression, difficult-to-treat depression, ketamine, esketamine, second-generation antipsychotics, neurostimulation, electroconvulsive therapy, precision medicine, personalized medicine, patient-reported outcomes

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It is amply documented that major depressive disorder (MDD) is highly prevalent and associated with substantial burden and economic costs[1-5]. According to the World Health Organization (WHO), MDD is the single largest contributor to loss of healthy life, and this contribution has apparently further increased during the COVID-19 pandemic[6-8].

Notwithstanding the evidence supporting the efficacy of conventional antidepressants as well as manual-based psychotherapies and specific neurostimulation modalities, the majority of individuals with MDD are inadequately responsive to first-line treatments. Moreover, a substantial proportion of them fail multiple antidepressant interventions, resulting in what is described as treatment-resistant depression (TRD)[5,9-16].

Although non-response is a common outcome of treatment with multiple conventional antidepressants, a consensus definition of TRD with predictive utility does not currently exist. Instead, a host of definitions have been proposed, differing in their conceptual framework, operational criteria and working assumptions. This heterogeneity of definitions has resulted in a wide range of estimates of the prevalence of TRD[16]. The proportion of people with TRD would be expected to be higher when multidimensional definitions are used, especially those including patient-reported outcomes[17,18].

There are multiple serious public health implications associated with TRD, which provide the impetus for a specific focus on its detection and algorithmic management. First, TRD is common in the general population: based on international epidemiological estimates, it is extrapolated that more than 100 million people globally meet one or more definitions of this condition[19]. In addition, cost of illness studies have documented staggering direct and indirect economic costs associated with MDD, of which

more than half globally are attributable to TRD[20].

The relatively higher cost of illness attributed to TRD is directly due to higher health care utilization and the need for higher intensity treatments[20-23]. Higher indirect costs are also reported in TRD as a consequence of relatively greater impairment in psychosocial function, greater need for disability benefits, higher workplace disability and absenteeism, as well as the negative impact on carers [10,21,24-35]. Moreover, the rate of suicidality, including completed suicide, is disproportionately higher in TRD populations[36].

Additional public health implications of TRD relate to the established association between MDD and multiple common and chronic non-communicable physical diseases[37-39]. For example, it is established that MDD is a risk factor for cardiovascular disease, obesity and type 2 diabetes mellitus, and this is especially apparent in individuals with more severe and/or persistent depressive syndromes, which are over-represented in TRD populations[40,41].

Notwithstanding the foregoing public health implications of TRD, relatively few interventions have been established as efficacious for persons having multiple failed trials with conventional antidepressants. Instead, the emphasis of treatment development in depressive disorders has been on non-TRD populations. In addition, prevention of TRD is not a national health policy priority in any country worldwide, nor is progress in its management a quality outcome measure in any national public health care system.

Currently, more than 90 clinical practice guidelines are available that aim to provide decision support to clinicians caring for adults with mood disorders, originating from 83 countries and published in 27 languages[42]. Most of them have been produced in high-income countries and integrate scientific evidence with expert opinion[42-45]. Major limitations of extant guidelines, as it specifically relates to TRD, are that they do not adopt a consensus definition of this condition, and are not consistent in their selection or sequencing of recommendations.

In addition, extant guidelines vary in how they define an adequate antidepressant regimen and frequently conflate the treatment of TRD with non-TRD populations (i.e., partial responders to antidepressants). For example, second-generation antipsychotics (SGAs), of which most have not been proven to be effective in TRD, are often recommended for this condition in combination with antidepressants, despite their evidentiary base comprised largely of populations defined as partial responders to antidepressants.

Herein, we aim to provide a synthesis of current definitions of TRD, with an emphasis on their limitations, and recommendations for the development of an improved consensus definition; to summarize best estimates of the prevalence of TRD on the basis of current definitions; to review the available evidence on risk factors for TRD; to provide recommendations concerning the detection and management of TRD, based on research evidence when available and opinions from international experts; and to review investigational interventions for TRD. We do not intend to review and/or supplant existing recommendations for depression which is not treatment-resistant[44-48].

DEFINITIONS OF TREATMENT-RESISTANT DEPRESSION

The absence of a consensus and validated definition of TRD is a major limitation from the viewpoints of translational research, treatment development, as well as clinical and policy decision-making. Indeed, the pathway towards more targeted treatments in psychiatry requires a more precise delineation of the phenotype being evaluated[49-51].

The lack of a consensus definition results in the heterogeneity of populations enrolled in clinical trials evaluating new interventions for TRD, greatly limiting the interpretability and generalizability of the results. At a clinical level, the heterogeneity of patient samples contributes to differences in recommendations on the sequencing of treatments for people not responding to conventional first-line antidepressants. Disparity in practice behavior is likely compromising optimal health outcomes amongst those living with and receiving interventions for TRD. Moreover, from a policy perspective, reimbursement and access to treatment for populations with TRD will understandably vary in the absence of a universal definition, further compromising real-world outcomes in these patients.

The definition of TRD adopted by the US Food and Drug Administration (FDA)[52] and the European Medicines Agency (EMA)[53] is failure to respond to two or more antidepressant regimens despite adequate dose and duration and adherence to treatment. These regulatory agencies recognize the lack of precision of this definition and its overlap with definitions of "partial response" to antidepressant treatment[53]. The EMA definition, contrary to the FDA one, explicitly states that the failed antidepressants can be from the same or different mechanistic classes. Limitations of the FDA and EMA definitions are that they do not explicitly operationalize non-response, and do not consider psychotherapeutic interventions, regarded as first-line treatments for mild or moderate depression by most guidelines[48].

Other definitions of TRD have tried to overcome one or more of the above drawbacks (see Table 1). A commonly cited framework for the definition of inadequate response to antidepressants is the Thase and Rush staging model[54,55]. This model does not define TRD categorically, but instead operationalizes and tacitly implies TRD along a continuum of failed antidepressant trials. Stage I is defined by failure of at least one adequate trial of one major class of antidepressants; stage II by failure of at least two adequate trials of at least two distinctly different classes of antidepressants; stage III by stage II resistance plus failure of an adequate trial of a tricyclic antidepressant (TCA); stage IV by stage III resistance plus failure of an adequate trial of a monoamine oxidase inhibitor (MAOI); and stage V by stage IV resistance plus failure of a course of bilateral electroconvulsive therapy (ECT). In the text of the reference paper, it is made clear that the first trial should be a 4-week one with a selective serotonin reuptake inhibitor (SSRI) in moderate dosages[54].

Strengths of the Thase and Rush model are its simplicity, pragmatism, and close proximity to behavior in everyday clinical practice. In addition, this model prioritizes treatments that are better tolerated, which is in line with clinical practice guidelines and treatment algorithms. A first limitation of the model is that "failure" of treatment trials is not operationalized. Furthermore, the model reflects

Table 1 Definitions of treatment-resistant depression (TRD)

	FDA	EMA	Thase & Rush	Maudsley Model	GSRD	DM-TRD	MGH-S
Categorical definition	+	+	–	+	+	+	–
Number of requested treatment failures	2	2	1	1	2	1	1
Operationalization of "failure" of treatment	–	–	–	–	+	–	–
Indication that failed antidepressants must be of different classes	–	–	+	–	+	–	–
Indication of required duration of failed treatments	+	+	+	+	+	+	+
Implication of a hierarchy of efficacy of antidepressants	–	+	+	–	–	–	–
Failure of psychotherapies included	–	–	–	–	–	+	–
Failure of ECT included	–	–	+	+	–	+	+
Failure of augmentation/combination treatments included	–	–	–	+	–	+	+
Patient-reported outcomes considered	–	–	–	–	–	–	–
Baseline severity included	–	–	–	+	+	+	–
Duration of current episode included	–	–	–	+	+	+	–
Baseline psychosocial impairment included	–	–	–	–	–	+	–
Presence of comorbidities included	–	–	–	–	–	+	+
Comorbid anxiety symptoms included	–	–	–	–	–	+	+
Comorbid personality disorder included	–	–	–	–	–	+	+
Quality of life included	–	–	–	–	–	–	–
History of psychosocial stressors included	–	–	–	–	–	+	–
History of childhood adversity included	–	–	–	–	–	–	–

FDA – US Food and Drug Administration, EMA – European Medicines Agency, GSRD – European Group for the Study of Resistant Depression, DM-TRD – Dutch Measure for quantification of Treatment Resistant Depression, MGH-S – Massachusetts General Hospital Staging, ECT – electroconvulsive therapy

some non-validated assumptions: for instance that, in a patient initially not responding to an SSRI, a non-classmate antidepressant is more likely to be efficacious as a next-step treatment strategy; or that MAOI exposure should be limited to populations with treatment resistance. In addition, there is no explicit consideration of depression features such as duration and severity of the index episode, and no mention of psychotherapeutic interventions. Finally, although augmentation or combination strategies are mentioned in the text of the reference paper[54], they are not explicitly included in the staging model.

The Maudsley Staging Model (MSM) was developed to improve upon the limitations of the Thase and Rush model[56]. It defines treatment resistance as failure to attain significant level of improvement (i.e., clinical remission) from an accurately diagnosed depressive episode following treatment with an antidepressant given at an adequate dose for a minimum of six weeks. Three dimensions of resistance are included: treatment failure, duration of the depressive episode, and severity of depression[56].

A maximum of seven points can be assigned for the treatment dimension: one point for failure on 1-2 medications; two points for failure on 3-4 medications; three points for failure on 5-6 medications; four points for failure on 7-10 medications; five points for failure on more than 10 medications. One further point is assigned if augmentation treatment has failed, and one further point if ECT has not been effective. A maximum of three points can be assigned for the duration of the depressive episode: one if the episode is acute (up to 12 months); two if it is subacute (from 13 to 24 months); three if it is chronic (more than 24 months). A maximum of five points can be assigned for the severity of depression: one if it is subsyndromal; two if it is mild; three if it is moderate; four if it is severe without psychosis; and five if it is severe with psychosis. The overall staging of TRD is defined as mild (total score between 3 and 6), moderate (total score between 7 and 10) or severe (total score between 11 and 15).

Thus, in the MSM, resistance is assessed on the basis not only of treatment but also of illness variables, which has been reported to be useful in predicting short- and intermediate-term outcomes in TRD populations[57,58]. Overall, the threshold for the definition of TRD is low, requiring failure of just one adequate treatment. Failure of treatment is not operationalized, although a discussion of the complexity of defining clinical remission is provided in the text of the main paper presenting the model[56]. The assignment of scorings is in some respects arbitrary: for instance, a differential weighting is assigned to populations who fail at least five vs. less than five treatments, in the absence of validation. Failure of manual-based psychotherapies is not considered.

The European Group for the Study of Resistant Depression (GSRD)[14] separately defined non-response (failure to respond to one trial of 6-8 week duration of any antidepressant treatment); TRD (failure to respond to two or more adequate trials of different classes of antidepressants, with five different levels

of resistance depending on the overall duration of trials); and chronic resistant depression (failure to respond to several antidepressant trials, including augmentation strategies, of the overall duration of at least 12 months) [14].

Strengths of the GSRD staging method are the explicit definition of treatment non-response as a reduction of less than 50% in the total score on the Hamilton Depression Rating Scale (HAM-D)[59] or the Montgomery-Åsberg Depression Rating Scale (MADRS)[60], and the lack of any implicit hierarchy of efficacy of antidepressants. Limitations are the lack of validation of any of the provided time-based subcategories, including the definition of chronic depression based on a duration of at least one year, which is considerably briefer than what is generally accepted (i.e., longer than two years).

The Dutch Measure for quantification of Treatment Resistant Depression Model (DM-TRD) was developed to improve upon the point system proposed in the MSM[61]. To the variables considered in that system, this model adds functional impairment (with a score from 0, no impairment, to 3, severe impairment); comorbid anxiety symptoms (with a score from 0, not present, to 1, fulfilling criteria for at least one DSM-IV anxiety disorder); comorbid personality disorder (with a score from 0, not present, to 1, present based on formal interview); psychosocial stressors (with a score of 0, no psychosocial stressor, or 1, at least one psychosocial stressor); several categories of augmentation/combination regimens (with a score from 0, not used, to 3, five or six medications); use of psychotherapy (with a score from 0, not used, to 2, at least two empirically supported psychotherapies); and intensified treatment (with a score from 0, not used, to 2, inpatient treatment). The maximum total score becomes 27.

This model is the most comprehensive in terms of variables included, although physical comorbidities and childhood adversities are not considered. As in the MSM, the threshold for the definition of TRD is low, requiring failure of just one adequate treatment, and non-response is not operationalized. The predictive validity of the model has been supported to some extent[61].

The Massachusetts General Hospital Staging Model (MGH-S) definition of TRD integrates the number of failed trials with the intensity/optimization of each trial, without assumptions on the hierarchy of antidepressant classes[62]. One point is assigned for non-response to each adequate trial of a marketed antidepressant (duration of at least six weeks and adequate dosage). Half a point is assigned for each trial based on optimization of dose, optimization of duration, or an augmentation/combination strategy. Three points are assigned for non- response to ECT.

Limitations of the MGH-S include the lack of operationalization of "failure" of trials; the arbitrary scores attributed to treatments; the fact that optimization of dose or duration of treatment is weighted equally as augmentation/combination strategies (which is not empirically supported); and the assignment of one point for each failed antidepressant, which may generate a very high total score[63].

None of the extant TRD definitions are universally accepted and/or implemented at point-of-care in clinical practice[11,32,64-68]. In addition, no existing TRD definition is supported by an external validator and/or biomarker. Most TRD definitions do not explicitly consider failure of manual-based psychotherapies in their hierarchical characterization of treatment resistance. As psychotherapeutic interventions are recommended as first-line treatments in persons presenting with depression of mild or moderate severity, any working definition of TRD with clinical utility will need to explicitly include non-response to these interventions.

Also, common across most definitions of TRD is the absence of a quantifiable and consensus endpoint defining response versus non-response to antidepressants. An additional limitation is that the definition of outcome is based on a clinician assessment, while patient-reported outcomes are not considered. Indeed, even amongst patients classified as "responders", many continue to manifest debilitating residual symptoms[69,70]. This was highlighted in the STAR*D trial, in which it was observed that only 10% of persons "in remission" were fully asymptomatic[71]. If, for example, a person is classified as "responder" to treatment but continues to experience cognitive deficits that are impairing, it would be incorrect to consider this an adequate antidepressant response[72].

None of the extant definitions of TRD includes reference to quality of life. This is a major limitation, given the importance assigned to this variable by persons with lived experience[73]. The predictive utility of quality of life as a critical outcome measure when defining TRD is underscored by the observation that persons remitting with antidepressants who continue to report decreased quality of life are at greater risk of relapse and recurrence[74,75].

Further drawbacks of existing TRD definitions are that they fail to take into consideration the social, economic, anamnestic (e.g., adverse childhood experiences) and interpersonal factors which, alone or in combinations, are known to moderate antidepressant response[1,44,47,71,75-81]. Furthermore, an unintended consequence of a TRD framework that is hierarchical is encouraging multiple unproven treatment strategies, with polypharmacy and the possibility of associated safety and tolerability concerns[70,75].

Moreover, results of a recent analysis in the WHO World Mental Health Surveys underscores that persistence with next-step treatments is uncommon in persons with MDD[82]. Also, in those who do switch to next-step treatments, a considerable treatment delay (i.e., 6-9 months) elapses before switching occurs[82,83].

An example of a patient-centric framework describing persons with multiple antidepressant failures is the construct of difficult-to-treat depression (DTD)[84]. This construct relies on a biopsychosocial approach when considering causal, perpetuating and treatment factors of poor outcomes in depression[70]. The therapeutic emphasis in DTD pivots away from symptomatic remission towards symptomatic control, functional recovery and quality of life improvement as part of chronic disease management[70].

For several patients, despite non-remission status, more modest improvement in overall depressive symptom severity may result in significant self-assessed improvement in well-being[85-87]. For example, an approximate 35% improvement from baseline in total MADRS score may be associated with significant improvement of quality of life in persons with TRD[87]. These data support the notion that more modest improvements in symptom severity in persons with TRD may be clinically meaningful, and invite the need for multidimensional definitions that are not solely dependent on threshold symptomatic improvement[86,88,89].

Surveys of persons with lived depression experience have highlighted the importance of dimensional symptomatic outcomes in addition to categorical ones[90,91]. For example, alleviation of emotional blunting, anhedonia, anxiety and rumination are often prioritized by persons living with depression over full symptomatic remission[92]. Shared-decision making, patient-centered care focusing on specific symptoms of concern, and integrating treatment modalities become paramount in DTD, in keeping with the guiding principles of chronic disease management[84,93-96]. Although DTD is not currently recognized by regulators as a pathway for treatment approval and marketing authorization, it more closely approximates real-world presentations and outcomes among persons with TRD, and could serve as a clinical heuristic or even a framework informing the further characterization of TRD.

Overall, there is a confluence of research, clinical, policy, and public health reasons to have a validated and universal TRD definition. Existing definitions would be best characterized as frameworks that vary in their constituent variables and working assumptions. The existing TRD frameworks reviewed herein have not provided any substantive insight into the pathogenesis, treatment discovery and development, or clinical care of persons with TRD.

Moreover, there is no compelling evidence that any of the foregoing TRD frameworks have been implemented at large scale by the clinical or research community. A consensus definition of TRD at the very least will need to provide a quantifiable endpoint defining response, integrate manual-based psychotherapies, empirically validate assumptions surrounding differential treatment weighting, and integrate multiple factors known to influence antidepressant response. A TRD definition that is consistent across disparate clinical care ecosystems, and fulfills both research and clinical needs, is badly needed.

PREVALENCE OF TREATMENT-RESISTANT DEPRESSION

Differences in the definition of TRD have resulted in highly variable estimates of its prevalence rate[99]. TRD is often stated to affect approximately 30% of persons receiving antidepressant treatment in research settings, while its prevalence in real world practice is estimated to range between 6 and 55% [32,98-101].

Most individuals with MDD access mental health care initially through the primary care system, where measurement-based care is rarely implemented[102-104]. A tentative estimate of the prevalence of TRD in primary care can be made only indirectly by using a "depression treatment cascade" approach[105]. Approximately 10-15% of patients in primary care present with clinically significant depressive symptoms, and only about half of these cases are diagnosed, of which an estimated 25% are prescribed an antidepressant[106]. Replicated evidence indicates that, of those prescribed antidepressants, the majority discontinue treatment prematurely. Hence, only about 5-7% of persons with depression treated in primary care settings would be expected to achieve remission[106]. The foregoing cascade approach – which integrates aspects of misdiagnosis, non-adherence, inadequate treatment trials, as well as implementation gaps – underscores the high prevalence of poor outcomes of depression in primary care, of which a significant percentage would be expected to meet criteria for TRD[10,30,64,71,107,108].

A more precise estimate of the prevalence of TRD can be done by referring to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, a National Institute of Mental Health (NIMH)-sponsored multisite study (18 primary care and 23 psychiatric care settings) carried out in the US[33]. All eligible subjects enrolled in the STAR*D trial initiated treatment with citalopram. After a 12-week trial (level 1 treatment), those persons not in remission were randomly assigned to one of seven switch/combination approaches (level 2). Non-response to a switch/combination level 2 treatment resulted in randomization to further treatments (levels 3 and 4). The FDA and EMA definitions of TRD would align with failure to level 1 and 2 treatments in the STAR*D trial. On this basis, it can be estimated that approximately 55% of persons with MDD would meet the FDA/EMA criteria for TRD (i.e., inadequate response to two or more antidepressants despite adequate treatment intensity and duration)[33].

In summary, while it is often stated that TRD is affecting approximately 30% of persons receiving antidepressant treatment, a more stringent and multidimensional definition of this condition emphasizing symptomatic remission increases this estimate to about 55%.

RISK FACTORS FOR TREATMENT-RESISTANT DEPRESSION

Many factors have been identified as being associated with reduced antidepressant response, but relatively few are established as risk factors specifically for TRD. In addition, most factors identified as negatively affecting antidepressant outcomes are reported in small studies and are described with a particular antidepressant intervention. Amongst the relatively few studies that have sought to identify factors associated with TRD, most are limited by the inconsistent definition of this condition, and primarily evaluate outcomes with monoamine-based antidepressants.

Herein, we endeavour to identify factors that are associated with TRD. As most studies have evaluated factors associated with reduced response to conventional antidepressants rather than TRD, we provide clarity and attempt to separate these two aspects.

Sociodemographic factors

It is established that older persons more frequently fail multiple monoamine-based antidepressant treatments, which may be taken as evidence that TRD is more common in this subpopulation[109,110]. However, there is no evidence of an attenuated response in older adults with depression receiving manual-based psychotherapeutic treatments[111], and the efficacy of ECT does not seem to be reduced as a function of age[112]. It is also reported that repetitive transcranial magnetic stimulation (rTMS) may have similar (or potentially greater with increased pulse dose) efficacy in older adults with MDD[113].

It is not established whether female sex is a risk factor for TRD[114]. Whether depression during reproductive life events (e.g., peripartum onset depression) is more likely to be treatment-resistant is also not sufficiently established[115]. It is, however, well known

that females are affected by depression at twice the rate of males, and are more likely to be prescribed antidepressants[116]. Consequently, females would be expected to represent the majority within a TRD population, although it remains uncertain whether their relative risk is higher.

Socioeconomic position is a risk factor for TRD in persons receiving monoamine-based antidepressants. For example, in the STAR*D trial, persons meeting level 2 criteria (i.e., inadequate response to two sequential antidepressant regimens) were more likely to report lower income and dependence on the public health system[117]. In addition, persons of lower educational attainment or unemployed are found to be more often resistant to multiple sequential antidepressant strategies[17,118].

Future research should evaluate whether racial and/or ethnic factors contribute to the occurrence of TRD, and also endeavour to explore whether sexual orientation and/or gender identity, marital status, interpersonal connectedness, and measures of loneliness are risk factors for TRD.

Adverse experiences and trauma

It is well established that childhood maltreatment is associated with greater severity of depression, earlier age at onset, cognitive dysfunction, presence of psychotic symptoms, and physical/psychiatric comorbidities, each of which is also associated with attenuated response to antidepressants and manual-based psychological interventions[119-123].

There are also studies providing evidence that a reported history of childhood emotional abuse is associated with recurrent depression, persistent depression, as well as treatment resistance to antidepressants[124]. The international Study to Predict Optimized Treatment for Depression (iSPOT-D) reported that, amongst adults with MDD and a history of trauma between the ages of 4 and 7 years, only 15.9% achieved remission after 8 weeks of treatment with escitalopram, sertraline or venlafaxine, compared to 84.1% in individuals with no history of childhood trauma[125].

The attenuated response to antidepressants in persons with a history of childhood maltreatment may not, however, occur with all antidepressants. For example, preliminary evidence suggests that response to vortioxetine or ketamine treatment in depression is not reduced in persons with trauma, suggesting different outcomes as a function of the putative mechanism of action of medications[126,127].

More in general, life stress events have been directly associated with a poorer response to commonly prescribed antidepressants, as well as with a greater occurrence of suicidal behavior and comorbidities and a greater severity of symptoms, which are variables that could mediate the association with an attenuated response to antidepressants and possibly to TRD[128].

Clinical factors

Greater baseline severity is a highly replicated risk factor for TRD, and is indeed included in some frameworks as a variable in the hierarchical characterization of the condition. Illness duration is also highly associated with TRD, with replicated evidence indicating that the length of a depressive episode is inversely proportional to the probability of treatment response[129].

Evidence also suggests that some phenomenological characteristics of depression may be associated with treatment resistance. Psychotic symptoms affect approximately 20% of adults with MDD and are highly associated with TRD[130]. Mixed features are reported to be present in approximately 25% of persons with MDD and are associated with attenuated antidepressant response, although it remains to be determined whether they are a risk factor specifically for TRD[47,131].

Anhedonia is a core component of depression endorsed by 35-75% of patients, and may be a risk factor for TRD in persons whose treatment history is delimited to SSRIs [132,133]. Cognitive deficits in MDD are prevalent, persistent, and often progressively increase as a function of illness severity and duration; they are associated with attenuated response to select antidepressants, and may represent a risk factor for TRD[72,134-136].

Anxiety symptoms are frequently reported in TRD populations, and their presence in MDD is associated with a more severe illness presentation, lower probability of remission, comorbidities and suicidality[137-140]. Results from the STAR*D trial indicate that persons presenting with anxious depression exhibit attenuated antidepressant response and are more likely to develop TRD[141]. The GSRD study also reported that anxiety disorders were over-represented in persons meeting criteria for TRD[142].

It is well established that TRD populations have a higher rate of psychiatric and physical comorbidities as compared to non-TRD populations[143]. In addition, TRD is a risk factor for incident physical comorbidities, such as cardiovascular disease, type 2 diabetes mellitus, osteoporosis, and metabolic syndrome[40,144-146]. Evidence indicates that the foregoing physical diseases are in their turn risk factors for TRD[145,147-152].

DETECTION OF TREATMENT-RESISTANT DEPRESSION

The assessment of an individual with MDD towards personalization of treatment selection and sequencing has been previously reviewed in this journal[13]. Herein, we specifically focus on the assessment process aimed to confirm that TRD is present, and to rule out the possibility of pseudo-resistance.

Reviewed herein are the most common modifiable contributors to pseudo-resistance, including inaccuracy of the MDD diagnosis, inadequacy of current and past treatment trials, inaccurate assessment of response, and individual differences in the metabolism of antidepressants[153,154].

Accurate diagnosis of MDD

Inaccuracy of the MDD diagnosis is a common reason for pseudo-resistance. It is estimated that approximately half of individuals with MDD are not correctly diagnosed[155]. A not uncommon scenario in clinical practice is the depressed patient presenting with resistance to multiple sequential antidepressants whose correct diagnosis should be bipolar disorder instead of MDD[156].

For most individuals with bipolar disorder, depression is the index presentation, which warrants reconsideration of the MDD diagnosis in any person presenting with TRD. Indeed, it is reported that individuals prescribed multiple failed antidepressant trials

(i.e., TRD) have a much greater likelihood of an underlying diagnosis of bipolar disorder as compared to persons prescribed a single antidepressant trial[157]. Furthermore, it is reported that the transition from a diagnosis of MDD to one of bipolar disorder occurs at a rate of approximately 1-3% per year, indicating that diagnostic assessment must be reconsidered in all TRD presentations[130,158,159].

Multiple screening tools for bipolar disorder have been validated, including the Rapid Mood Screener (RMS)[160], the Patient Mania Questionnaire (PMQ)[161], the Mood Disorder Questionnaire (MDQ)[162], and the Hypomania Checklist-32[163]. Although screening tools are not sufficient to diagnose bipolar disorder, they can be used routinely in clinical practice and, if positive, warrant a more comprehensive assessment of the possible presence of bipolar disorder.

In addition to screening for bipolar disorder, relevant comorbid conditions should be diagnosed and managed if present. They include substance and alcohol use disorders, anxiety disorders, personality disorders, and some physical diseases such as hypothyroidism.

Determining the adequacy of treatment trials

The adequacy of an antidepressant treatment refers to the choice of medication, its dose, the duration of treatment, and the patient's adherence. A comprehensive and precise characterization of current and past medication regimens is required in order to confirm the presence of TRD, and can be captured by several instruments.

The Antidepressant Treatment History Form (ATHF) is a data capture instrument suitable for implementation at point-of-care. It was originally developed in studies of ECT and has subsequently undergone a broader clinical and research application[164]. It has explicit criteria for evaluating response to pharmacological and neurostimulation treatments, and is also available in a shorter version (the ATHF-Short Form, ATHF-SF)[165]. Other instruments that capture and record current and prior antidepressant regimens are the self-rated Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ)[166] and the Maudsley Treatment Inventory[56].

First of all, the appropriateness of the antidepressant regimen needs to be confirmed. It is well established that a knowledge-implementation gap exists between what are proven treatment strategies in MDD and what are actually implemented[42]. The adequacy of the dose of the medication has then to be considered: dosing recommendations are established for all approved antidepressants and are described in their respective product monographs.

The adequate duration of an antidepressant trial is generally considered to be 4-6 weeks at optimal dosing, although 60% of persons who achieved remission in the STAR*D trial with level 1 treatment did so after week 6 of treatment, indicating that a subpopulation of adults with MDD may require longer treatment trials[167,168].

Adherence to treatment has also to be assessed. A replicated observation is the high rate of non-adherence to antidepressants in persons with MDD. Persons with less than 80% adherence to antidepressant regimen recommendations are commonly defined as non-adherent[169]. Using this definition, about 30-50% of persons prescribed with antidepressants are non-adherent in acute phase treatment[169]. Assessing adherence to therapy includes pill counts and patient self-report. Digital sensor systems have been used in academic studies to document adherence, but are not readily available for clinical implementation.

Assessing outcome of previous antidepressant trials

Defining TRD implies quantification of therapeutic outcome with previous antidepressant treatments. However, as already stated, most definitions of TRD do not provide a quantifiable and consensus endpoint defining response versus non-response to antidepressants. An exception is the GSRD staging method[14], which explicitly defines treatment non-response as a reduction of less than 50% in the total score on the HAM-D or the MADRS. This may represent a useful reference in ordinary clinical practice.

However, it is noticed that, in some patients, a reduction of total MADRS score of about 35% may be associated with significant improvement of quality of life[87], supporting the need for multidimensional definitions that are not solely dependent on threshold symptomatic improvement[86,88,89]. The use of measures such as the World Health Organization-Five Well-Being Index (WHO-5) may be suggested for this purpose[170]. More in general, therapeutic endpoints that integrate patient-reported outcomes along with symptomatic measures may provide a more precise characterization of response to treatment[82].

Although "failure" of one or more antidepressant trials is an integral part of all definitions of TRD, it must be acknowledged that there is no consensus in the field about how this "failure" should be defined and ascertained. Overcoming this major limitation is an obvious priority for future research on TRD.

Pharmacogenomic testing and evaluating antidepressant blood levels

Evidence indicates that a subset of MDD patients presenting with TRD may exhibit a failed antidepressant response as a consequence of a suboptimal bioavailability of the administered antidepressant, due to rapid metabolizer status[171-174]. Available evidence indicates that allelic variations of cytochromes P450-2D6 (CYP2D6) and P450-2C19 (CYP2C19) are especially associated with antidepressant outcome. In particular, CYP2D6 phenotypes may be important in some patients taking TCAs and venlafaxine, and CYP2C19 phenotypes in some individuals receiving TCAs, citalopram, escitalopram and sertraline[171]. Although pharmacogenetic testing cannot be recommended as a routine assessment in TRD, some preliminary evidence does suggest that, in select circumstances, it may be warranted.

Furthermore, blood levels should be monitored in non-responding persons receiving some TCAs (i.e., imipramine, desipramine, nortriptyline), as therapeutic levels/windows have been established for these agents[175-177].

MANAGEMENT OF TREATMENT-RESISTANT DEPRESSION

Herein, we review tactics which can be considered for managing TRD once the presence of this condition is confirmed. These

tactics include extending the current antidepressant trial, switching antidepressants, combining antidepressants, use of esketamine/ketamine, and neurostimulation (see Table 2).

Although manual-based psychotherapies are not proven to be efficacious as a standalone intervention in TRD, their efficacy in combination with antidepressants is briefly reviewed. Also, we briefly review the evidence for other strategies (e.g., lithium, thyroid hormone) that are better established in patients with partial response to TCAs and MAOIs rather than principally studied in TRD.

We also review data for SGAs, despite the fact that – with the exception of the olanzapine-fluoxetine combination – these medications are not approved for TRD, but only for

Table 2 Options for management of treatment-resistant depression (TRD)

Option	Rationale	Limitations
Extending antidepressant trial	Delayed time to response amongst subpopulations with TRD.	Modest evidence base supporting the strategy. Unlikely to be acceptable to most patients living with TRD. Alternative strategies for TRD better established (e.g., ECT, esketamine).
Switching antidepressants	Mechanistically dissimilar antidepressants from different classes may offer improved health outcomes in TRD in some cases. Especially appropriate when index antidepressant class is poorly tolerated.	Modest evidence base supporting the strategy. Newly initiated antidepressant will require at least 4 weeks before outcome can be assessed.
Combining antidepressants	May target symptoms not responding to index antidepressant (e.g., fatigue, cognitive impairment, sleep problems). May improve tolerability via antidote of emergent adverse events (e.g., bupropion for antidepressant-induced sexual dysfunction).	Limited evidence base in TRD. Potential for drug-drug interactions. Decreased adherence with polypharmacy regimens. Greater cost of treatment.
Ketamine	Acute efficacy established in TRD. Beneficial effects on suicidality. Rapid onset of symptomatic improvement.	Insufficient long-term efficacy, tolerability and safety data. Access to treatment limited in many jurisdictions. Specialized personnel required for safe administration. Long-term safety profile in TRD not established (e.g., abuse liability, gateway activity).
Esketamine	Acute and maintenance efficacy established in TRD. Beneficial effects on suicidality. Rapid onset of symptomatic improvement. Superiority to SGA (i.e., quetiapine XR) in acute and maintenance treatment of TRD.	Access to treatment limited in many jurisdictions. Acquisition cost. Recommendation to co-prescribe with underlying antidepressant in TRD.
Second-generation antipsychotics (SGAs)	Scalable and accessible treatments. Evidence established for olanzapine-fluoxetine combination.	With exception of olanzapine-fluoxetine combination, studied in partial responders rather than TRD. Short- and long-term tolerability concerns.
Electroconvulsive therapy (ECT)	Highly effective in acute and maintenance treatment of TRD. Non-inferiority to IV ketamine suggested by available evidence. Efficacy in TRD across the age span.	Relative lack of availability in many contexts. Stigma and lack of acceptability to many patients with TRD. Tolerability concerns (e.g., memory deficits).
Repetitive transcranial magnetic stimulation	Shown to be effective in TRD. More acceptable to patients than ECT. Accelerated protocol demonstrates significant remission rates within one week. Tolerability advantages compared to ECT (i.e., persisting cognitive deficits not observed).	Relative lack of availability in many jurisdictions. Inferiority to ECT in TRD with non-accelerated protocols. Insufficient long-term data in TRD.
Vagus nerve stimulation	Proven efficacy in TRD in persons with extensive antidepressant failure histories. Treatment does not need to be administered on a daily basis.	Not available in most countries globally. Complexity of procedure limits scalability. Complications of implant. Cost of treatment.
Psychotherapies	Evidence supports efficacy when used adjunctively in TRD. Opportunity to target comorbidities. Facilitate coping strategies with improved effects on patient-reported outcomes. Highly acceptable to persons with lived experience of TRD. Opportunity to tailor treatment targeting specific therapeutic outcomes.	Lack of availability of treatment or adequately trained providers. Low adherence to therapy. Lack of evidence as standalone treatment in TRD.

individuals with MDD exhibiting partial response to an index antidepressant.

Extending the antidepressant trial

As mentioned earlier, results from the STAR*D trial indicated that a proportion of individuals who responded to level 1 treatment did so after week 6. A systematic review of available studies sought to evaluate the likelihood of response during weeks 5-8 and 9-12 in individuals with MDD not responding after four weeks[178]. It was concluded that approximately 20% of patients with MDD not responding in the first four weeks responded during weeks 5-8, while approximately 10% responded during weeks 9-12[178].

However, it is not established that extending an antidepressant trial in patients defined as having TRD results in any considerable likelihood of treatment success. In addition, persons with lived depression experience prioritize rapidity of antidepressant action, so that prolonging antidepressant trials for an additional one to two months is unlikely to be acceptable in most cases of TRD[92].

Switching antidepressants

Meta-analytic data are conflicting as to whether switching antidepressants increases the likelihood of response in TRD[179,180]. A related but separate concept that would justify switching class of antidepressants is that of "broadening the spectrum of efficacy". For example, a patient prescribed an SSRI who continues to manifest debilitating anhedonia, fatigue, and psychomotor retardation may exhibit significant improvement when switching to an antidepressant with a different mechanism of action[181,182].

Overall, switching antidepressants may be considered in some cases of TRD, and the new agent should be a "non-classmate" antidepressant.

Combining antidepressants

Persons with TRD are commonly treated with antidepressant polypharmacy, but few relevant studies have been conducted specifically in populations with TRD[183-187].

Results from a meta-analysis have supported the efficacy of adding mirtazapine or bupropion in persons with "early-stage" TRD (i.e., non-response to one adequate pharmacological or psychological therapy for depression)[188]. As mentioned earlier, level 2 treatment (i.e., TRD) from the STAR*D trial included seven possible switch/augmentation strategies in adults with non-psychotic depression not achieving remission with citalopram. The three augmentation approaches were bupropion, buspirone, and cognitive therapy. The proportion of patients achieving remission after receiving bupropion combined with citalopram was 39.0%, compared to 25.5% when switching to bupropion sustained release (SR) monotherapy[33].

A recent meta-analysis concluded that alpha-2 autoreceptor antagonists (i.e., mirtazapine, mianserin, trazodone) combined with SSRIs are superior to monotherapy in mixed populations including TRD, but the composition of the patient samples studied precludes any definite interpretation of the finding[189].

Overall, data supporting the combination of antidepressants as an efficacious treatment strategy is modest in TRD populations.

Ketamine/esketamine

Intravenous (IV) racemic ketamine has been found to rapidly improve depressive symptoms and suicidal ideation in adults with TRD, and its efficacy has been confirmed in real-world patient samples. Clinically meaningful benefit has been observed in both single and multiple infusion studies [190-193]. Intranasal esketamine spray co-initiated with an antidepressant has also demonstrated rapid clinically meaningful efficacy in patients with TRD. Unlike IV ketamine, there are also data demonstrating long-term (i.e., greater than 3-year) safety and tolerability for esketamine[194,195].

Item analysis indicates that ketamine and esketamine not only significantly improve overall symptoms of TRD, but also specific depressive symptoms that are over-represented in adults with TRD, such as anhedonia[196-199]. Meta-analytic data also indicate that glutamatergic treatment strategies may be superior to antipsychotic agents in adults with TRD[200,201].

In 2019, the FDA approved intranasal esketamine spray combined with antidepressants in adults with TRD, with subsequent approvals by other regulators globally (e.g., EMA). Less evidence is available for ketamine and/or its derivatives delivered through other routes of administration[191]. Moreover, the concomitant administration of ketamine and psychological interventions ("ketamine-assisted" therapy) is insufficiently characterized and as such cannot be recommended for TRD[202].

Results from the recent ESCAPE-TRD trial indicate that intranasal esketamine combined with an antidepressant is significantly more effective than quetiapine XR in TRD, with a remission rate at week 8 of 27.1% vs. 17.6% ($p=0.003$)[203]. Remission rates continued to increase in both arms after the primary endpoint, with a significantly greater proportion of patients in remission at week 32 in the intranasal esketamine than in the quetiapine XR arm (55% vs. 37%, $p< 0.001$)[203].

Preliminary evidence indicates that the effectiveness of IV ketamine in individuals with TRD and history of non-response to neurostimulation (i.e., ECT or rTMS) is not reduced as compared to individuals with TRD and no prior neurostimulation treatment[204]. Available evidence also indicates that the efficacy of ketamine/esketamine in the acute treatment of TRD is also apparent in individuals with greater degrees of antidepressant resistance[205].

Safety concerns attributable to long-term ketamine/esketamine exposure include potential for abuse and misuse, tolerance and withdrawal, effects on liver function, and possibly kidney and/or urogenital toxicity[206]. The risks for the foregoing safety concerns would be expected to be mitigated when administering ketamine/esketamine under medical supervision in accordance with best practices[205].

Second-generation antipsychotics

The only SGA evaluated in patients failing two or more prior antidepressant treatments (i.e., TRD) is the fixed dose olanzapine-fluoxetine combination[207-209]. The other SGAs assessed in MDD (i.e., aripiprazole, brexpiprazole, cariprazine, risperidone and quetia-

pine XR) have been studied only in patients with a partial response to at least one antidepressant[187,201,210-224].

Head-to-head comparisons of SGAs as augmentation in TRD are not available, nor are long-term recurrence prevention data. The absence of long-term data with SGAs is a point of differentiation with esketamine, which has long-term multi-year establishment of efficacy and safety[195]. Limitations of longer-term use of SGAs in MDD relate to tolerability and safety concerns (e.g., metabolic dysregulation, weight gain, and extrapyramidal adverse effects)[225].

Relatively few studies have compared the antipsychotic augmentation of antidepressants versus the combination of antidepressants in patients presenting with suboptimal antidepressant response. The VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) trial was a multisite randomized, single-blind, parallel-assignment trial of depression unresponsive to at least one course of antidepressant treatment[226]. Eligible subjects were randomly assigned to one of three treatments: switch to bupropion SR, augmentation of current treatment with bupropion SR, or augmentation of current treatment with aripiprazole. The remission rate at week 12 was higher for the aripiprazole group (28.9%) compared with the switch to bupropion SR group (22.3%), but not with the bupropion SR add-on group (26.9%). Response rates were significantly higher for the aripiprazole group (74.3%) than for both bupropion SR monotherapy and bupropion SR augmentation groups (62.4% and 65.6%, respectively)[226].

The VAST-D trial results replicate and extend the efficacy and tolerability of SGAs in individuals with MDD partially responding to antidepressants. As mentioned earlier, there are insufficient data for SGAs in TRD. However, results of the ESCAPE-TRD trial suggest superiority of intranasal esketamine to quetiapine XR.

Neurostimulation

Neurostimulatory treatments evaluated in TRD include vagus nerve stimulation (VNS), ECT, rTMS, magnetic seizure therapy, deep brain stimulation, and transcranial direct current stimulation[227-233].

VNS has proven to be efficacious in patients with higher-order TRD (i.e., equal or greater than four prior antidepressants), and has also demonstrated durability of effect with maintenance treatment[234-236]. The FDA has approved VNS in TRD patients with a history of at least four prior failed antidepressants.

ECT is a well-established therapeutic intervention in the treatment of TRD, with an average open-label remission rate of 48% in non-psychotic depression[237]. Efficacy may be higher in individuals with psychotic depression. Many modifications to the implementation of ECT have retained efficacy in TRD with improved tolerability profile (e.g., bilateral brief pulse ECT vs. right unilateral ultra-brief pulse ECT)[238].

Results from systematic reviews and meta-analyses consistently support the efficacy of rTMS in TRD[233]. Results also indicate that greater severity at baseline and higher number of prior antidepressant failures are associated with attenuated rTMS efficacy[239-243]. The cost-effectiveness of rTMS in adults with TRD is well established, and possibly higher compared to ECT, but available evidence also shows that ECT may be more effective than conventional rTMS in the acute and recurrence prevention treatment of TRD[244-246].

Newer forms of rTMS are being validated, including conventional intermittent theta burst stimulation (iTBS), whose efficacy in adults with TRD when compared to sham treatment is well established[247,248]. An accelerated high-dose iTBS protocol with magnetic resonance imaging (MRI)-guided functional connectivity targeting (Stanford neuromodulation therapy, SNT) has been found, in a double-blind randomized controlled trial (RCT), to be significantly superior relative to sham treatment four weeks after the end of the five-day protocol. The significant benefit observed was evident despite an average of five prior antidepressant medication trials[249]. The SNT approach was recently cleared by the FDA for TRD.

In addition, results from RCTs have supported the efficacy of magnetic seizure therapy, with additional evidence demonstrating continuation of effect[250,251]. A Cochrane review did not identify a significant difference between this therapy and ECT in adults with TRD[252].

Results of RCTs have not documented the efficacy of deep brain stimulation, when compared to sham treatment, in TRD[253-257]. Transcranial direct current stimulation is associated with variable outcomes across RCTs in the treatment of adults with TRD: the heterogeneity in response may be due to the broad range of treatment resistance included in the original trials, from treatment-naïve to ECT failing individuals[258].

In summary, of the foregoing neurostimulation modalities, ECT, rTMS, VNS and SNT are recommended in adults with TRD. Although there is a lack of head-to-head comparator data of proven treatments in TRD, preliminary evidence suggests that ECT may be non-inferior when compared to IV racemic ketamine in adults with TRD[259].

Psychotherapeutic interventions

There are multiple reasons for considering psychotherapeutic interventions in persons with TRD. For example, evidence indicates that these interventions are a preferred treatment option over pharmacotherapy amongst persons with lived depression experience[73,260,261]. Residual symptoms and comorbidities in persons with TRD are frequently amenable to psychological treatments. Psychotherapies, when combined with pharmacological treatments, are conceptually supported insofar as they facilitate learning, coping and resilience mechanisms that synergize with the hypothesized biological mechanisms of action of antidepressants[262]. Finally, individuals with persistent depression and history of trauma, both of which are more common in TRD populations, exhibit significant response rates with psychological interventions[263,264].

Notwithstanding the rationale for use of psychotherapies in TRD, data supporting them as standalone interventions in TRD are limited[265,266]. Available evidence does, however, support the efficacy of adjunctive psychological interventions in persons with TRD[267-271].

The psychotherapeutic modalities most frequently investigated include cognitive behavioral therapy (CBT), interpersonal psychotherapy, and mindfulness-based cognitive therapy[272]. Meta-analytic data have determined that psychotherapy added to on-

going treatment as usual (TAU) had a moderate and significant effect size (Hedges' g= 0.42) in comparison with TAU alone in TRD [272].

Overall, the available evidence indicates that manual-based psychotherapies are effective in persons with TRD when combined with antidepressants. There is insufficient evidence about combining these interventions in persons with a higher number of prior antidepressant failures and/or ECT non-response. Patient preference, potential for scalability with digital solutions, and efficacy in the treatment of comorbidities (e.g., anxiety disorders) are additional rationales for considering psychotherapies in patients with TRD. Preliminary evidence suggests that CBT may be capable of prolonging the effect observed in adults with TRD who acutely benefited from ketamine treatment[202].

However, a recent European study that rigorously defined TRD failed to demonstrate the efficacy of adjunctive psychological treatment[266]. It may be surmised that patient characteristics and the type of psychological intervention are critical moderators of efficacy in TRD populations.

INVESTIGATIONAL INTERVENTIONS IN TREATMENT-RESISTANT DEPRESSION

The public health implications of TRD provide the impetus for the development of new interventions specifically for this subpopulation. It is noteworthy that enrollment in most clinical trials of investigational agents in MDD exclude patients with TRD, especially those with a high number of failed prior antidepressant trials in the current episode, or those who have failed ECT or IV ketamine in this episode.

The class of agents imprecisely referred to as psychedelics has received the most attention as a potential investigational intervention in TRD[273]. Preliminary evidence suggests that psilocybin, combined with psychotherapy, may offer rapid and possibly sustained symptom relief in adults with TRD. For example, a phase 2 double-blind trial randomly assigned adults with TRD to receive a single dose of psilocybin 25 mg, 10 mg or 1 mg (control) along with psychological support[274]. All persons had failed at least two prior treatments before enrollment. Participants receiving the 25 mg dose, but not the 10 mg dose, exhibited a significantly greater least-squares mean change from baseline to week 3 compared with the 1 mg dose. The response and remission rates for the participants receiving the 25 mg dose were 37% and 29%, respectively[274].

Several methodological problems affect available controlled trials with psilocybin in TRD. Aspects of unblinding as well as expectancy are undoubtedly contributing to the observed effects, as are the psychotherapeutic modalities that are considered integral to the process of taking psychedelics. Nevertheless, the results of available RCTs with psilocybin have provided the impetus for evaluating this drug in phase 3 pivotal trials for TRD[275]. Deconstructing the contribution of psychotherapy from the psychedelic intervention will be an inexact yet necessary endeavor in order to interpret study findings and provide appropriate treatment and implementation recommendations. Moreover, the psychotherapy that is currently combined with psychedelics does not have a standardized evidence-based protocol.

Additional investigational interventions in TRD include lithium, thyroid hormone, buspirone, L-methylfolate, S-adenosylmethionine, anti-inflammatory agents (e.g., COX-2 inhibitors, minocycline, statins, and tumor necrosis factor-alpha antagonists), zuranolone and dextromethorphan-bupropion combination[276-280]. The extant evidence supporting lithium and thyroid hormone largely refers to their combination with TCAs and MAOIs in patients with partial response to these agents. Medications that have been studied in TRD and demonstrated not to be efficacious are pindolol and buprenorphine[281,282].

Despite the widespread prescription of multiple psychotropic agents off-label in patients with TRD, there are no rigorous studies with large samples establishing the efficacy of any of the foregoing strategies.

CONCLUSIONS

Amongst individuals meeting criteria for MDD with access to high-quality measurement-based care, at least 30% will meet criteria for TRD. This estimate is derived from efficacy and/or effectiveness research findings. The prevalence of TRD in real world practice is not known, but would be expected to be higher, due to knowledge-implementation gaps, barriers to access, and illness presentation complexity[283].

With respect to illness presentation complexity, most individuals with TRD encountered in clinical practice would not be eligible for most clinical research studies, on the basis of illness characteristics (e.g., severity, number of prior episodes, suicidality), comorbidity and treatment history[13,284].

Multiple definitions of TRD have been proposed and are reviewed herein. The lack of a universal definition of TRD is a barrier to advancing mechanistic and translational research, as well as to identifying innovative and precision-based therapeutics. In addition, public policy decisions, as well as clinical decision-making, would be benefited by a more precise and valid definition of TRD. For example, considerations for reimbursement in TRD which are critical for access to treatment are limited by the fact that multiple definitions of this condition exist. Hence, decisions by policy makers on whether to include treatments for TRD as part of a reimbursement schedule are highly variable across jurisdictions. From a clinical perspective, the lack of a universal definition of TRD contributes to heterogeneity in treatment selection and sequencing. This heterogeneity is also reflected in clinical practice guidelines for MDD, that have different recommendations with respect to selection and sequencing of treatments for adults with TRD.

Consensus exists that the lack of a clinically meaningful improvement with a minimum of two antidepressants should be retained in any working definition of TRD. A quantifiable endpoint defining non-response should be provided. A comprehensive and conceptually valid definition of TRD with clinical utility should also include aspects of patient-reported outcomes, psychosocial function, as well as dimensional outcomes (e.g., anhedonia)[285].

The related, but separate, notion of DTD seems more aligned with the realities of the clinical ecosystem, and with patient experience of depression and sequential non-response to treatments[94,286]. A compelling case

is made that TRD is potentially judgmental insofar as it may be interpreted as blaming the patient. Instead, DTD is agnostic and represents a patient-centered and pragmatic approach to identifying therapeutic targets[84]. The construct of DTD could serve as a useful framework informing further characterization of TRD.

The variability in antidepressant response is widely recognized[287]. A confluence of sociodemographic and clinical characteristics is known to moderate this response. Clinicians are encouraged to identify modifiable factors that attenuate antidepressant outcomes and allocate resources to these factors in patients prescribed antidepressants. For example, non-adherence, illness and treatment illiteracy, stigma, and attitude towards treatment are modifiable with psychoeducation efforts and possibly peer-support[73].

In addition, psychiatric and physical comorbidities not only attenuate antidepressant response but may also be a consequence of TRD. Targeting comorbidities at the same time as depressive symptoms would be predicted to improve treatment outcomes as well as reduce cost and health resource utilization in adults with MDD. In addition, closing the implementation-knowledge gap with fidelity to evidence-based treatments is a near-term cost-effective priority in the management of MDD today.

The evidence supports select SGAs, as well as rTMS and manual-based psychotherapies (in combination), as proven strategies in adults who have failed one prior antidepressant. For individuals with TRD (failing multiple antidepressants), evidence is best for ketamine, esketamine, adjunctive psychotherapy, ECT and rTMS. Psychotherapeutic interventions in combination with antidepressants may offer partial symptomatic relief in persons with TRD, but their efficacy as monotherapy is not established. Combination antidepressants, switching antidepressant treatment, dose optimization and the use of a host of augmentation strategies (e.g., lithium, thyroid hormone) have mixed data supporting their usefulness[288].

Intranasal esketamine combined with an antidepressant is the most rigorously evaluated pharmacologic strategy in the acute and maintenance treatment of adults with TRD. In addition to demonstrating acute efficacy, it has established relapse prevention, tolerability and safety in persons with TRD, with more than three years of maintenance data. IV racemic ketamine has also demonstrated robust rapid antidepressant efficacy in mostly acute studies. There are relatively few controlled studies, however, that have documented maintenance efficacy of repeat-dose IV ketamine in adults with TRD [289].

The relative efficacy of intranasal esketamine to ECT in TRD is unknown, but is currently being evaluated. Preliminary evidence suggests that ECT may be non-inferior to IV racemic ketamine in the acute treatment of TRD[259]. Results from large and rigorous controlled studies comparing IV ketamine to ECT are expected to provide further decision support and inform recommendations for treatment sequencing in TRD[259].

The investigational interventions in TRD that have received the most research, media and public attention have been psychedelics. Available evidence for psilocybin suggests acute efficacy that is rapid and sustained in well-characterized samples of persons with TRD. Unanswered questions as to the contribution of integrated psychotherapy in persons receiving psilocybin have not only conceptual and clinical relevance, but are also critical to address from an implementation perspective.

Future research vistas with respect to pharmacological treatment are testing whether ketamine derivatives or other glutamatergic agents may be useful in TRD. Additionally, GABAergic agents (e.g., zuranolone), opioid receptor modulators, orexin antagonists, voltage-gated ion channels modulators, anti-inflammatories, as well as agents targeting cellular metabolic processes are also under investigation in TRD[290].

It is recognized that TRD is an under-researched clinical population with disproportionate morbidity and mortality. Mechanistically novel interventions that offer meaningful benefit may be eligible for FDA "breakthrough status", incentivizing treatment discovery and development in this area.

Identifying biomarkers and biosignatures associated with TRD is an important future research vista. As reviewed herein, pharmacogenomic testing has preliminary support as a tactic in assessing TRD patients, especially in cases of medication poor tolerability. Notwithstanding, it cannot be recommended as a routine assessment in all persons presenting with TRD. It is anticipated that pharmacogenomics will advance, as will the ability to computationally interrogate multi-omic data, providing insights into the neurobiology of TRD and also potentially informing patient stratification and precision therapeutics with clinical ecosystem application potential.

Digital psychiatry encompasses aspects of health care delivery, illness surveillance, disease management and treatment[291-294]. Multiple proprietary and academically led product developments are underway to identify digital therapeutics that may have application in TRD populations.

The next decade can reasonably expect the regulatory approval of innovative pharmacological treatments targeting systems implicated in the pathophysiology of depression. The foregoing, along with advances in the digital delivery of psychological interventions and refinement of parameters of neurostimulation (notably rTMS with accelerated protocols), hold promise to improve general health outcomes and cost-effectiveness of care in TRD.

The extraordinary public health burden of TRD will unlikely be extinguished in the near future, but the proportion of individuals with debilitating symptoms of depression and dissatisfaction with treatment may be reasonably expected to be decreased with successful targeting of modifiable factors, reducing the knowledge-implementation gap, and rapid adoption of innovations across therapeutic modalities.

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Recent developments pertaining to treatment-resistant depression: a 40-year perspective

With the increasing recognition that major depressive disorder (MDD) is one of the world greatest public health problems[1,2], there have recently been concerted efforts to ensure that people suffering from this condition are promptly recognized, accurately diagnosed, and vigorously treated. Indeed, a relatively wide range of proven treatments are now available to help depressed people, and health care systems and agencies throughout the world have prioritized implementation strategies to efficiently deliver cost-effective interventions[1]. Without established primary prevention strategies to reduce the incidence of MDD, maximizing access to treatment and ensuring optimal delivery of care represents the best way to reduce the morbidity, mortality, and personal and societal costs of this common condition[1].

That said, no more than one half of people who receive an adequate course of a first-line antidepressant medication will obtain an acceptable response (i.e., at least a 50% reduction in depressive symptom severity, coupled with a tolerable level of side effects) and, as illustrated by the results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[3], the likelihood of benefit diminishes substantially after the second sequential treatment trial. Episodes that follow this course are commonly called treatment-resistant depression (TRD), and account for a disproportionately large proportion of the illness burden associated with MDD[1]. This is the subject of the excellent paper by McIntyre et al[4], which provides a concise, yet comprehensive review of the topic, including up-to-date summaries of the best studied and most promising treatment strategies.

The concept of TRD is nearly as old as the first generation of effective treatments for depression, namely electroconvulsive therapy (ECT), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). The first papers using that concept were published in the 1970s[5]. In that era, an almost intuitive hierarchy emerged on the basis of the clinical effort needed to implement the treatment: TCAs were generally used first, MAOIs second and ECT third for most patients. There were no randomized controlled trials (RCTs) of TRD in that era, though clinical wisdom taught that MAOIs worked in about one half of the cases in which TCAs failed, and ECT was expected to benefit at least 80% of antidepressant non-responders[5]. As a result, clinicians might have predicted that 70-90% of depressed patients could be treated effectively with this three-step proto-algorithm.

By the mid-1990s, selective serotonin reuptake inhibitors (SSRIs) and several other newer-generation antidepressants had supplanted the TCAs as first-line treatments, expanding that intuitive algorithm to four levels of treatment. When we first reviewed the growing literature on this topic[5,6], we reached a similar conclusion: a four-step treatment algorithm, in theory, might be expected to yield up to a 90% cumulative response rate. Yet, the 1980s and 1990s ushered in an era of increasing methodological rigor, and the first RCTs of TRD began to emerge. Results indicated that our estimates were overly optimistic, and methodological conventions such as intention-to-treat analyses, which account for the impact of attrition on response rates, and use of "blinded" evaluators to minimize expectancy biases, revealed more sobering estimates of benefit. For example, in the STAR*D trial, the cumulative response to a sequence of four treatment trials was in the order of 50-60%.

So, the public health problem of TRD turned out to be much larger than anticipated and, as reviewed by McIntyre et al, subsequent methods to refine and expand upon the simple hierarchical system that we had proposed have strengthened our ability to assess and classify depressions that do not respond to standard therapies. The introduction of a broader and more inclusive term, difficult-to-treat depression[7], further enriches the conceptual framework of understanding the clinical context of non-response to antidepressants: there are many reasons that might explain why an antidepressant will not deliver the desired result, and only some of them pertain to neuropharmacological actions of our medications.

Nearly 20 years have passed since the publication of the main findings of the STAR*D trial. In the post-STAR*D era, it can be argued that the greatest unmet need in the psychopharmacology of depression is for antidepressants that work via mechanisms other than modulation of monoaminergic neurotransmission. McIntyre et al provide a particularly useful summary of the data on several of the more recent therapeutic developments that have truly improved the outcomes of some people who do not respond to standard antidepressants.

Switching antidepressants, which was once the quintessential second step in most algorithms, is now more of a default option for patients who have tolerability issues with the index antidepressant, and only rarely are patients switched to an MAOI. More commonly used second-line options include combinations of SSRIs and either mirtazapine or bupropion, and several adjunctive strategies. Among the adjunctive options, a large amount of empirical data supports use of a group of second-generation antipsychotics (SGAs). Given the well-known risk of weight gain, the potential for other metabolic side effects, and a small but real ultimate risk of tardive dyskinesia, more extensive data from longer-term studies are sorely needed to help to more accurately gauge the relative merits and cost-effectiveness of this adjunctive strategy.

Although clinically tested and widely used, combining antidepressants and adjunctive therapy with SGAs can be thought of as incremental options, because they target somewhat complementary monoaminergic mechanisms and require that patients continue to take an SSRI or other newer antidepressant. There was a frustratingly long pause between the introduction of the various members of the so-called "newer" generation of antidepressants – it is, after all, more than 35 years since the US Food and Drug Administration (FDA) first approved fluoxetine – and the discovery of interven-

tions with truly novel mechanisms of action. Fortunately things are changing, with the serendipitous observation that a sub-anesthetic intravenous dose of ketamine could have large and remarkably rapid antidepressant effects. Now confirmed by the findings of a large number of RCTs in patients with various forms of TRD[8], the relatively rapid acceptance of this "off-label" use of intravenous ketamine has opened the gates to a new wave of potential therapies that target glutamatergic neurotransmission.

While it remains to be seen whether intravenous ketamine or intranasal esketamine – the first FDA-approved therapy to result from these observations – will continue to be widely used a decade from now, it is a fact that the paradigm for drug discovery for TRD has changed for the foreseeable future. In this respect, the path for studying the therapeutic potential of neurosteroid drugs such as zuranolone, which is thought to indirectly affect glutamatergic neurotransmission through GABA-A receptor positive allosteric modulation, has been much less arduous than previously possible. Likewise, the paradigm change determined by the proven efficacy of intravenous ketamine, a controlled substance with abuse liability and characteristic dissociative effects, has prepared the field for a new wave of studies examining the therapeutic benefit of psilocybin and related psychedelic compounds that were once considered essentially off limits for therapeutic research. Finally, descendants of transcranial magnetic stimulation, including intermittent theta burst stimulation (iTBS) and an accelerated high-dose iTBS protocol utilizing magnetic resonance imaging to guide or target functional connectivity[9], have given hope for the possibility of viable alternate neuromodulation strategies for patients with more advanced levels of TRD.

McIntyre et al's outline of the evidence concerning TRD, therefore, is timely and provides a thought-provoking overview of an exciting new era in the therapeutics of depression.

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Treatment-resistant depression invites persistent reflection

As admirably detailed by McIntyre et al[1], most definitions of treatment-resistant depression (TRD) weight failure to respond to a set of antidepressant medications and other physical treatment options. Is this the optimal paradigm when major depressive episodes may be caused not only by biological factors, but also by social and psychological ones? Wouldn't we expect, for example, that a woman depressed due to abuse by a coercive husband, or a man whose procrastinating perfectionism leads his manager to heap opprobrium and deep depression on him, fails to respond to two or three antidepressants of different classes and at appropriate doses? If the incorrect treatment paradigm is employed in the latter instances (i.e., antidepressant medication rather than respective social and psychological interventions being prioritized) is non-response better viewed as "treatment failure" (and accorded TRD status) or more as "paradigm failure"? Similarly, delivery of multiple psychotherapy approaches alone to an individual with severe melancholic depression might generate TRD status but more correctly reflect paradigm failure.

In concept and operation, most TRD models and definitions constrain the heterogeneity of depressive disorders and then effect a Procrustean management model weighted to physical treatments. McIntyre et al[1] consider an alternate "difficult-to-treat" framework, which they regard as relying more on a biopsychosocial approach. Such an approach theoretically allows alternative definitional and management strategies.

The authors note that psychotherapeutic interventions are recommended as first-line strategies for those with mild or moderately severe depressions. This might allow TRD definition to be weighted by baseline depression severity. For example, for those with "severe" depression, TRD status would be assigned by failure to respond to a sequential and operationalized set of drug and physical treatment strategies, thus weighting their management to biological treatments, while those with less severe depression would achieve TRD status by failure to respond to cogent psychotherapies. However, immediate concerns about such a model include severity of depression not being linked with depressive subtype, while "failure to respond" to a cogent psychotherapy would be limited by judging of "cogency".

A second option would emphasize a biopsychosocial definition (e.g., failure to respond to a therapeutic intervention salient to cause – including psychological and social determinants and not biological ones alone) and weight a subtyping model as against a severity-based one. Such a model would aim for TRD status to be operationalized in relation to specified biologically-weighted depressive conditions (i.e., melancholia, psychotic depression, bipolar I and II depression, depression caused by medical conditions) and a set of residual non-melancholic depressive conditions with presumed social and/or psychological causes. Differing type-specific criteria for according TRD status, and logical type-specific sequential management strategies, would be developed. Rather than seeking a TRD definition that has universal application, do we not

need one that has disorder-specific nuances as is observable in general medicine?

Turning to narrower issues, McIntyre et al importantly note that some people meeting TRD status do so as a consequence of being "rapid metabolizers". Such a state affects up to 30% of some races, but is a TRD determinant that may be overlooked by practitioners. The clinical clues are that the individual rarely has side effects from any antidepressant medication, is seemingly unaffected by moderate amounts of alcohol, and fails to obtain analgesic benefit from paracetamol. In my pursuit of this possibility, I do not find genomic testing informative but, less anecdotally, note a report by De Leon et al[2] quantifying that up to 80% of ultra-metabolizers are missed by genetic testing. I generally initiate a tricyclic (TCA), increase its dose to 150 mg/day and then obtain a "tricyclic level", finding serum TCA level results to have high sensitivity and specificity[3]. The impact on management is that some people whose TRD status is so established then become "responders" when taking a higher dose of the TCA (although TCA metabolites may produce serious side effects). Further, some people with rapid metabolizing status can be "converted" to normal metabolizing status by adding paroxetine or fluoxetine, with De Leon et al[2] noting that such a strategy increases the concentration of the active drug and reduces the concentration of the hydroxylated metabolites.

Some TRD criteria include failure to respond to two or more antidepressants of differing classes – a non-specific model which allows random progression from narrow-action to broader-action antidepressant classes, but also allows the converse and other sequences. Unspecified progression might be appropriate if all antidepressant classes have comparable efficacy, which is the general finding in relation to treating "major depression". However, broad-action tricyclics have been quantified as superior to narrow-action selective serotonin reuptake inhibitors (SSRIs) in those with melancholic depression, with differential effectiveness increasing with older age of the patient[4], while the dual-action antidepressants appear to have intermediate efficacy. Any such gradient might then logically argue for a TRD management model whereby those with melancholia not responding to an SSRI then receive a broader-action antidepressant – perhaps a dual-action antidepressant, followed by a TCA, and then possibly a monoamine oxidase inhibitor (MAOI) – with MAOIs long positioned as strong candidates for managing treatment-resistant melancholia[5].

While I have previously employed MAOIs when narrow- or dual-action antidepressants failed in those with a melancholic depression, I now trial augmentation of a baseline antidepressant drug with a psychostimulant (e.g., methylphenidate or dexamphetamine) prior to any trialling of an MAOI – in light of dietary and other concerns related to the MAOIs. While earlier meta-analyses of psychostimulants failed to indicate distinct efficacy, a more recent meta-analysis by McIntyre et al[6] supported their efficacy, but with these authors suggesting that their benefits might operate across "select domains". I view melancholia as being one such key domain, finding such psychostimulant augmentation commonly beneficial in those with melancholia who have failed to respond to several antidepressants, and with tolerance rarely emerging.

A recent review[7] summarized two previous reports of people with unipolar and bipolar melancholic depression meeting common TRD criteria (subjects having received a mean of five previous antidepressants in both samples, and seven and eight psychotropic drugs in total across the two samples). Overall, some 20% reported the psychostimulant augmentation as "very effective", while an additional one-half reported the strategy as "somewhat effective". Some 45% described the psychostimulant as the best or equal best to previously prescribed antidepressants, and 48% reported a sustained benefit. Such effectiveness rates in those with TRD are impressive, and argue for such a strategy being trialled – in those with melancholia – before more demanding treatments such as electroconvulsive therapy are enlisted.

While major depression is a diagnostic entity, it is not a clinical entity[8]. To the extent that TRD status is defined by failure of people with major depression to respond to multiple antidepressants, then TRD is also not an entity. Then, it must be expected that its specific and fuzzy-set constituent conditions will show differential response gradients to differing interventions. McIntyre et al provide an extraordinarily rich review of current definitions and management options, and thus set up a base camp for future exploratory studies. These will benefit from the recognition that heterogeneity reigns and needs to be constrained.

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Challenges of research on treatment-resistant depression: a clinician's perspective

I think we should be grateful to McIntyre et al[1] for their extraordinarily thorough and balanced review of treatment-resistant depression (TRD). They note that this condition poses a plethora of clinical research challenges. Here I offer a few suggestions that might make research more cost-efficient and clinically generalizable.

First, we should develop tools to system-

atically identify treatable causes of depression. Many medical conditions (e.g., neurological, infectious, oncological, endocrine) as well as medications may cause depression that appears to be treatment resistant. Without a thorough medical review, depression-causing disorders and medications will escape notice.

To my knowledge, there is no evidence-based or widely agreed upon set of laboratory tests with demonstrated "yield" rates to detect treatable medical, iatrogenic and even post-surgical causes of depression in any patient population. This issue is analogous to searching for treatable causes of cognitive impairment before diagnosing Alzheimer's disease. We need to launch a multi-care-system clinical research effort to gather evidence in apparent TRD patients and key subgroups (e.g., elderly, medically underserved) by which to prioritize laboratory, neuropsychological and other assessments to effectively identify treatable causes of depression, before embarking on an often-lengthy series of TRD treatments.

Second, TRD studies should recruit both early and delayed treatment failures, to reduce cost and enhance generalizability. Regulatory authorities require unsatisfactory acute-phase treatment response to at least two well-delivered antidepressant regimens. However, both acute and later (continuation or maintenance phase) failures are commonly seen in practice[2,3]. Late failures are not rare. For example, relapse rates in active medication arms in randomized, placebo-controlled continuation and maintenance phase studies of recurrent depression range from 3 to 45%[3], with the majority around 20-25%. Most of these relapses typically occur within 3-4 months after the successful acute-phase treatment in continuation trials. These are cases of TRD, because they have failed on the same initially successful acute treatment – just a bit later. Indeed, the greater the number of initially failed acute-phase treatment trials, the greater the relapse rate and the sooner relapse occurs on the active treatment[2].

Whether acute and delayed failures are biologically distinct is unknown. Certainly, they present the same clinical challenge: the failure of a specific medication to which most clinicians will not return. Their treatment options are the same: augmentation, combination, switch, or dose adjustments. Many clinicians believe that patients who respond acutely but cannot sustain the benefit (the late or delayed failures) are more likely to benefit from the next-step treatment as compared to those who have no benefit at all acutely. To address this concern, one could stratify patients based on acute vs. delayed failure.

Another revision of TRD trial design to increase feasibility, generalizability and cost-efficiency might be to include patients whose depression has been insufficiently responsive to either two sequential monotherapies or one monotherapy followed by an augmentation trial. In both treatment sequences, these depressions have not responded to two different agents in two distinct attempts, each of which is expected to have an antidepressant effect. This revision would include only augmentation agents approved either by the US Food and Drug Administration or the European Medicines Agency (e.g., aripiprazole or quetiapine), or possibly lithium, given the positive randomized controlled trials (RCTs). While this revision also raises the issue of heterogeneity, patients with TRD are biologically heterogeneous regardless of the types and numbers of prior treatment failures. Again, stratification could address this concern if needed.

TRD trials to evaluate a next treatment step, whether monotherapy or augmentation, would simply require that eligible participants' depressions be severe and persistent enough to call for a new treatment and that participants consent. For those switching (as in studies of new monotherapies), the control could be a low dose of the experimental agent or placebo. If the aim is to evaluate a new adjunctive agent, those choosing to switch would be ineligible. This approach avoids the issue of deciding how much of a prior benefit is needed to enter either type of study. In short, wouldn't a sample of TRD patients with either acute or delayed failures from representative treatment sequences (monotherapy-monotherapy or monotherapy-augmentation) be more ecologically valid (be a truer representation of the most common types of TRD), more generalizable and less costly, yet with well-protected internal validity?

On the other hand, ensuring both an adequate dose and duration for each of the two failed treatment trials is essential to establishing *valid* cases of TRD. In typical practice, doses are not titrated consistently, and trial durations vary from 2 to 6 weeks. These shortcomings are often addressed with standardized tools, such as the Antidepressant Treatment History Form (ATHF)[4] or the Maudsley staging method[5]. However, these approaches use 4-6-week thresholds to define an adequate duration. While earlier responses are common, especially in non-TRD patients, even 6 weeks is likely too short, as suggested by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial[6], in which half of the remissions and one third of the responses occurred after 6 weeks in the first step. We found similar results from STAR*D in the second medication switch step, with half the responses occurring after 6 weeks[7].

More recent RCTs conducted for regulatory approval also indicate that a 6-week threshold is too short, because response rates in the placebo or control arms were much higher than the "expected" 15% based on the third step of STAR*D[2]. For example, in a pivotal trial with esketamine[8], there was a 52% response rate in the control condition (initiating a new antidepressant along with placebo), as compared to 64% for esketamine, following at least two failed prior trials, using the 6-week threshold. Similarly, higher-than-expected response rates were reported in the placebo cell (35%) in a study of cariprazine as an adjunct treatment for TRD[9]. Notably, this study also required only the minimum effective dose to qualify for a prior "failed" trial, and just one failed trial was sufficient for study entry. Both factors likely contributed to the higher-than-expected placebo response rates in this "TRD" group.

The 15% remission rate in the third treatment step of STAR*D occurred after two prior steps each of which could take 12+ weeks, during which doses were driven to individually titrated maximum, using increases informed by symptom and side-effect measures at each visit. Accepting patients with a minimum or "adequate" dose based on a staging method or historical assessment tool likely leads to acceptance of some underdosed apparent TRD patients into treatment trials.

In summary, the quality, generalizability, cost-efficiency and validity of TRD trials could be improved by admitting a wider range of patients with acute and delayed failures from typical treatment steps, but trial durations and dosages should be elevated, when possible, to ensure that each case of TRD is valid.

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Does treatment-resistant depression need psychotherapy?

Congratulations are well deserved for this review by 27 psychiatric leaders, representing 14 countries, including 294 references[1]. This highly researched, well-written paper describes the characteristics of treatment-resistant depression (TRD), including prevalence, risks, clinical features, costs, public health burden, management and treatments. Despite the wealth of information provided, lingering throughout the paper is mention of the instability and inconsistency of the TRD definition. Since the paper is about TRD, the reader is left uneasy about what to assume. In fact, the criticism of the term TRD could be a major conclusion of the review.

The authors state that "a consensus definition of TRD with predictive utility does not currently exist" and that "this is a major limitation from the viewpoints of translational research, treatment development, as well as clinical and policy decision making"[1]. Comments like this permeate the paper. At first, only the reader is uneasy, but, as the paper progresses, it is clear that the authors may be as well. They conclude with many suggestions for this dilemma, which make this a landmark paper on a shifting topic.

As reviewed by the authors, the most common definition of TRD is the failure to respond to two or more antidepressants despite adequate dose, duration and adherence. This definition – the authors say – does not operationalize response, ignores partial response, does not take social functioning into account, is based on the use of standard medications, and usually does not include psychotherapy.

Quite discouragingly, the authors note that most individuals meeting the criteria for major depressive disorder with access to high-quality measurement-based care will meet the criteria for TRD. Hence, treatment resistance is one of the most commonly encountered therapeutic outcomes in persons prescribed conventional antidepressants.

Despite this pessimism, the report provides at least two suggestions for improving the situation: the inclusion of evidence-based psychotherapy and the implementation of more nuanced clinical approaches, which may improve treatment selection and patient adherence, and may even be therapeutic (what is often called the therapeutic alliance).

The authors note that, according to several studies, psychotherapy is preferred over pharmacotherapy by most people with a lived experience of depression, and, when combined with medication, facilitates coping and resilience. With this encouragement, I started to follow up on their treatment guideline references to check what has been said about psychotherapy.

Indeed, psychotherapy is included as a first line intervention in the practice guidelines for treatment of depression by both the American Psychiatric Association and the American Psychological Association[2,3]. Can we classify patients as resistant to treatment if the guidelines for recommended treatments are not included in the definition?

One can understand historically the reluctance to include psychotherapy in the TRD definition due to the old belief that you cannot test psychotherapy because every situation is unique. But there has been a revolution in psychotherapy development and research over the last 30 years, which has challenged that belief. Psychotherapy is now precisely defined in manuals used for training of therapists with different backgrounds. These manualized psychotherapies have been tested in numerous clinical trials in different populations and settings. The formats of treatment have evolved, and there are now individual, group and digital forms. The treatments are no longer interminable, but are time limited in frequency and duration.

Evidence-based psychotherapies for depression are now recommended by treatment guidelines in the US, Canada and Australia. In 2019, the US Preventive Task Force recommended two evidence-based psychotherapies for treatment and prevention of depression during pregnancy[4]. The World Health Organization (WHO), in its Mental Health Gap Action Plan (mhGAP) Intervention Guide, included evidence-based psychotherapy[5]. These treatments are being widely disseminated throughout the world, and recently also in low-income countries. For example, a large-scale clinical trial of interpersonal psychotherapy was carried out in Uganda[6].

Let's glance at the substantial database of clinical trials. In 2021, a meta-analysis of efficacy, acceptability and long-term outcomes of psychotherapies was published in this journal[7]. This meta-analysis included cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), problem-solving, behavioral activation, and non-directive supportive counseling, compared with each other or to usual care, waiting list, or pill placebos. Three hundred and thirty-

one randomized clinical trials with over 34,000 patients with depression were included. A 50% reduction in symptoms was the primary outcome. The authors found that all psychotherapies were more efficacious than usual care or waiting list. There were no consistent differences between psychotherapies, with a few exceptions. The effects for most psychotherapies were still evident at one-year follow-up.

In a separate report also published in this journal[8], a network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination for adult depression was conducted. Included were 101 clinical trials and 11,010 patients with moderate or severe major depression. In general, combined treatment was more effective than psychotherapy alone or pharmacotherapy alone in achieving response (50% reduction in symptoms) and remission. There were no significant differences between psychotherapy alone and pharmacotherapy alone. Patient found combined treatment or psychotherapy alone as more acceptable than pharmacotherapy alone.

Thus, the exclusion of evidence-based psychotherapy in the evaluation of treatment resistance may be a significant omission in the TRD definition[9].

Let's consider the second issue raised about TRD, which is adherence to the implemented pharmacological treatments. Patients may be prescribed correct medications at proper doses, may even fill the prescriptions, but may not be taking the drugs. The authors note that 30 to 50% of patients are non-adherent to medication in the acute phase of treatment. The patient may be resistant to taking the treatment prescribed and not necessarily resistant to the treatment itself.

Accurate information to ensure adherence may revolve on the therapeutic relationship. The time spent with the patient (by the physician or a trusted team member) in a supportive manner might allow a more comprehensive assessment of the patients' symptoms, social situations surrounding the symptom onset, attitudes and knowledge, experience and fears about medications, treatment options, costs, family attitudes, lifestyle barriers, and a whole host of factors which may potentially be leading to non-adherence or non-recovery. This is not formal psychotherapy, but it can be therapeutic. The information obtained could unlock the mystery of patient resistance. What is involved may be misinformation, misunderstanding, mistrust, or mistaken treatment, rather than resistance to a treatment.

The possible addition of an evidence-based psychotherapy or the time spent to obtain a comprehensive patient evaluation may reduce the high rate of TRD. This is not a recommendation for long-term psychotherapy. Most evidence-based treatments are time-limited. It is not even a call for evidence-based psychotherapy for everyone, but it does suggest the need for a thorough evaluation and a therapeutic relationship as a beginning. Before the patient, the disease or the treatment is blamed for resistance, a therapeutic alliance and perhaps psychotherapy may be worth a try. Indeed, TRD may need psychotherapy.

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From treatment resistance to sequential treatments of depression

McIntyre et al[1] provide an excellent overview of "treatment-resistant depression" (TRD) and of the ways future research can contribute to a better knowledge on how to handle the many patients with depression who do not respond to treatment. However, I argue here that the notion of TRD is based on a misconception of the effects of treatments in depression, and that it is much better to focus research on sequential treatments of depression in general. I also argue that the literature on TRD is biased towards pharmacological treatments and ignores several of the best available therapeutic interventions.

One major problem with TRD (defined as inadequate response to a minimum of two antidepressants despite adequacy of the treatment trial and adherence to treatment) is that it is very much based on a misconception of the effects of treatments of depression. On the one hand, many patients with depression recover without treatment; on the other, response rates of treatments are modest. For example, we found that 41% of patients receiving psychotherapy responded (50% symptom reduction), while 31% responded to placebo and 17% to usual care[2]. If we assume, for the sake of argument, that a next treatment will have the same effects as the previous one, we would need on average 2.5 treatments per patient in order to realize response in 100% of patients. Many of them would need only one or two treatments (65%), but the other 35% would need more treatments (up to 10). In reality, the number of treatments needed to realize response in all patients is even larger, because the number of patients responding to a treatment is lower when they have received a treatment before[3].

Remission rates following the first round of psychotherapy (26% after treatment with psychotherapy; 17% in placebo conditions; 12% in usual care) are even lower than response rates, and the total number of treatments needed to realize remission in all patients is even higher than the average 2.5

treatments that are needed for response in all patients (>3)[2]. And many patients who respond or remit would have actually responded or remitted with pill placebo as well. This all means that TRD is simply the logical result of the limited effects of treatments. The concept of TRD suggests that there is a threshold that patients should pass (two unsuccessful treatments), while in fact there is no threshold. There is only a limited number of patients who will respond to the next treatment, just as only a limited number responds to the first treatment.

There are many pharmacological, psychological and other treatments of depression and they all have comparable, but limited effects[2,4]. At the same time, hardly anything is known about who benefits from which treatment. Very little is known about the first treatment that should be offered to a patient. Any treatment is as good as another. That means that we very much need research on who benefits from which treatment. But we also need research on sequential treatments. If a patient does not respond to one treatment, what treatment should be offered next, and which one if the second treatment also does not work, and the third and the fourth? From this perspective, research on TRD is very useful, because that is exactly the focus of this research: what should we do if patients do not respond to several treatments? So, although the concept of TRD is based on a misunderstanding of the effects of treatments, the research on interventions for TRD is very much needed.

Unfortunately, there is another major problem with research on TRD: the almost complete absence of psychological treatments. In one systematic overview, a total of 148 different definitions of TRD were collected from the literature[5]. All definitions included at least one failed treatment with antidepressants, but only six definitions (4%) included one failed treatment with psychotherapy. This is remarkable, because there is not only much evidence that psychotherapy overall is as effective as antidepressants in the short term[6], but also that psychotherapy is more effective in the longer term[6,7], and that combined treatment is more effective than either pharmacotherapy or psychotherapy, in the short and longer term[7]. Also, almost all treatment guidelines for depression not only recommend antidepressants but also psychotherapy as first line treatment. This suggests that almost all people who meet one of the current definitions of TRD have not received the best available treatments. Fortunately, the review by McIntyre et al[1] tries to repair this omission in the literature. But it still means that most of the other literature on TRD is flawed and biased towards pharmacological treatments of depression.

There is also some evidence that pharmacotherapy and psychotherapy work independently from each other, and that their effects are additive, without interfering with each other[8]. At the same time, there is some evidence that prior use of antidepressants results in lower response rates when another antidepressant is used[4]. This makes it even less understandable why previous definitions of TRD usually do not include psychotherapies. It further illustrates the biased nature of this research area, and that many patients with TRD just received suboptimal treatments before being defined as having TRD.

Taken together, one could argue that the concept of TRD should be abandoned, because it is based on a misconception of the effects of treatments of depression, and we should move towards an agenda for research on sequential treatments. The current research on TRD fits very well into this agenda, but also has serious limitations, especially the focus on antidepressants and the exclusion of psychological and combined treatments.

Such an agenda should also include other research questions. For example, there is very little research on sequential psychological treatments of depression. Although there are now almost 1,000 randomized controlled trials on these treatments, hardly anything is known about which treatment should be used when a patient does not respond. The same is true for combined treatments. Although it is clear from a considerable number of trials that combined treatment is more effective than either psychotherapy or pharmacotherapy alone[6,7], very little is known about what to do when a patient does not respond to that treatment. Should we change the antidepressant, the psychotherapy, or both? We simply do not know, while these are the questions that need to be answered if we want to help as many patients as possible.

It is time that we move away from the concept of TRD and focus on research on sequential treatments, because that is what patients need most.

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Complexities of treatment-resistant depression: cautionary notes and promising avenues

Depressive episodes can be of mild intensity and transient, but – especially in tertiary care settings – they are often chronic and/or relapsing. As clinicians we often see people towards the latter end of this spectrum, including "treatment-resistant depression" (TRD), and spend much of our efforts in treating them. McIntyre et al[1] competently and comprehensively review the TRD definition, prevalence and management, and portray our ways forward. Here I present a few further perspectives on this topic.

First, patients with TRD can still experience spontaneous full remission. In randomized controlled trials examining various pharmacological switching or augmentation strategies, one in four patients remitted even when they were allocated to the control conditions, i.e. continued the same antidepressants on which they had been judged refractory[2]. There is a paucity of systematic long-term prospective studies on the prognosis of TRD. One small study found that even among patients who were treatment-refractory and were depressed chronically over two years (average: 8.4 years), 8% (95% CI: 3-20) achieved complete remission in the next two years[3]. When nothing seems to help, hope can still be there.

How to get out of TRD is naturally of utmost concern once patients are in there, and McIntyre et al provide a cutting-edge summary of various strategies available today and possibly in the future. As clinicians, however, our first concern should be about how not to let patients get there. In general, pharmacotherapies and psychotherapies are equally efficacious[4], with only some small differences among the various antidepressants and no demonstrable differences among the various psychotherapies, as acute phase treatments. However, a recent systematic review and network meta-analysis[5] found an important difference between psychotherapies and pharmacotherapies when we aim not only to make the patients well, but also to keep them well. Starting treatment of a new depressive episode with psychotherapies increased the proportion of patients with a sustained response (i.e., responding to the acute phase treatment and maintaining that response) by more than 10 percentage points over starting the treatment with antidepressants and keeping them on these medications after response. Scaling up psychotherapies may be one indirect yet important way to decrease the suffering due to TRD.

It may also be important to point out that too aggressive pharmacotherapies may lead to what McIntyre et al call "pseudo-resistance". Selective serotonin reuptake inhibitors (SSRIs) achieve the optimum balance between efficacy and side effects towards the lower end of their approved dose ranges[6] and, despite the commonly accepted clinical wisdom, titrating up the dosage flexibly in view of the patient's response does not increase the response rate[7]. Dose increase after initial non-response does not help, but only increases dropouts due to side effects.

One small caveat is needed concerning discussion of the incidence of TRD. An often cited source for this estimate is the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, arguing that failure of Level 1 and 2 treatments in that study corresponds to the US Food and Drug Administration (FDA)/European Medicines Agency (EMA) criteria for TRD, i.e. inadequate response to two or more antidepressants. The estimate of the TRD incidence is then said to be 55%. However, we should consider that 17% of the patients starting Level 1 treatment in that study had already received some antidepressant medication for the index episode before enrolment, and that the average length of the index episode was already over two years at baseline. The true estimate of non-response to antidepressants in hitherto untreated episodes of major depression could then be lower. Another large trial of antidepressant therapies (the Strategic Use of New generation antidepressants for Depression, SUN☺D) entered only untreated episodes of depression and estimated, after imputation for missingness, the cumulative remission rate to be 37% (95% CI: 35-39) by 9 weeks and 52% (95% CI: 50-54) by 25 weeks[8].

McIntyre et al highlight the lack of consensus on the definition of TRD. We agree that this makes the identification of risk factors and effective therapies more difficult. However, we also wonder whether such variability in the definition of TRD might be commensurate with the heterogeneity of depression itself. In other words, treatment resistance comes in different colors and in different shades. If the diagnosis of TRD is aimed to indicate the next treatment choices, could different definitions actually suggest different treatments? For example, could TRD type 1 be best treated with added antipsychotics; type 2 with added glutamatergic agents; type 3 by neurostimulation therapies, including electroconvulsive therapy or transcranial magnetic stimulation; and type 4 by combined psychotherapies? When TRD develops into persistent depressive disorder, exploratory analyses suggest that patients' characteristics – including baseline severity of depression and anxiety, prior treatment and adverse childhood experiences – may moderate the relative efficacy of psychotherapies, pharmacotherapies or their combination[9]. We are yet far from personalized, differential therapeutics for TRD, but with systematic and consorted efforts we can perhaps reach this level of knowledge within the next decade or two.

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The psychedelic experience and treatment-resistant depression

Interest in the use of serotonergic agonists such as psilocybin in treatment-resistant depression (TRD) has grown more quickly than the evidence on which to base a final opinion, as emphasized by McIntyre et al[1] in their review.

Psilocybin, once metabolized to psilocin, activates 5-HT2A receptors, enhancing GABA function in local circuits in the cor-

tex and increasing connectivity between functional modules in the brain. The emergent consequences can be measured in healthy volunteers and patients by the Altered States of Consciousness Rating Scale (5D-ASC) in five domains: oceanic boundlessness, anxious ego dissolution, visual restructuralization, auditory alterations, and reduction of vigilance[2,3]. While the content of these experiences is very personal, their form is relatively stereotyped and very similar between various study populations. While aspects of personality or emotionality may influence the strength of effects, it is impossible to regard them as simply imaginary or the results of suggestibility.

The largest randomized control trial (RCT) of psilocybin in TRD (COMP 001) showed a striking dose-effect relationship[4]. A 25 mg dose of the investigational drug, COMP360 (a synthetic psilocybin formulation), produced an effect on depressive symptoms significantly greater than a 1 mg dose at the 3-week primary endpoint. The effect of a 10 mg dose was intermediate and tended to fade towards the 1 mg arm over time. A superiority for the 25 mg compared with the other two doses was seen up to 12 weeks. The strength of oceanic boundlessness, in particular, correlated with the outcome measured by conventional scales for mood.

The main objections to a simple interpretation that psilocybin acts to improve depressive symptoms in TRD, or in general in major depressive disorder (MDD), are summarized by McIntyre et al[1]. First, the psychedelic experience is often said to be unblinding. In conventional RCTs, this implies that the active drug is identified because of some adverse effect or other cue when it should ideally be indistinguishable from placebo. In the case of psilocybin and related drugs, the actual problem is the *absence* of a psychedelic experience, which will reveal to patients that they have received placebo, a low dose of psilocybin, or another drug. Does such unblinding necessarily occur, and does it matter? I would argue that it may not[5]. The reason is that the psychedelic experience within the dose ranges currently in use is quite variable. The overlap between active doses due to this variability means that a dose-response relationship cannot credibly be attributed to "unblinding", since patients and staff cannot be certain of what dose has been administered. This will be particularly the case if patients do not have previous psychedelic experience, as in over 90% of participants in the COMP 001 trial.

In addition, the problem with unblinding of an inactive dose is, in theory, the potential for a nocebo effect. Nocebo in this context refers to the possibility that unblinding leads to patients scoring lower when reporting a subjective outcome such as mood than they would if they had simply failed to respond to an active dose. This effect can be checked in all adequately sized trials by comparing the non-response profile in the placebo group with that in the active group. This is not usually done in conventional trials, but in the case of escitalopram a pooled analysis shows very clearly that responders and non-responders have very similar profiles irrespective of whether they receive drug or placebo[6]. In addition, unblinding might be expected to lead to more adverse events, including suicidality. This was not observed for the 1 mg arm in COMP 001[4].

Second, any psychotherapy provided alongside a drug could be potentially confounding: indeed, it is common to hear the expression "psychedelic-assisted psychotherapy" overused uncritically as synonymous with psilocybin treatment. That expression is appropriate for 3,4-methylenedioxymethamphetamine (MDMA), which increases the potential for empathy and interaction with a therapist[7]. It is instead an oxymoron when applied to psilocybin, since the full psychedelic experience is largely incompatible with psychotherapy as usually understood. The psychological support that has been provided in clinical trials of psilocybin means preparation, a supportive presence on the day of drug administration, and integration soon afterwards. Preparation entails instruction, explanation and the establishment of trust. Support during a psychedelic experience is usually minimal: patients don eye shades, listen to music and are encouraged to direct their attention inwards. Integration is non-directive enquiry about the experience and how patients see it affecting their future beliefs and behavior. In most of the depression trials, it was scheduled to be two visits of up to 1 hour each.

In all the MDD and TRD studies published so far, high depression scores were registered at baseline, *after* preparation had occurred. Moreover, in COMP 001, the obvious mood change registered on the day after drug treatment was fully developed before integration had taken place. Hence, there is little reason to attribute clinical improvement to anything other than drug effect on the day of administration. From the perspective of mechanism of action, this is an important conclusion because, if psychotherapy provided the main mechanism of change, understanding the drug contribution would be more difficult, and its approval as a medicine could be compromised.

The assumption that psilocybin treatment is necessarily "combined with psychotherapy" has another risk. Unregulated psychotherapy practice can lead to ethical violations. The risk of such practice in "psychedelic-assisted psychotherapy" is very real and has been highlighted recently[8]. This is another reason for de-emphasizing the role of psychotherapy unless, as with MDMA, it is clearly a key part of the treatment. To refer accurately to psychological support does not diminish its importance in facilitating an optimal psychedelic experience. This support is also ethically essential as a safeguard for patients on the day of drug administration. The qualifications and training of the people providing such support must be to high standards, and a clear protocol should be used. However, the professional background of the therapist is probably less important, because what is involved is not psychotherapy. It is difficult to see how a more minimal package could be safely used as a comparator to "deconstruct" the approach and generate "an evidence base" as suggested by McIntyre et al.

The potential for psilocybin to enhance the effect of conventional psychotherapies remains of great interest. Work in animals suggests that activation of 5-HT2A receptors produces changes in synaptic function that could underpin greater behavioral plasticity[9]. The challenge for the future, along with safe delivery of the experience, appears likely to be the choice of appropriate additional treatment which may have the potential to enhance outcomes in the long term, be it pharmacological, neurostimulatory or psychotherapeutic. For the present, however, the challenge is to complete a

convincing phase 3 programme leading to eventual approval of psilocybin as a medicine. We are not there yet.

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Treatment-resistant depression: where to find hope?

McIntyre et al's paper[1] is not just another literature review on the topic of treatment-resistant depression (TRD). It puts everyone in agreement and offers a concrete basis for a constructive reflection on the subject. More than that, it invites us to approach TRD in all its facets, the most complex but also those still unsuspected.

Since the 1970s, the scientific literature on TRD has abounded with proposals on how to define this condition[2]. In the early days, extraordinarily complex definitions were proposed, all very elaborated and clever, but impractical or even impossible to apply in the clinic.

McIntyre et al provide a comprehensive picture of how we currently define TRD and emphasize that the picture remains blurry, as it is loaded with multiple elements resulting from too many angles of view. Beside the pragmatic definition proposed by regulatory authorities both in the US and in Europe, clinicians and researchers have nourished the picture extensively.

In general, the vast majority of attempts to define TRD describe the concept through the lens of treatment failures, i.e. the number and type of antidepressants that have not been effective in treating a depressive episode. Although this approach is fair and pragmatic, it must be said that it does not lead to a complete understanding of the problem. Some definitions have gone a step further and propose to include other parameters that are not directly related to treatment. This is the case, for example, of the Maudsley Staging Model, which attempts to define the degree of resistance by the severity and duration of the depressive episode, in addition to treatments that have not yielded results[3]. These measurable variables certainly have an impact on treatment resistance. Including these further data in the equation that defines TRD is certainly very helpful.

But, what if we were actually on the wrong track? TRD may be just an indication that different elements should be addressed. Elements that are not necessarily the target of antidepressants. No doubt that substantial results may be obtained by juggling with different antidepressants and how to use them in TRD. McIntyre et al's paper exhaustively reviews the different "tactics" that can be adopted. But it is clear that extending the antidepressant trial, or switching or combining antidepressants, are tactics which too often show their limits. As if with antidepressants we only targeted the visible, symptomatic component, while there are further upstream, more fundamental dimensions that cause resistance to treatment.

Some evidence in this respect comes from the fact that the use of substances other than antidepressants shows better results in TRD. As summarized in the paper, using second-generation antipsychotics or ketamine/esketamine in combination with an antidepressant is amongst the most efficient strategies in TRD. Preliminary evidence also suggests that psilocybin, combined with psychotherapy, may offer rapid and possibly sustained symptom relief in adults with TRD. So, treatments which target dimensions other than the depressive symptomatology can significantly improve the insufficient results of antidepressants. It could be that these treatments act on neurophysiological or psychological dimensions upstream of depression, which may have a significant role in the lack of response to antidepressants. For example, an insufficient neural plasticity could be a basic factor in TRD, on which ketamine/esketamine or psylocibin may act. Moreover, at least six references in the paper are related to the link between childhood trauma and TRD. This can be seen as another example of a key fundamental dimension producing treatment resistance which could be targeted by approaches to TRD. A patient-centric framework describing persons with multiple antidepressant failures, which focuses on causal, perpetuating and treatment factors[4], may be needed.

All these considerations may also be a prompt to consider treatment resistance in the light of a transdiagnostic approach. It could be that factors such as childhood trauma, its negative impact on brain plasticity, and the disturbances that it generates in the circuits of fear and emotion management, are transdiagnostic elements involved in resistance to treatments in general.

In the section dedicated to therapeutic strategies, the authors also address the controversy over the switch within or across antidepressant classes in TRD. Actually, the evidence supporting the use of antidepressants from two different classes is weak. Papakostas et al[5] published the first meta-analysis of data comparing switching strategies for depressed patients who failed to respond to a selective serotonin reuptake inhibitor (SSRI), i.e., switch to a second SSRI or a different antidepressant class. Results suggested only a marginal benefit of switching from one antidepressant class to another on remission rates. However, not all antidepressant classes were considered: only venlafaxine, mirtazapine and bupropion were included in the meta-analysis. There-

after, several reports have shown no advantage in switching to a different class of antidepressants[6-9].

In conclusion, in the management of TRD, hope may lie in a vision that takes into account more fundamental elements than the mere depressive symptomatology. Antidepressants are of some use, but could not target these deeper elements. Depressive symptomatology may be only the last component activated by a multitude of upstream factors that should be the subject of more attention and research.

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20-year trajectories of positive and negative symptoms after the first psychotic episode in patients with schizophrenia spectrum disorder: results from the OPUS study

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This study aimed to identify the 20-year trajectories of positive and negative symptoms after the first psychotic episode in a sample of patients with an ICD-10 diagnosis of schizophrenia spectrum disorder, and to investigate the baseline characteristics and long-term outcomes associated with these trajectories. A total of 373 participants in the OPUS trial were included in the study. Symptoms were assessed at baseline and after 1, 2, 5, 10 and 20 years using the Scales for the Assessment of Positive and Negative Symptoms. We used latent class growth mixture modelling to identify trajectories, and multinominal regression analyses to investigate predictors of membership to identified trajectories. Five trajectories of positive symptoms were identified: early continuous remission (50.9% of the sample), stable improvement (18.0%), intermittent symptoms (10.2%), relapse with moderate symptoms (11.9%), and continuous severe symptoms (9.1%). Substance use disorder (odds ratio, OR: 2.83, 95% CI: 1.09-7.38, p=0.033), longer duration of untreated psychosis (OR: 1.02, 95% CI: 1.00-1.03, p=0.007) and higher level of negative symptoms (OR: 1.60, 95% CI: 1.07-2.39, p=0.021) were predictors of the relapse with moderate symptoms trajectory, while only longer duration of untreated psychosis (OR: 1.01, 95% CI: 1.00-1.02, p=0.030) predicted membership to the continuous severe symptoms trajectory. Two trajectories of negative symptoms were identified: symptom remission (51.0%) and continuous symptoms (49.0%). Predictors of the continuous symptoms trajectory were male sex (OR: 3.03, 95% CI: 1.48-6.02, p=0.002) and longer duration of untreated psychosis (OR: 1.01, 95% CI: 1.00-1.02, p=0.034). Trajectories displaying continuous positive and negative symptoms were linked to lower neurocognition, as measured by the Brief Assessment of Cognition in Schizophrenia (BACS) (z-score: –0.78, CI: –1.39 to –0.17, for continuous positive symptoms; z-score: –0.33, CI: –0.53 to –0.13, for continuous negative symptoms). The same trajectories were also linked to higher use of antipsychotic medication at 20-year follow-up (continuous positive symptoms: 78%; continuous negative symptoms: 67%). These findings suggest that the majority of patients with first-episode schizophrenia spectrum disorder have a trajectory with early stable remission of positive symptoms. Long duration of untreated psychosis and comorbid substance abuse are modifiable predictors of poor trajectories for positive symptoms in these patients. In about half of patients, negative symptoms do not improve over time. These symptoms, in addition to being associated with poor social and neurocognitive functioning, may prevent patients from seeking help.

Key words: First-episode psychosis, schizophrenia spectrum disorder, positive symptoms, negative symptoms, trajectories of symptoms, predictors of symptom trajectories, social functioning, neurocognition

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Schizophrenia affects roughly 1-2% of the world's population[1,2] and is a leading cause of disability worldwide[3]. The disorder often has its onset early in life and is associated with long-term impairments of social and occupational functioning[4], and with significant adversities to both patients and their relatives.

The evolution of the disorder can vary between patients[5]. Some are affected by chronic symptoms, while others experience phases of remission or full recovery[6-8]. The main clinical manifestations are positive and negative symptoms, but patients may also exhibit cognitive deficits and experience a wide range of other subjective symptoms[9,10]. This means that the large group of patients collectively diagnosed with a schizophrenia spectrum disorder experience different patterns of illness course, some much worse than others. Latent class models and growth mixture modeling enable today the identification of clusters of individuals with specific trajectories of symptoms[11], allowing to explore their sociodemographic, clinical and social functioning correlates.

Studies conducted in the 20st century reported great heterogeneity in the course of illness among first-episode psychosis patients[12,13]. Their cross-sectional design provided valuable knowledge on levels of psychopathology at specific timepoints, but no information on illness manifestation over time. Research collecting longitudinal data has contributed to a better understanding of the course of illness. The Suffolk County Study explored trajectories of social functioning, reporting that 75% of patients with psychotic disorders had severe and persistent social impairments[14]. Other studies have determined symptom trajectories in schizophrenia, with follow-ups ranging from weeks to a maximum of 10 years[10]. In these studies, most patients experienced early or delayed improvement of positive symptoms followed by stable symptom levels, while a large group of patients usually experienced only minimal improvement of negative symptoms[10,15]. These latter symptoms are of increasing interest, since patients with a persistence of these symptoms are at high risk of poor outcomes, such as social isolation, unemployment and poor health[16,17]. In addition, treatment options for persistent negative symptoms are scarce[18,19]. Poor symptom trajectories have been previously associated with some sociodemographic and clinical variables, such as male sex, poor premorbid functioning, substance abuse, and a schizophrenia diagnosis[20,21].

Determining symptom trajectories in a modern-day treatment environment and characterizing homogeneous subgroups of patients with schizophrenia spectrum disorder based on long-term symptom levels is a research and clinical priority, as it might help the planning of treatment and possibly the identification of bio-

logical correlates. Identifying characteristics that predict chronic illness could also help target new integrated interventions.

The aim of this study was to identify 20-year trajectories of positive and negative symptoms after the first psychotic episode in patients with an ICD-10 diagnosis of schizophrenia spectrum disorder. We also examined if any baseline characteristics could predict illness trajectories, and explored whether specific illness trajectories were associated with clinical and functional outcomes after 20 years.

METHODS

Study design and participants

This 20-year follow-up study reassessed participants from the OPUS randomized controlled trial. Five hundred seventy-eight participants with an incident schizophrenia spectrum diagnosis (ICD-10 classification: F20-F25, F28-F29) were recruited between 1998 and 2000. Inclusion criteria were a first psychotic episode, age between 18 and 45 years, and not having received more than 12 weeks of continuous antipsychotic treatment. Patients were randomized to specialized early intervention treatment (comprised of assertive community treatment, family involvement, and psychoeducation) or treatment as usual[22]. All participants were given a comprehensive description of the study and provided written consent.

Patients were assessed at baseline and after 1, 2, 5, 10 and 20 years. Each follow-up was conducted by independent clinical staff blinded to the original treatment allocation. Participants were assessed using semi-structured face-to-face interviews followed by questionnaires. Regular sessions were conducted to secure high inter-rater reliability in the use of the assessment instruments.

For this current study, we combined the two treatment groups into one large cohort, because our main aim was to explore heterogeneity in the development of positive and negative symptoms, and allocation to either specialized early intervention treatment or treatment as usual had been found not to affect clinical outcomes at 5 years[22]. In the 20-year trajectory analysis, we included 373 participants with complete data on symptoms at baseline and follow-up. Of these patients, 23 participated in two interviews, 31 in three interviews, 94 in four interviews, 132 in five interviews and 93 in all six interviews (see supplementary information).

Measures of positive and negative symptoms

Symptoms were assessed at baseline and after 1, 2, 5, 10 and 20 years using the Scale for the Assessment of Positive Symptoms (SAPS)[23] and the Scale for the Assessment of Negative Symptoms (SANS)[24]. For both dimensions, we calculated composite scores ranging from 0 to 5. The "positive dimension" was the mean score of the global ratings for hallucinations and delusions. The "negative dimension" was the mean score of all four global ratings of negative domains in the SANS[25]. We regarded a symptom score of 2 or less on all global ratings of symptoms as clinical remission[26].

Baseline risk factors

The variables examined as possible baseline predictors of trajectory membership were: age; sex; main ICD-10 diagnosis ascertained by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)[27]; diagnosis of substance use disorder ascertained using the same interview; global level of functioning measured by the Global Assessment of Functioning (GAF) scale (from 0, poor to 100, good)[28]; negative, positive and disorganized symptoms assessed using the SANS and the SAPS and rated as a continuous variable from 0 to 5; allocation to either early intervention treatment or treatment as usual; completion or not of high school; premorbid social and academic functioning assessed using the Premorbid Adjustment Scale (PAS)[29]; duration of untreated psychosis assessed by the Interview for Retrospective Assessment of Onset of Schizophrenia (IRAOS)[30] and defined as the number of months with at least one psychotic symptom definitely present until the initiation of treatment[31].

Distal outcomes

We examined the association between trajectories of positive and negative symptoms and distal outcomes measured at the 20-year follow-up. The outcomes measured were: a) rate of recovery, defined as no psychotic episode, no psychiatric hospitalization and no use of supported housing in the past two years, being engaged in studying or working, and a present GAF score ≥60; b) for positive symptom trajectories, remission of negative symptoms; for negative symptom trajectories, remission of positive symptoms; c) social functioning assessed by the Personal and Social Performance (PSP) scale[32], which measures four domains of social functioning (useful activities, personal relationships, self-care, aggressive and disturbing behaviour), combined and rated with a score ranging from 0 to 100; d) cognitive functioning measured by the Brief Assessment of Cognition in Schizophrenia (BACS)[33] and reported as z-score; e) current diagnosis of schizophrenia based on the SCAN interview; and f) current treatment with antipsychotic medication.

Statistical analysis

We applied latent growth mixture modelling (LGMM) and latent class growth analysis (LCGA) to estimate trajectories of positive and negative symptom dimensions[34]. These are data-driven, person-centered approaches, that identify population subgroups (classes) based on prototypical patterns in intercepts and slopes. To handle missing data, we applied the full information maximum likelihood approach[35].

We estimated LGMM and LCGA models with different growth functions (i.e., linear, quadratic or cubic) and an increasing number of classes. We examined a number of model fit estimates and model features to select the model with the best fit of the data, including Akaike information criteria (AIC), Bayesian information

criteria (BIC) and sample-size adjusted BIC (adj. BIC), entropy of the model, class size and accuracy, and test of model fit with addition of an extra class by Lo-Mendell-Rubin and Vuong-Lo-Mendell-Rubin likelihood ratio tests.

We tested baseline variables as predictors of class membership by applying the Three-Step approach[36], in which covariates are not included in the modelling of trajectories but treated as auxiliary variables, so that they do not influence the formation of trajectories. Therefore, class membership is established first, and subsequently predictors for membership of identified trajectories are examined. We first tested baseline variables univariably, and then included all significant covariates in a multivariable multinomial logistic regression model. Level of significance was set at $p<0.05$. The results are presented as odds ratios (OR) with 95% confidence intervals (95% CI) and corresponding p values. In order to examine the association between trajectory membership and distal outcomes, we used the Lanza method[37]. All statistical analyses were conducted in Mplus statistical software version 7.

RESULTS

Dropout analysis

A total of 373 participants were included in this study. In the dropout analysis, we found that participants did not differ from non-participants with respect to baseline psychopathological characteristics (including the proportion of those with a diagnosis of schizophrenia and of substance use disorder, and the mean scores on the positive and negative dimensions), the median duration of untreated psychosis, the employment rate, the proportion of those who completed high school education, and the mean scores for premorbid social and academic functioning. Participants were slightly younger than non-participants (26.2±6.2 vs. 27.8±6.8 years), were less frequently male (55.1% vs. 64.0%), had higher levels of global functioning (mean GAF score: 41.0±13.7 vs. 37.7±11. 9), and had higher rates of independent living (95.5% vs. 87.6%) (see also supplementary information).

Trajectories of positive symptoms

For positive symptoms, we estimated a series of linear, quadratic and cubic term LCGA and LGMM models from one to six classes (see supplementary information). We chose the five-class model based on likelihood ratio tests indicating that it had a superior goodness of fit compared with the four-class model. Entropy scores were high for both the four- and five-class models (0.834 vs. 0.949), but the individual class accuracy scores in the five-class model were higher (all above 0.95), expressing a better classification accuracy (see supplementary information).

We named the five positive symptom trajectories as follows: *early continuous remission* (50.9% of the sample), characterized by early and continuous remission of symptoms; *stable improvement* (18.0%), marked by a slower decrease of symptoms in the first five years followed by stabilization; *intermittent symptoms* (10.2%), characterized by relapse and remission of symptoms; *relapse with moderate symptoms* (11.9%), marked by improvement of symptoms in the first years followed by a slow but continuous increase of symptoms subsequently; and *continuous severe symptoms* (9.1%), characterized by a small decrease in symptoms in the first year followed by a stable continuous course of symptoms (see Figure 1).

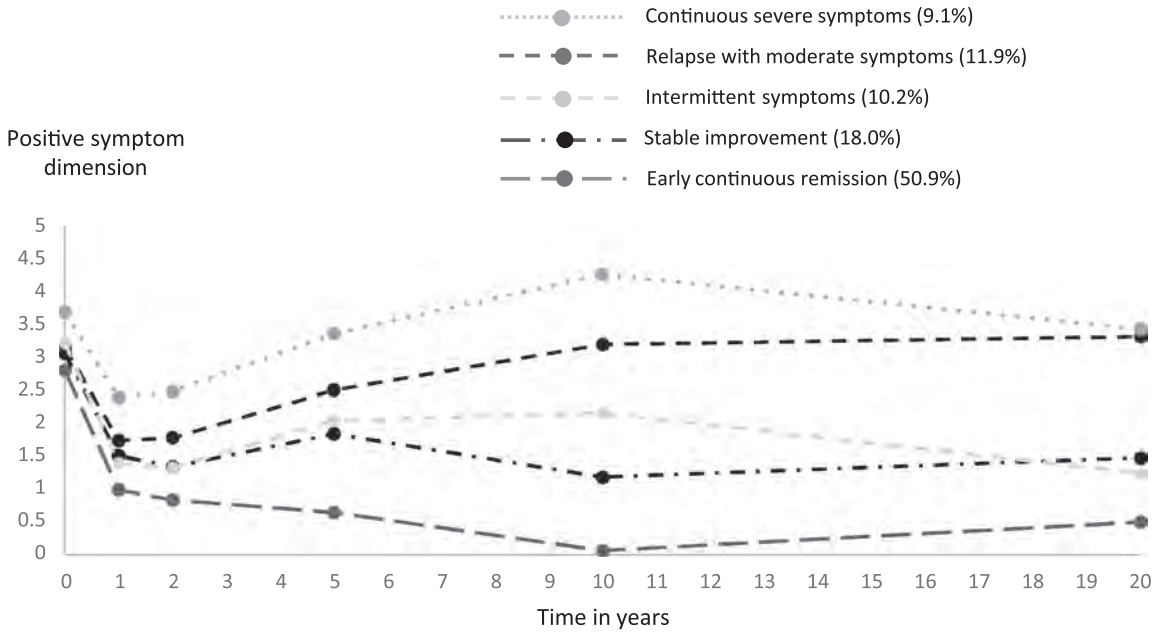

Figure 1 20-year trajectories of positive symptoms after the first psychotic episode in patients with an ICD-10 diagnosis of schizophrenia spectrum disorder

Trajectories of negative symptoms

For negative symptoms, we estimated a series of LCGA and LGMM models from one to five classes (see supplementary information). The two-class LCGA model was chosen because it had higher entropy and class accuracies (both classes above 0.93) than models with additional classes (all class accuracies lower than 0.93). The two trajectories of negative symptoms were named *symptom remission* (51.0% of the sample), characterized by a low mean level of negative symptoms initially, followed by remission within the first two years, and *continuous symptoms* (49.0%), marked by a high mean level of negative symptoms at baseline and no changes over time (see Figure 2).

Baseline predictors of trajectory membership

Positive dimension

Using univariable multinomial logistic regression analysis, we first identified baseline characteristics associated with positive symptom trajectories using *early continuous remission* as a reference (see supplementary information). Significant predictors were then entered into multivariable analysis. Substance use disorder (OR: 2.83, 95% CI: 1.09-7.38, p=0.033), longer duration of untreated psychosis (OR: 1.02, 95% CI: 1.00-1.03, p=0.007), and higher level of negative symptoms (OR: 1.60, 95% CI: 1.07-2.39, p=0.021) remained significant predictors of membership to the *relapse with moderate symptoms* trajectory, while only duration of untreated psychosis (OR: 1.01, 95% CI: 1.00-1.02, p=0.030) predicted membership to the *continuous severe symptoms* trajectory. Male sex (OR: 3.69, 95% CI: 1.42-9.58, p=0.007) predicted membership to the trajectory of *intermittent symptoms* (see Table 1).

Negative dimension

A similar univariable multinomial logistic regression analysis was conducted for predictors of negative symptom trajectories (see supplementary information). In multivariable analysis, male sex (OR: 3.03, 95% CI: 1.48-6.02, p=0.002) and longer duration of untreated psychosis (OR: 1.01, 95% CI: 1.00-1.02, p=0.034) increased the risk of belonging to the *continuous symptoms trajectory* compared with the *symptom remission* trajectory. Higher level of global functioning (OR: 0.95, 95% CI: 0.92-0.98, p=0.001) and finishing high school (OR: 0.41, 95% CI: 0.17-1.00, p=0.049) were associated with lower risk of belonging to the *continuous symptoms* trajectory (see Table 2).

Associations between trajectory membership and distal outcomes

Positive dimension

Social functioning scores at the 20-year follow-up were significantly higher in patients with the *early continuous remission* trajectory (mean PSP score: 60.7, CI: 57.6-63.8) and the *stable improvement* trajectory (mean PSP score: 59.0, CI: 52.7-65.3) compared to those with the other trajectories (mean PSP scores between 40.4 and 47.9). Patients with the *early continuous remission* trajectory had a significantly higher recovery rate (22%) than those with the other trajectories. Neurocognitive function was significantly more impaired in patients with the *continuous severe symptoms* trajectory (z-score: –0.78, CI: –1.39 to –0.17) than in those with the *early continuous remission*, *stable improvement* and *intermittent symptoms* trajectories (see Table 3).

The number of patients qualifying for a schizophrenia diagno-

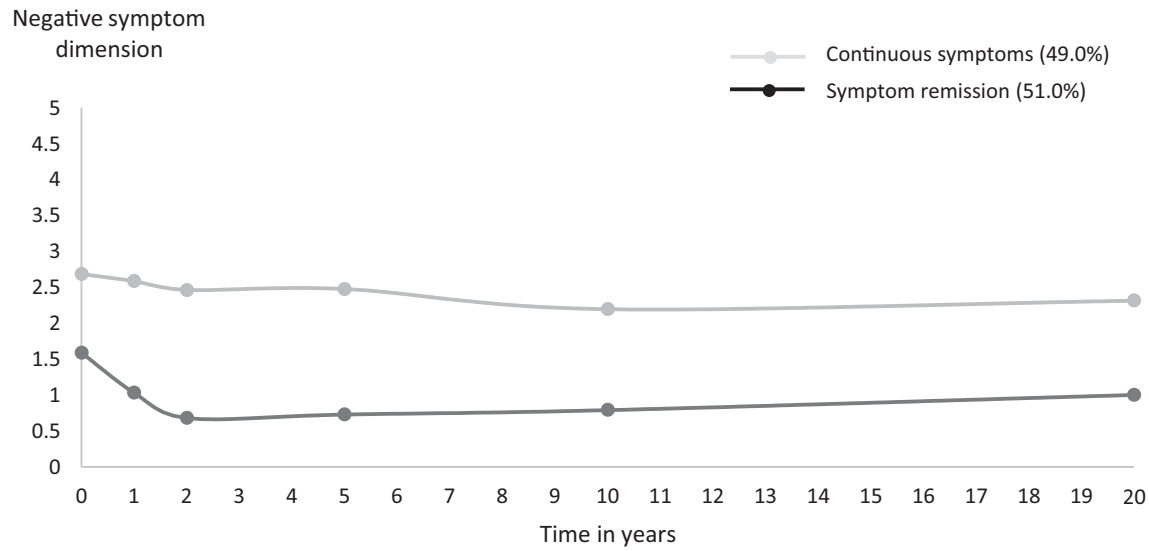

Figure 2 20-year trajectories of negative symptoms after the first psychotic episode in patients with an ICD-10 diagnosis of schizophrenia spectrum disorder

Table 1 Predictors of membership to positive symptom trajectories using patients with the *early continuous remission* trajectory as reference group

	Stable improvement		Intermittent symptoms		Relapse with moderate symptoms		Continuous severe symptoms	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Male	1.01 (0.49-2.08)	0.977	3.69 (1.42-9.58)	0.007	2.47 (0.96-6.38)	0.061	0.84 (0.35-2.03)	0.697
Completed high school	1.24 (0.58-2.67)	0.575	0.36 (0.10-1.25)	0.108	0.51 (0.14-1.83)	0.301	0.74 (0.24-2.29)	0.602
Employment	1.32 (0.66-2.66)	0.437	0.67 (0.22-2.02)	0.483	0.46 (0.13-1.73)	0.253	0.49 (0.14-1.69)	0.257
Substance use disorder	0.90 (0.37-2.16)	0.806	0.75 (0.25-2.28)	0.747	2.83 (1.09-7.38)	0.033	2.05 (0.78-5.40)	0.148
Poorer level of premorbid social functioning	2.50 (0.49-12.82)	0.270	2.36 (0.17-32.44)	0.521	2.47 (0.24-25.29)	0.445	0.88 (0.04-19.51)	0.934
Poorer level of premorbid academic functioning	5.85 (0.67-50.95)	0.081	0.16 (0.01-2.20)	0.172	2.30 (0.11-46.74)	0.588	2.55 (0.09-68.77)	0.577
Longer duration of untreated psychosis	1.01 (1.00-1.02)	0.179	1.01 (1.00-1.02)	0.122	1.02 (1.00-1.03)	0.007	1.01 (1.00-1.02)	0.030
Higher level of global functioning	0.99 (0.96-1.01)	0.349	0.97 (0.93-1.01)	0.168	1.00 (0.96-1.04)	0.985	0.99 (0.95-1.02)	0.497
Higher level of negative symptoms	0.98 (0.72-1.32)	0.869	1.12 (0.69-1.81)	0.637	1.60 (1.07-2.39)	0.021	1.21 (0.80-1.84)	0.360

OR – odds ratio

sis at the 20-year reassessment was significantly lower in patients with the *early continuous remission* trajectory (55%) than in those with the *continuous severe symptoms*, *relapse with moderate symptoms* and *stable improvement* trajectories. Remission of negative symptoms (all global SANS scores ≥2) was lower in patients with the *relapse with moderate symptoms* trajectory (9%) than in those with *early continuous remission* and *stable improvement* trajectories (51% and 53%, respectively). The probability of being on antipsychotic medication at the 20-year follow-up was higher for patients with the *continuous severe symptoms* (78%) and the *relapse with moderate symptoms* (80%) trajectories compared with the *early continuous remission* group (48%) (see Table 3).

Negative dimension

Social functioning scores at the 20-year follow-up were significantly higher in patients with the *symptom remission* trajectory (mean PSP score: 65.8, CI: 62.7-68.9) than in those with the *continuous symptoms* trajectory (mean PSP score: 47.7, CI: 44.0-51.4). Patients with the *symptom remission* trajectory had a significantly higher recovery rate (37%) than those with the *continuous symptoms* trajectory (0%). Neurocognitive function was more impaired in patients with the *continuous symptoms* trajectory (z-score: –0.33, CI: –0.53 to –0.13) than in those with the *symptom remission* trajectory (z-score: 0.36, CI: 0.16 to 0.56) (see Table 4).

The number of patients qualifying for a schizophrenia diagnosis at the 20-year reassessment was significantly lower in patients with the *symptom remission* trajectory (50%) than in those with *continuous symptoms* (78%). The probability of being on antipsychotic medication at the 20-year follow-up was significantly higher for patients with the *continuous severe symptoms* trajectory (67%) than in those with *symptoms remission* (36%) (see Table 4).

Table 2 Predictors of membership to negative symptom trajectories using patients with the *symptom remission* trajectory as reference group

	Continuous symptoms	
	OR (95% CI)	p
Male	3.03 (1.48-6.02)	0.002
Finishing high school	0.41 (0.17-1.00)	0.049
Employment	0.83 (0.36-1.88)	0.652
Schizophrenia diagnosis at baseline	2.09 (0.90-4.85)	0.085
Poorer level of premorbid social function	3.27 (0.45-23.84)	0.240
Poorer level of premorbid academic functioning	2.57 (0.28-23.54)	0.403
Longer duration of untreated psychosis	1.01 (1.00-1.02)	0.034
Higher level of global functioning	0.95 (0.92-0.98)	0.001
Higher level of disorganized symptoms	1.52 (0.94-2.44)	0.085

OR – odds ratio

DISCUSSION

This study is the first to explore the trajectories of positive and negative symptoms over the 20-year period following a first psychotic episode in patients with an ICD-10 diagnosis of schizophrenia spectrum disorder.

We found five distinct trajectories of positive symptoms, characterized by *early continuous remission* (50.9%), *stable improvement* (18.0%), *intermittent symptoms* (10.2%), *relapse with moderate symptoms* (11.9%), and *continuous severe symptoms* (9.1%). So, about 69% of the sample did not have sustained positive symptoms. Similarly, in the AESOP 10-year follow-up study[38], an improvement of positive symptoms was observed in 65% of patients. Moreover, in our study, patients with the *intermittent symptoms* trajectory had a mean SAPS score below 2 at the 20-year follow-up, suggesting that the proportion of the sample which did not experience significant positive symptoms at follow-up was close to 80%.

Table 3 Associations between trajectories of positive symptoms and distal outcomes at 20-year follow-up

	Early continuous remission (ECR)	Stable improvement (SI)	Intermittent symptoms (IS)	Relapse with moderate symptoms (RMS)	Continuous severe symptoms (CSS)	p (interclass X^2)	Significant differences between classes ($p<0.05$)
Current treatment with antipsychotics	48%	49%	62%	80%	78%	0.040	ECR vs. RMS and CSS
Current schizophrenia diagnosis	55%	78%	51%	90%	85%	0.002	ECR vs. RMS, CSS and SI
Remission of negative symptoms	51%	53%	22%	9%	30%	0.003	ECR and SI vs. RMS
Clinical recovery	22%	15%	16%	0	0	<0.001	ECR vs. RMS and CSS
Social functioning, mean PSP score (CI)	60.7 (57.6-63.8)	59.0 (52.7-65.3)	44.8 (36.6-53.0)	40.4 (33.4-48.2)	47.9 (40.5-55.3)	<0.001	ECR and SI vs. RMS, CSS and IS
Cognitive function, BACS z-score (CI)	−0.10 (−0.32 to 0.12)	0.31 (−0.06 to 0.68)	0.25 (−0.44 to 0.94)	−0.42 (−1.18 to 0.34)	−0.78 (−1.39 to −0.17)	0.029	CSS vs. ECR, SI and IS

PSP – Personal and Social Performance scale, BACS – Brief Assessment of Cognition in Schizophrenia

Table 4 Associations between trajectories of negative symptoms and distal outcomes at 20-year follow-up

	Symptom remission	Continuous symptoms	p (interclass X^2)
Current treatment with antipsychotics	36%	67%	<0.001
Current schizophrenia diagnosis	50%	78%	<0.001
Remission of negative symptoms	84%	41%	<0.001
Clinical recovery	37%	0%	<0.001
Social functioning, mean PSP score (CI)	65.8 (62.7-68.9)	47.7 (44.0-51.4)	<0.001
Cognitive function, BACS z-score (CI)	0.36 (0.16-0.56)	−0.33 (−0.53 to −0.13)	<0.001

PSP – Personal and Social Performance scale, BACS – Brief Assessment of Cognition in Schizophrenia

However, only the group with *early continuous remission* displayed a significantly higher recovery rate (22%) compared with patients with other trajectories. This finding supports the idea that early remission of positive symptoms is an indicator of a higher chance for recovery, as suggested by other long-term follow-up studies[4,39].

Both patients with the *relapse with moderate symptoms* and the *continuous severe symptoms* trajectories showed a higher probability of being on antipsychotic medication at the 20-year follow-up than patients with other trajectories. This could be interpreted as a sign of treatment resistance. Indeed, these two trajectories accounted for about 20% of patients, similar to the rates of treatment-resistant schizophrenia found in other studies[40,41]. We also found that these two trajectories were associated with lower social and neurocognitive function, and that these patients were less likely to show a remission of negative symptoms. This supports a division of schizophrenia into subgroups based on broader clinical features.

We found that longer duration of untreated psychosis, higher baseline levels of negative symptoms and a diagnosis of substance use disorder predicted membership to less favourable trajectories of positive symptoms. These baseline variables have previously been associated to poor outcome in schizophrenia[42-44]. It is noteworthy that they remain significant predictors of 20-year trajectories. This emphasizes the importance of efforts to reduce the time before patients receive psychiatric treatment (promoting the development of early intervention services), and the need to address substance abuse timely and comprehensively (overcoming the current lack of integration between management of severe mental illness and substance abuse observed in several countries).

We found two trajectories of negative symptoms: *symptom remission* (51.0%) and *continuous symptoms* (49.0%). This finding differs from other studies, all with a follow-up ranging between 1 and 10 years, which identified three or more trajectories, often including one with symptom remission[17,21,45,46]. In one of these studies[21], 85% of patients achieved and maintained low levels of negative symptoms. A meta-analysis also suggested that negative symptoms improve in the vast majority of outpatients after an initial schizophrenia spectrum diagnosis[47]. However, the Suffolk County 20-year follow-up study reported an average increase of negative symptoms over time[14]. So, the longer-time perspective may explain the less favourable scenario observed in our sample. Moreover, according to the criteria suggested by Andreasen et al[26], we regarded symptom levels above 2 on the SANS as defining a *continuous negative symptoms* trajectory. Other studies might have viewed such a level of symptoms as mild and categorized the relevant patients as being in remission.

Baseline predictors associated with membership to the *continuous symptoms* trajectory of negative symptoms were male sex, longer duration of untreated psychosis, lower level of global functioning, and not finishing high school. These baseline variables have previously been associated with poor outcomes in schizophrenia [43,48,49]. We further found the *continuous symptoms* trajectory to be associated with lower social and cognitive functioning at 20-year follow-up. This is in line with research showing that negative symptoms are associated with poor functional outcomes in schizophrenia[50-53]. The clinical recovery rate in the *continuous symptoms* trajectory was 0%, while it was 37% in the *symptom remission* trajectory, emphasizing the urgent need for the development of innovative multimodal interventions for this dimension of schizophrenia spectrum disorder.

The main limitation of this study is the relatively high dropout rate. Conducting long-term follow-up studies in this patient population is difficult, as patients with severe mental illness can be hard to reach. The European data protection law has also restricted the ways patients may be contacted, complicated the matter further. The participants in the 20-year follow-up did not differ from non-participants with respect to any psychopathological variable, including the mean scores on positive and negative dimensions, but they had a slightly but significantly higher level of global functioning at baseline than those lost to follow-up. So, our findings could potentially be biased towards a more positive direction. Moreover, some of the classes of positive symptoms were small in size, which affected power to determine predictors of class membership. Finally, the large time gap between the 10- and 20-year follow-up might have led to an oversimplification of symptom trajectories.

Our analyses are based on a sample of patients originally included in a randomized controlled trial. We know that the interventions impacted differentially on symptom levels for the first two years after inclusion, but we also know that this effect was not seen at any following assessment[22,54,55]. The inclusion of the treatment group in the analyses did not change the results, so we ruled out any significant impact of treatment on the trajectories.

In conclusion, our study is the first to identify 20-year trajectories of positive and negative symptoms after a first psychotic episode in patients with schizophrenia spectrum disorder. We recruited par-

ticipants from both inpatient and outpatient settings, making the study population representative of the real-world schizophrenia spectrum population. Understanding the course of illness can help clinicians inform patients and their families about what can happen after the diagnosis has been made. Identifying different symptom trajectories after the initial diagnosis can improve the way we plan treatment[56,57].

Our study suggests that a high proportion of patients with schizophrenia spectrum disorder recover from positive symptoms, but not from negative symptoms. These latter symptoms are associated with poor functioning and increased mortality[18]. Moreover, negative symptoms may prevent patients from seeking help. This could mean that a subgroup of patients with schizophrenia fall outside the treatment system, because they no longer require treatment for florid symptoms, and negative symptoms prevent them from seeking help for other health issues. The development of innovative multimodal treatment strategies for negative symptoms of schizophrenia spectrum disorder represents today an urgent priority.

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Transdiagnostic risk of mental disorders in offspring of affected parents: a meta-analysis of family high-risk and registry studies

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The offspring of parents with mental disorders are at increased risk for developing mental disorders themselves. The risk to offspring may extend transdiagnostically to disorders other than those present in the parents. The literature on this topic is vast but mixed. To inform targeted prevention and genetic counseling, we performed a comprehensive, PRISMA 2020-compliant meta-analysis. We systematically searched the literature published up to September 2022 to retrieve original family high-risk and registry studies reporting on the risk of mental disorders in offspring of parents with any type of mental disorder. We performed random-effects meta-analyses of the relative risk (risk ratio, RR) and absolute risk (lifetime, up to the age at assessment) of mental disorders, defined according to the ICD or DSM. Cumulative incidence by offspring age was determined using meta-analytic Kaplan-Meier curves. We measured heterogeneity with the I^2 statistic, and risk of bias with the Quality In Prognosis Studies (QUIPS) tool. Sensitivity analyses addressed the impact of study design (family high-risk vs. registry) and specific vs. transdiagnostic risks. Transdiagnosticity was appraised with the TRANSD criteria. We identified 211 independent studies that reported data on 3,172,115 offspring of parents with psychotic, bipolar, depressive, disruptive, attention-deficit/hyperactivity, anxiety, substance use, eating, obsessive-compulsive, and borderline personality disorders, and 20,428,575 control offspring. The RR and lifetime risk of developing any mental disorder were 3.0 and 55% in offspring of parents with anxiety disorders; 2.6 and 17% in offspring of those with psychosis; 2.1 and 55% in offspring of those with bipolar disorder; 1.9 and 51% in offspring of those with depressive disorders; and 1.5 and 38% in offspring of those with substance use disorders. The offspring's RR and lifetime risk of developing the same mental disorder diagnosed in their parent were 8.4 and 32% for attention-deficit/hyperactivity disorder; 5.8 and 8% for psychosis; 5.1 and 5% for bipolar disorder; 2.8 and 9% for substance use disorders; 2.3 and 14% for depressive disorders; 2.3 and 1% for eating disorders; and 2.2 and 31% for anxiety disorders. There were 37 significant transdiagnostic associations between parental mental disorders and the RR of developing a different mental disorder in the offspring. In offspring of parents with psychosis, bipolar and depressive disorder, the risk of the same disorder onset emerged at 16, 5 and 6 years, and cumulated to 3%, 19% and 24% by age 18; and to 8%, 36% and 46% by age 28. Heterogeneity ranged from 0 to 0.98, and 96% of studies were at high risk of bias. Sensitivity analyses restricted to prospective family high-risk studies confirmed the pattern of findings with similar RR, but with greater absolute risks compared to analyses of all study types. This study demonstrates at a global, meta-analytic level that offspring of affected parents have strongly elevated RR and lifetime risk of developing any mental disorder as well as the same mental disorder diagnosed in the parent. The transdiagnostic risks suggest that offspring of parents with a range of mental disorders should be considered as candidates for targeted primary prevention.

Key words: Familial risk, mental disorders, psychosis, depression, bipolar disorder, substance use disorders, eating disorders, anxiety disorders, transdiagnostic risk, targeted primary prevention

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Mental disorders run in families. Decades of epidemiological research have documented that having an affected biological parent is a potent risk factor for mental disorders in the offspring. For some mental disorders, the relationship to offspring's risk is so strong that a parent's diagnosis has been considered as an indication for primary targeted prevention[1,2]. For example, preventive approaches have been developed for young offspring of individuals affected with psychosis, bipolar disorder or depressive disorder[1,3-6]. Another area of clinical application is genetic counselling, which helps people make meaning out of genetic information, including familial risk, and use that information in alignment with their wishes, needs and values, to manage their health in the face of uncertainty[7,8].

The preventive potential of these approaches relies on accurate knowledge of the likelihood of mental disorders and their age of onset among offspring of affected parents. Such knowledge remains incomplete in several respects. First, while numerous studies examined offspring of parents with major depressive,

bipolar or psychotic disorders, the impact of other parental disorders on offspring risk is less mapped out. Second, most prior publications focused on one parental mental disorder at a time (e.g., only examining risk in offspring of parents with bipolar disorder), making a comparison of risks associated with different parental disorders difficult.

Moreover, the findings differ among study designs, populations and settings, leaving uncertainty about the accuracy of estimates. For example, traditional family high-risk studies and reports from national registries draw different conclusions about the magnitude and extent of familial risk. A synthesis drawing on the complementary strengths of family high-risk and registry studies is therefore needed to provide accurate estimates for clinical practice and prevention.

Finally, both degree and specificity of familial risk is undetermined. The causes of mental disorders' clustering in families include genetic variants, shared environment, and the interplay between genetic and environmental factors[9,10]. Most genetic variants and environmental risk factors are not specific to a particular diagnosis[11-13]. Common causal factors and high rates of comorbidity between disorders have motivated the move to transdiagnostic approaches in psychiatry[14]. Yet again, there are discrepancies between study designs. For example, some family high-risk studies reported that increased risk in offspring was specific to the disorder diagnosed in their parent[15,16], while analyses of nationwide registries suggest a pattern of non-specific risk that extends across all mental disorders[10,17]. An earlier meta-analysis by our group drew on data from 33 studies of 3,863 offspring of parents with schizophrenia, bipolar and major depressive disorders to reveal a pattern of partial specificity and broad transdiagnostic risks[18].

The last decade has seen more publications on offspring of parents with a range of mental disorders. Additional meta-analyses have focused on offspring of parents with bipolar disorder[19,20], offspring of parents with anxiety disorders[21,22], offspring of parents with attention-deficit/hyperactivity disorder (ADHD)[23], or anxiety and disruptive disorders among offspring of parents with multiple diagnoses[24,25]. However, there has been no comprehensive transdiagnostic synthesis across offspring of parents with various types of mental disorders that could inform clinical practice. Transdiagnostic approaches may be especially relevant to prevention, as early developmental manifestations of psychopathology often change in ways that cross diagnostic boundaries[26,27].

The present study aims to fill this gap in the literature, by providing a transdiagnostic synthesis of the available studies in offspring of parents affected with all types of mental disorders to inform targeted prevention and genetic counselling. For the first time, we combine, compare and synthesize family high-risk studies and registry studies. We compare the relative risk between offspring of affected and unaffected parents, and examine both transdiagnostic and diagnosis-specific risk to offspring. We quantify the probability (absolute risk) of developing a range of mental disorders for offspring of affected parents up to the assessment age (lifetime). We further estimate the cumulative incidence by offspring age, and test the impact of study design. We then leverage the evidence to formulate recommendations for targeted primary prevention and genetic counselling. We conclude by drafting a research agenda for the next generation of studies in this field.

METHODS

We performed a systematic review and meta-analysis of the available literature on the relationship between any mental disorder in parents and the risk of mental disorders in the offspring. We followed a protocol that was registered at PROSPERO (CRD42022358509) on September 22, 2022. We report the review process and results according to the PRISMA 2020 statement[28].

Literature search

We searched Web of Science with a combination of terms tagging family studies (offspring, parent*, matern*, patern*) and terms capturing mental disorders, to identify publications from database inception until September 16, 2022, with no language restrictions. We validated the search strategy against a set of 62 relevant publications obtained through expert suggestions and a prior systematic review[18]. The search identified all 62 publications in this validation set.

Inclusion and exclusion criteria

Inclusion criteria were: a) original family high-risk (cross-sectional or prospective) or registry study that reported quantitative data on the relationship between one or more mental disorders in a parent and one or more mental disorders in their biological offspring; b) offspring sampled from the general population or selected based on parent diagnosis; c) definitions of mental disorders in parents and offspring based on the ICD or the DSM (any version), established with a diagnostic interview or a standard clinical assessment; d) published in any language.

Exclusion criteria were: a) inadequate study design, including adoption studies (because they systematically differ from family high-risk studies in separating genetic from environmental aspects of familial risk), case reports (to avoid highly selective sampling), and intervention studies (in which the risk of disorders in offspring could be reduced through an intervention); b) offspring selection (where offspring were selected based on their own health or an environmental exposure, as such selection could inflate the risk of disorders in the offspring); c) lack of ICD/DSM parent diagnosis (when no ICD/DSM diagnosis in parents was reported, or parent assessment was limited to self-report questionnaires that do not clearly identify ICD/DSM diagnoses); d) lack of ICD/DSM offspring diagnosis (when no ICD/DSM diagnosis in offspring was reported, or offspring assessment was limited to self-report questionnaires that do not clearly identify ICD/DSM diagnoses); and e) lack of relevant data (when there was no numeric information on the relationship between ICD/DSM

diagnoses in parents and in offspring, or data on offspring were only reported as part of a larger group of first-degree relatives).

Selection of relevant publications

The selection of eligible publications proceeded in two stages, implemented in Covidence[29]. First, two independent reviewers screened all titles and abstracts against a list of eligibility criteria, to remove studies that were ineligible and select publications for full-text review. Second, two independent reviewers went through full texts of the pre-selected publications, to confirm that eligibility criteria were met and select a final list of publications for data extraction. At both stages, a senior investigator resolved discrepancies between the reviewers.

Data extraction

We extracted the information on parent-offspring disorder relationships as relative risk and absolute risk, using Covidence extraction 2 interface[29]. To assess relative risk, we extracted the risk ratios (RR), odds ratios (OR) or hazard ratios (HR) reflecting the increased (values greater than 1) or decreased (values smaller than 1) rates of disorder in offspring of parents with a given diagnosis, relative to control offspring of parents without a diagnosis. We recorded the type of the relative risk (RR, OR or HR), and its 95% confidence interval (CI) or standard error (SE). To assess absolute risk, for each group of offspring defined by a given parental diagnosis, we extracted the number of offspring with and without each mental disorder and the total number of offspring assessed for the disorder. We extracted the absolute risk of the same disorders for control offspring of parents without a diagnosis, if such control group was included. We use the term "lifetime risk" to describe these absolute risks measured up to age at assessment.

In addition, we extracted the country of origin of the study, the study design (prospective, cross-sectional, registry), the population (general, high-risk), the diagnostic instruments and classification system used to make diagnoses in parents and in offspring, and the mean offspring age at assessment. For prospective studies, we extracted the offspring age at first and last assessment and additional information on the cumulative incidence of developing mental disorders by offspring age (from available Kaplan-Meier plots, see the data analysis section).

Where two or more publications reported data on the same disorder from the same sample or a partially overlapping sample, we selected the report with the largest sample size. For prospective studies, we extracted data from all time points, to inform analyses of cumulative incidence by offspring age.

Study design

We defined the two primary study types based on their design: i.e., family high-risk studies and registry studies. We further subdivided family high-risk studies into cross-sectional and prospective ones. Cross-sectional studies are those where offspring are assessed only once for presence or absence of mental disorders[30-32]. Prospective studies are those where researchers follow the offspring over time and repeatedly assess them for mental disorders at two or more time points[33-35]. Registry studies are those where offspring are not systematically assessed for the presence or absence of diagnosis, but information on the presence of a mental disorder is obtained from a health care record database or national registry[9,17].

Family high-risk studies systematically assess offspring with diagnostic interviews covering the full range of mental disorders and including comorbidity (high psychometric validity). However, samples are often selected from clinical populations and therefore are prone to selection bias (low ecological validity). This is of particular concern in cross-sectional studies, which recruit participants when the target disorders are already present. Prospective studies mitigate disorder-related sources of selection bias by recruiting participants before they develop mental disorders of interest, but they may still be prone to selection bias and confounding because of factors pre-dating enrolment and attrition of participants over time leading to incomplete follow-up. Typically, each one of these studies is too small to individually provide conclusive results (low statistical power)[36].

Registry studies avoid most sources of sampling bias and provide adequate statistical power to detect even weak relationships with high ecological validity, as they take advantage of data on an entire population[37]. However, registries only contain diagnostic information on mental disorders which received treatment, and this information is based on unstructured clinical assessments (low psychometric validity)[37]. Individuals who meet diagnostic criteria for a mental disorder but do not seek treatment are misclassified as not having a disorder[37]. This misclassification may result in significant underestimates of risk of mental disorders that often remain untreated or are not seen as the primary reason of hospital admissions or clinic visits.

Risk of bias

To capture the various sources of bias in prospective, cross-sectional, and registry studies, we rated the risk of bias using the Quality In Prognosis Studies (QUIPS) tool[38]. For each included report, we rated six bias domains: participation, attrition, parent diagnosis assessment, offspring diagnosis assessment, blinding of offspring assessors to parent diagnosis, and analysis reporting. Each domain is rated as low, moderate or high risk of bias. A "high" score in any domain indicates that a study is at high risk of bias.

Transdiagnosticity assessment

To meet the TRANSD criteria, we defined the gold standard by including specific ICD/DSM diagnoses, acknowledged the primary outcome of the study, defined the transdiagnostic con-

struct as relative or absolute risk, appraised it across ten diagnostic groups, performed three types of multiple comparative analyses (RR, absolute risk, and risk of having the same mental disorder as the parent vs. having any other mental disorder), and validated the findings by focusing on those supported by at least three independent studies (see below)[14,39].

Outcome measures

We grouped parent and offspring disorders into ten diagnostic categories: psychosis (schizophrenia, schizophreniform, schizoaffective and other psychotic disorders); bipolar disorder (bipolar I, bipolar II, and other/not otherwise specified); depressive disorders (major depressive disorder, persistent depressive disorder, and dysthymia); anxiety disorders (generalized anxiety disorder, panic disorder, social anxiety disorder, and phobias); substance use disorders (alcohol or substance use disorder, excluding nicotine use disorder); borderline personality disorder; ADHD (inattentive, hyperactive/impulsive, combined); disruptive disorders (oppositional-defiant disorder and conduct disorder); obsessive-compulsive disorder (OCD); eating disorders (anorexia nervosa, bulimia nervosa, other/not otherwise specified eating disorder).

We also included "any mental disorder" where this was reported (here, "any mental disorder" refers to one or more mental disorder diagnoses; because of comorbidity, this number is distinct from a sum of individuals affected with specific disorders). When a study reported more than one specific disorder (e.g., several specific anxiety disorders), we used the one representing more affected individuals as a proxy for the number of individuals with any specific disorders, considering the high comorbidity between them. For specific eating disorders at the same time point, we added the number of individuals with anorexia and bulimia, as these diagnoses are mutually exclusive[40].

Statistical analyses

For each parent and offspring disorder combination, we performed two random-effect meta-analyses.

First, we conducted a meta-analysis of the RR of the target disorder among offspring of affected parents compared to control offspring (i.e., those with no affected parents). Specifically, we calculated RR as the disorder risk in the offspring of affected parents divided by the disorder risk in control offspring. When the statistic available was only a RR/HR/OR and its CI, we first used the "improve_ci" function of the "metaumbrella" R package[41] to unround the estimates, and then derived the SE. We forced estimated SEs to be at least 0.001, to avoid a few samples receiving exaggerated weights in the subsequent meta-analyses. When the risk estimate reported was an OR, we imputed the equivalent RR using a modified version of the "estimate_n_from_or_and_n_cases" functions of the "metaumbrella" package[41,42]. Then, we used the imputed number of affected offspring to derive the RR. As these imputations are not free from error, we forced the imputed RR to be equal to or smaller (in absolute logarithmic terms) than the corresponding OR, while we retained the variance, so that the imputed RR was similar or slightly lower and had a similar or slightly lower statistical significance than the reported OR.

To meta-analyze the RR, we used the "metafor" R package[43] to create random-effects models of the log-transformed RR. This package uses the restricted maximum likelihood (REML) to fit the model and adds 0.5 to any zero counts of affected and non-affected offspring. While computationally necessary, the addition of 0.5 can distort rate estimates in very small samples; therefore we restricted this procedure to groups of 50 or more individuals. We interpreted p values smaller than 0.05 as statistically significant. We estimated the heterogeneity between studies with the I^2 statistic.

Second, we completed a meta-analysis of the absolute risk, i.e., the proportion of offspring affected with the target mental disorder, which is the preferred metric in genetic counseling[7]. We followed the same methodology as for the RR meta-analysis, except for using the logit instead of the log-transform. We noted that some disorders are typically underdiagnosed in the population registries but frequently diagnosed in family high-risk studies, leading to the absolute risks of clinically meaningful disorders being systematically underestimated in registry studies and overestimated in non-registry studies. Since family high-risk and registry studies differ in more ways that can be accounted for, and neither is free from bias, we meta-analyzed registry and non-registry studies separately and then combined the two meta-analytic results, setting the weights to be 50% (rather than altering the variances). Of note, such weighting was not necessary for RR, under the assumption that under- and over-diagnoses applied to both offspring of affected parents and control offspring.

To further characterize the age-dependent risk, we performed a meta-analytic Kaplan-Meier assessment of the absolute risk (cumulative incidence) of severe mental disorders by offspring age. We first generated pseudo-individual participant data (pseudo-IPD), whose survival curve would be identical to the published survival curves, using an established methodology[44] as in previous meta-analyses[45,46]. For a study[47] which reported separate Kaplan-Meier plots for bipolar disorder and bipolar disorder not otherwise specified in the same sample, we matched the events of each curve with censors occurring at the same age in the other curve, to generate a single dataset. Second, we combined the datasets from the different studies to estimate a curve for the risk of psychosis in the offspring of parents with psychosis, a curve for the risk of bipolar disorder in the offspring of parents with bipolar disorder, and a curve for the risk of depressive disorders in the offspring of parents with depressive disorders. There were too few studies for other disorder combinations (all $n \leq 3$).

We then conducted some sensitivity analyses. First, we conducted meta-analyses of the relative and absolute risks restricted to prospective studies that had followed the offspring at least until the typical age of each disorder onset or diagnosis (childhood for ADHD, disruptive disorders and OCD; adolescence for depressive, anxiety and eating disorders; adulthood for psychosis,

bipolar, substance use and borderline personality disorders). For this purpose, we labeled the samples as "children" when the mean age was <12 years old, "adolescents" when it was ≥12 but <18 years old, and "adults" when it was ≥18 years old. When data from multiple age groups were available, we used multilevel random-effects models, including the age group as a moderator. These multilevel models are conceptually the same as subgroup analyses by follow-up age ranges, with the only difference being that they include studies with shorter follow-ups in the model to improve fit. For these multilevel models, we calculated I^2 as recommended by the creator of the "metafor" package at https://www.metafor-project.org/doku.php/tips.

Second, to formally assess whether absolute risks were significantly smaller in registry than in non-registry studies, we calculated the difference in (logit-transformed) absolute risks between registry and non-registry meta-analytic results, along with its variance and the (log-transformed) risk ratio. Then, we conducted a meta-analysis of these differences for each offspring disorder (across parental disorders and children age ranges) and applied the resulting weights to the (log-transformed) relative risks. Risk ratios <1 mean that the absolute risk of a disorder is smaller in registry than in non-registry studies.

Third, to address the risk of having the same mental disorder as the parent vs. having any other mental disorder, we conducted multilevel meta-analyses of the RR of having a mental disorder other than the disorder of the parent. The reason to use multilevel models, with the sample as a random factor, was that we include several RR estimates from each sample (i.e., an estimate for each mental disorder in offspring). We discarded offspring disorders with less than two studies and "having any mental disorder" because this grouping includes the parent's disorder. We then meta-analyzed the results of these meta-analyses to have an overall estimate of the RR of developing the same mental disorder as the parent and an estimate of the RR of developing a different mental disorder from the parent. We conducted this analysis separately for family high-risk and registry studies.

The main meta-analytic (i.e., based on at least three independent studies) results were presented stratified according to clinical-informative topics that may inform practice and prevention. The estimates based on fewer than three independent studies are reported in tables, but are not interpreted, as they are considered to be less reliable.

RESULTS

Meta-analytic database

Of 20,964 unique records identified by the literature search, we selected 911 reports for full-text review, and extracted data from 457 eligible publications (see Figure 1). Common reasons for exclusion at the full-text review stage were offspring sample selection based on their own health or environmental factors, missing or inadequate information on diagnosis in parents or offspring, and publications that contained no original data on the relationship between parent diagnosis and offspring disorders.

The 457 eligible publications reported data from 211 unique studies, including 3,172,115 offspring of parents with mental disorders. A subset of 157 studies reported data on 20,428,575 comparison offspring. Most studies were family high-risk studies, but the 18 registry studies included a disproportionately large number of participants (see Table 1). The sample size of the included studies ranged from 19 to 8,951,763. Offspring were assessed at a mean age of 4 to 42 years. One hundred and thirty-five (64%) studies reported data on children, 142 (67%) on adolescents, and 95 (44%) on adult offspring. Of the 211 included studies, 54% (n=113) were from the US, 23% (n=48) from Europe, 7% (n=15) from Asia, 7% (n=15) from Canada, 4% (n=8) from Australia, and 1% (n=3) from low- or middle-income countries. We computed 88 RRs (10 for the same disorder and 78 for different disorder combinations) and 96 absolute risks (10 for the same disorder and 86 for different disorders or controls).

How likely are the offspring of affected parents to develop any mental disorder?

Of the 211 eligible studies, 86 provided data on offspring's risk of developing any mental disorder. Compared to control offspring, the offspring of affected parents had a 1.5- to 3-fold elevated RR for developing any mental disorder (see Table 2): 3.0 in offspring of parents affected with anxiety disorders; 2.6 in those of parents affected with psychosis; 2.1 in those of parents affected with bipolar disorder; 1.9 in those of parents affected with depressive disorders; and 1.5 in those of parents affected with substance use disorders. No or few data were available on the RR of any mental disorders in offspring of parents with other mental disorders.

The absolute risk of any mental disorder among offspring of affected parents was 55% in offspring of parents affected with bipolar disorder or anxiety disorders; 51% in offspring of parents affected with depressive disorders; 38% in those of parents affected with substance use disorders, and 17% in those of parents affected with psychosis (see Table 3). In contrast, one in seven (14%) control offspring developed any mental disorder. No or few data were available on the lifetime risk of any mental disorders in offspring of parents with other mental disorders.

Sensitivity analyses restricted to prospective studies that had followed the offspring at least until the typical age of each disorder's onset reported similar RRs, but substantially higher absolute risks of mental disorders (see supplementary information).

How likely are the offspring to develop the same mental disorder as their parents?

Across all mental disorders examined, the offspring had increased risk of the same type of disorder that was diagnosed in their parents, with RRs ranging from 2.2 for anxiety disorders to 8.4 for ADHD (see Table 2). The other RRs were 5.8 for psychosis, 5.1 for bipolar disorder, 2.3 for depressive disorders, 2.8 for sub-

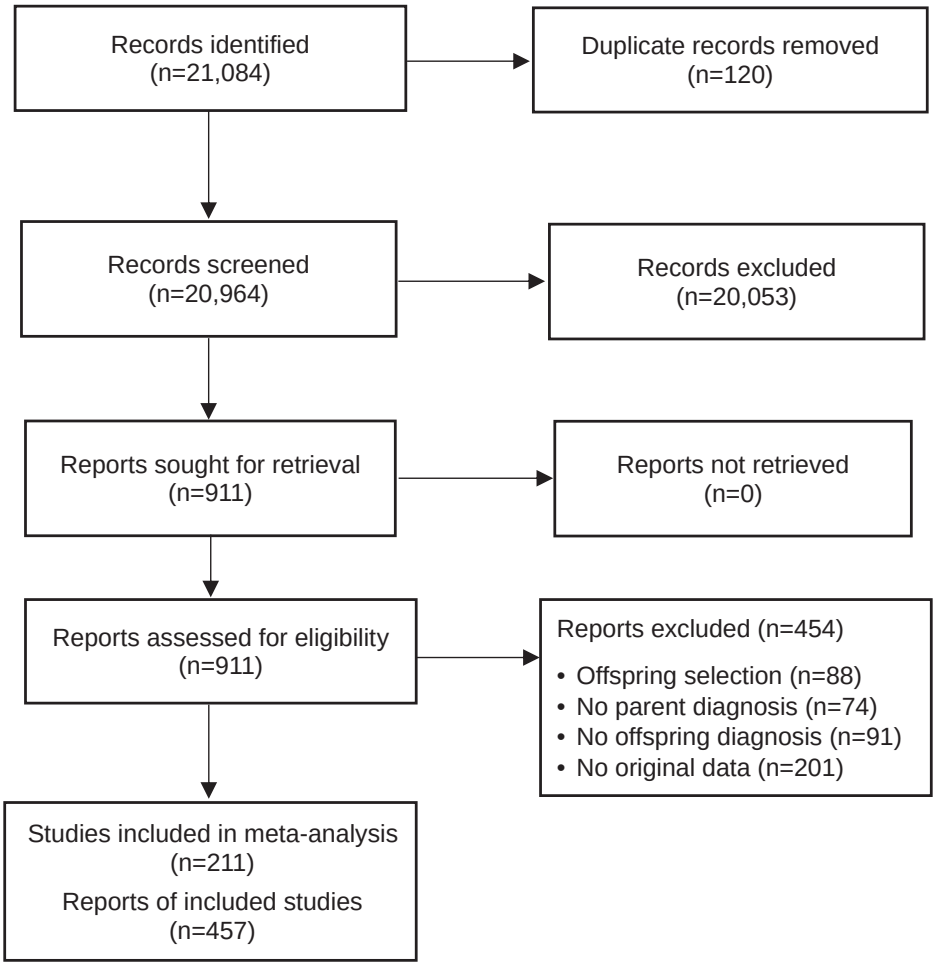

Figure 1 PRISMA 2020 flow chart

stance use disorders, and 2.3 for eating disorders. Small datasets of offspring of parents with borderline personality disorder and OCD precluded establishing statistical significance. There were no data for disruptive disorders.

The absolute risks of the same disorder diagnosed in parents were 32% for ADHD, 31% for anxiety disorders, 14% for depressive disorders, 9% for substance use disorders, 8% for psychosis, 5% for bipolar disorder, and 1% for eating disorders. There were no or too little data to reliably estimate the risk of other mental disorders. In terms of absolute risk, control offspring had a low risk of developing specific mental disorders, with estimates ranging from 1% (psychosis, bipolar disorder, eating disorders) to 7% (anxiety disorders).

Sensitivity analyses restricted to prospective studies that had followed the offspring at least until the typical age of each disorder's onset confirmed the overall direction and pattern of results, but showed a higher RR of bipolar disorder in offspring of parents with bipolar disorder (RR=9.0) and 2- to 3-fold higher absolute risks of disorders for which adequate data were available: 35% for substance use disorders, 34% for depressive disorders, 21% for psychosis, and 13% for bipolar disorder (see supplementary information). There were no prospective studies for ADHD.

Table 1 Included studies and participants by study type

	Offspring of affected parents		Control offspring		All offspring
Study type	n	N	n	N	N
Prospective family high-risk	81	21,477	62	11,389	32,866
Cross-sectional family high-risk	112	69,918	77	9,008	78,926
Registry	18	3,080,720	18	20,408,178	23,488,898
Total	211	3,172,115	157	20,428,575	23,600,690

How likely are the offspring to develop mental disorders other than those diagnosed in their parents?

The eligible studies provided data on 62 transdiagnostic relationships between parental mental disorders and the risk of a different mental disorder in the offspring (see the off-diagonal cells with white background in Table 2). Of the 62 transdiagnostic

Table 2 Meta-analytic estimates of the risk ratios (RRs) of DSM/ICD mental disorders in offspring of affected parents vs. offspring of unaffected parents

		Disorder in parents										
		Psychosis	**Bipolar disorder**	**Depressive disorders**	**Anxiety disorders**	**Substance use disorders**	**Borderline personality disorder**	**ADHD**	**Disruptive disorders**	**OCD**	**Eating disorders**	**Any mental disorder**
Disorder in offspring	Psychosis	5.8 (4.2-7.9) (n=21, N=7,545,374)	1.8 (0.6-5.0) (n=11, N=3,924,359)	2.0 (1.3-3.1) (n=6, N=1,746,667)	*1.7 (0.1-26.3) (n=2, N=521)*	2.2 (2.0-2.5) (n=5, N=2,153,172)		*1.8 (1.2-2.6) (n=2, N=348,808)*		*1.6 (1.3-2.0) (n=1, N=347,208)*		4.0 (2.3-6.9) (n=8, N=3,677,788)
	Bipolar disorder	1.3 (0.3-5.0) (n=6, N=4,286,168)	5.1 (3.3-8.1) (n=33, N=11,561,026)	2.1 (0.9-5.0) (n=12, N=6,318,061)	1.0 (0.4-2.6) (n=3, N=1,300)	*11.4 (1.3-96.8) (n=2, N=459)*	*3.1 (0.1-73.0) (n=1, N=45)*	2.3 (1.9-2.8) (n=3, N=4,486,959)		*1.6 (1.4-1.8) (n=2, N=347,286)*		*2.0 (0.6-6.9) (n=1, N=970)*
	Depressive disorders	1.9 (1.7-2.2) (n=14, N=2,989,314)	2.1 (1.5-2.9) (n=39, N=9,296,154)	2.3 (1.9-2.6) (n=53, N=11,895,688)	1.7 (1.4-2.0) (n=12, N=6,360,668)	1.8 (1.3-2.3) (n=13, N=8,180)	*9.4 (1.3-68.3) (n=1, N=45)*	*2.2 (1.4-3.6) (n=2, N=4,138,210)*	*1.3 (1.1-1.6) (n=1, N=2,764)*	*3.7 (0.8-15.9) (n=1, N=78)*		1.9 (1.6-2.3) (n=5, N=7,336,515)
	Anxiety disorders	1.7 (1.0-3.1) (n=13, N=283,363)	2.1 (1.7-2.5) (n=33, N=6,373)	2.0 (1.7-2.3) (n=33, N=9,807)	2.2 (2.0-2.5) (n=22, N=1,981,092)	1.4 (1.1-1.9) (n=12, N=4,576)	*9.3 (2.2-39.1) (n=2, N=135)*	*2.0 (0.4-9.3) (n=1, N=59)*		*2.0 (1.1-3.8) (n=1, N=78)*		1.7 (1.6-1.8) (n=5, N=1,078,763)
	Substance use disorders	2.0 (1.2-3.3) (n=10, N=423,316)	1.9 (1.6-2.2) (n=20, N=4,693)	2.4 (1.6-3.8) (n=15, N=5,875)	*8.2 (0.8-82.1) (n=2, N=607)*	2.8 (2.1-3.6) (n=23, N=685,252)	*6.3 (0.8-48.0) (n=1, N=45)*			*2.0 (0.4-9.9) (n=1, N=78)*		4.8 (2.4-9.7) (n=5, N=992,098)
	Borderline personality disorder	2.2 (0.9-5.8) (n=3, N=11,873)	*3.0 (0.1-71.7) (n=1, N=86)*				*3.8 (0.9-16.4) (n=1, N=44)*					
	ADHD	2.8 (1.7-4.7) (n=8, N=3,865,558)	1.9 (1.7-2.3) (n=28, N=7,913,589)	2.0 (1.8-2.3) (n=21, N=8,779,593)	1.4 (0.9-2.3) (n=7, N=243,711)	1.9 (1.4-2.6) (n=15, N=1,016,734)	*5.1 (1.5-17.2) (n=2, N=89)*	8.4 (3.3-21.8) (n=5, N=6,724,918)		*0.8 (0.4-1.7) (n=1, N=78)*		1.8 (1.3-2.3) (n=4, N=1,522,341)
	Disruptive disorders	3.0 (1.0-9.1) (n=6, N=282,343)	2.1 (1.6-2.9) (n=18, N=4,010)	1.8 (1.5-2.2) (n=16, N=6,566)	1.2 (0.8-1.8) (n=8, N=2,079)	2.7 (1.8-4.1) (n=13, N=5,604)		*1.6 (0.5-4.7) (n=1, N=59)*		*1.2 (0.4-4.1) (n=1, N=75)*		*2.4 (1.4-4.0) (n=2, N=1,545)*
	OCD	*1.9 (0.3-14.6) (n=2, N=225)*	2.0 (1.3-3.1) (n=13, N=3,347)	3.2 (1.8-5.6) (n=9, N=4,224)	3.1 (1.0-9.0) (n=4, N=991)	*2.4 (0.4-15.0) (n=2, N=417)*				*2.7 (0.7-10.8) (n=2, N=457)*		*1.1 (0.3-4.5) (n=1, N=970)*
	Eating disorders	1.1 (0.7-1.7) (n=5, N=285,787)	2.3 (1.6-3.5) (n=8, N=145,391)	*3.9 (0.2-79.1) (n=1, N=73)*	*1.3 (0.1-12.8) (n=2, N=242,834)*	2.0 (1.7-2.4) (n=3, N=148,704)	*1.0 (0.0-50.4) (n=1, N=45)*			*5.7 (0.3-107.3) (n=1, N=78)*	2.3 (1.4-3.6) (n=3, N=886,377)	*1.1 (1.0-1.3) (n=3, N=654,911)*
	Any mental disorder	2.6 (1.6-4.2) (n=12, N=2,115,213)	2.1 (1.7-2.5) (n=20, N=1,480,732)	1.9 (1.5-2.3) (n=19, N=1,480,550)	3.0 (1.8-5.0) (n=3, N=169)	1.5 (1.4-1.6) (n=9, N=136,727)	*8.4 (2.2-32.2) (n=1, N=45)*	*8.4 (0.8-3.9) (n=1, N=59)*				2.3 (1.6-3.4) (n=6, N=195,477)

Each RR is followed by 95% CI. Low-confidence RR estimates based on less than three studies are in italics. Empty cells indicate lack of data. Diagonal (grey-shaded) cells show RR for the same disorder that is present in the parent. Off-diagonal cells show RR for offspring disorders other than that diagnosed in the parent. ADHD – attention-deficit/hyperactivity disorder, OCD – obsessive-compulsive disorder.

Table 3 Meta-analytic estimates of the absolute lifetime risk of DSM/ICD mental disorders in offspring by parent diagnosis

		Disorder in parents											
		None	**Psychosis**	**Bipolar disorder**	**Depressive disorders**	**Anxiety disorders**	**Substance use disorders**	**Borderline personality disorder**	**ADHD**	**Disruptive disorders**	**OCD**	**Eating disorders**	**Any mental disorder**
Disorder in offspring	Psychosis	1% (1-2) (n=33, N=2,598,579)	8% (4-17) (n=26, N=20,403)	1% (1-2) (n=14, N=1,913)	2% (1-5) (n=6, N=734)	*1% (0-8) (n=2, N=124)*	3% (2-4) (n=4, N=15,863)						8% (0-72) (n=5, N=14,637)
	Bipolar disorder	1% (0-3) (n=42, N=2,254,022)	2% (1-8) (n=8, N=1,521)	5% (1-23) (n=46, N=102,980)	5% (3-9) (n=12, N=2,771)	*1% (0-6) (n=2, N=135)*	*4% (2-8) (n=2, N=168)*	*5% (1-26) (n=1, N=22)*			*1% (0-4) (n=2, N=32,251)*		*3% (1-10) (n=1, N=87)*
	Depressive disorders	5% (2-11) (n=99, N=1,017,601)	7% (2-20) (n=17, N=2,352)	18% (15-21) (n=49, N=4,282)	14% (5-36) (n=52, N=360,472)	2% (0-35) (n=11, N=545)	12% (8-18) (n=13, N=1,948)	*43% (29-58) (n=2, N=42)*	*3% (0-19) (n=1, N=33)*		*21% (11-36) (n=1, N=43)*		*37% (26-49) (n=2, N=183)*
	Anxiety disorders	7% (2-22) (n=89, N=345,063)	8% (2-30) (n=15, N=1,062)	26% (21-31) (n=46, N=4,069)	24% (20-28) (n=39, N=5,908)	31% (17-49) (n=14, N=23,394)	19% (14-25) (n=16, N=2,069)	*26% (16-39) (n=2, N=58)*	*15% (6-32) (n=1, N=33)*		*51% (37-66) (n=1, N=43)*		25% (16-37) (n=3, N=5,638)
	Substance use disorders	3% (1-17) (n=55, N=502,737)	13% (8-19) (n=13, N=1,122)	14% (10-20) (n=22, N=2,767)	23% (15-34) (n=16, N=4,909)	*2% (0-35) (n=2, N=166)*	9% (2-39) (n=20, N=42,167)	*27% (13-49) (n=1, N=22)*			*12% (5-25) (n=1, N=43)*		*6% (0-93) (n=2, N=6,010)*
	Borderline personality disorder	2% (0-17) (n=6, N=11,024)	5% (1-19) (n=5, N=991)	*2% (0-10) (n=2, N=69)*	*2% (1-4) (n=1, N=507)*			*33% (17-55) (n=1, N=21)*					
	ADHD	3% (1-14) (n=65, N=2,898,200)	11% (2-43) (n=10, N=20,279)	10% (3-30) (n=40, N=69,902)	10% (6-18) (n=25, N=224,003)	2% (0-34) (n=9, N=787)	13% (10-15) (n=17, N=2,542)	*49% (34-64) (n=2, N=43)*	32% (8-71) (n=5, N=44,287)		*23% (13-38) (n=1, N=43)*		*9% (1-39) (n=2, N=5,542)*
	Disruptive disorders	5% (4-6) (n=50, N=147,749)	4% (1-22) (n=9, N=666)	14% (11-19) (n=26, N=2,386)	12% (8-17) (n=16, N=1,329)	7% (3-14) (n=8, N=483)	12% (9-17) (n=15, N=2,355)		*24% (13-42) (n=1, N=33)*		*15% (7-29) (n=1, N=41)*		*10% (6-15) (n=2, N=183)*
	OCD	2% (1-3) (n=30, N=4554)	3% (1-7) (n=4, N=185)	4% (2-6) (n=17, N=2,152)	3% (2-4) (n=9, N=1,930)	5% (1-15) (n=3, N=128)	2% (1-4) (n=3, N=344)				*41% (13-77) (n=2, N=172)*		*2% (1-9) (n=1, N=87)*
	Eating disorders	1% (0-4) (n=19, N=1,599,968)	5% (2-12) (n=6, N=1,776)	2% (1-4) (n=11, N=1,892)	*5% (1-18) (n=1, N=41)*	*0% (0-2) (n=2, N=412)*	2% (1-6) (n=4, N=4,963)	*2% (0-27) (n=1, N=22)*			*7% (2-20) (n=1, N=43)*	1% (0-9) (n=3, N=3,089)	2% (1-7) (n=3, N=38,098)
	Any mental disorder	14% (3-42) (n=56, N=762,381)	17% (1-82) (n=13, N=7,830)	55% (48-61) (n=27, N=2,278)	51% (42-59) (n=20, N=2,134)	55% (37-72) (n=4, N=94)	38% (18-64) (n=12, N=24,913)	*73% (51-87) (n=1, N=22)*	*39% (24-57) (n=1, N=33)*				55% (7-95) (n=5, N=15,146)

Each percentage absolute risk estimate is followed by 95% CI. Low-confidence estimates based on less than three studies are in italics. Empty cells indicate lack of data. Diagonal (grey-shaded) cells show the lifetime risk for the same disorder that is present in the parent. Off-diagonal cells show the lifetime risk for offspring disorders other than that diagnosed in the parent. The first column shows the lifetime risks of disorders in offspring of parents without a mental disorder. Where both family high-risk and registry studies were available, data were weighted equally in the meta-analytic estimate. ADHD – attention-deficit/hyperactivity disorder, OCD – obsessive-compulsive disorder.

RR estimates, 60 (97%) were greater than 1.0, and 37 (60%) were statistically significant. However, most of these RRs were of small magnitude, and only psychosis in offspring of parents affected with substance use disorder had a lower bound of the 95% CI of at least 2 (see Table 2).

Table 3 shows the absolute lifetime risks of developing mental disorders other than those diagnosed in parents (in the off-diagonal white-background cells). For example, 10-13% of offspring of parents with psychosis, bipolar disorder, depressive disorders, or substance use disorders developed ADHD, but only 3% of offspring of parents without mental disorders did so. Notably, several RRs or absolute risk cells were characterized by small sample sizes, and there were little or no data on risk in offspring of parents with borderline personality disorder, ADHD, disruptive disorders, OCD and eating disorders.

Sensitivity analyses restricted to prospective studies that had followed the offspring at least until the typical age of each disorder's onset showed similar RRs and larger absolute risks of most disorders (see supplementary information). One notable difference was in the absolute risk of psychosis among offspring of parents with bipolar disorder, which was estimated at 1% in the overall analysis but at 4% in the sensitivity analysis of prospective studies.

How does the risk of having a mental disorder change with age?

Twenty-one prospective family high-risk studies provided detailed data on cumulative incidence of mental disorders in the form of Kaplan-Meier curves based on repeated diagnostic assessments. These detailed data were limited to psychotic, bipolar and depressive disorders in the offspring of parents with the same disorder (see Figures 2-4 and Table 4).

Among offspring of parents with psychosis, the onset of psychotic disorders became notable at age 16, increased to 3% at age 18, and continued to increase in an approximately linear fashion until age 30, when it reached 9%, then remaining stable (Figure 2). Among offspring of parents with bipolar disorder, the onset of that disorder became notable as early as age 5, increased to 9% at age 12, 19% at age 18, and 36% by age 28 (Figure 3). Among offspring of parents with depressive disorders, the onset of depressive disorders became notable at age 6, increased at first slowly, then accelerated around age 12, leading to a steep rise in cumulative incidence that continued until mid twenties, when it reached 43%, with sparse data indicating possible further increase beyond 50% (Figure 4).

Heterogeneity and risk of bias

Heterogeneity (I^2) ranged from 0 to 0.98, and 202 (96%) of included studies were at high risk of bias in one or more domains. The risk of bias was unevenly distributed across study types. The nine studies that had low or moderate risk of bias in all six domains were all prospective family high-risk studies[15,48-55].

What factors affect our knowledge about the risk to offspring?

Sensitivity analyses showed that study type (family high-risk vs. registry study) was a key contributor to heterogeneity in absolute risks. Specifically, the comparison of absolute risks between registry and family high-risk studies showed that the risk of any

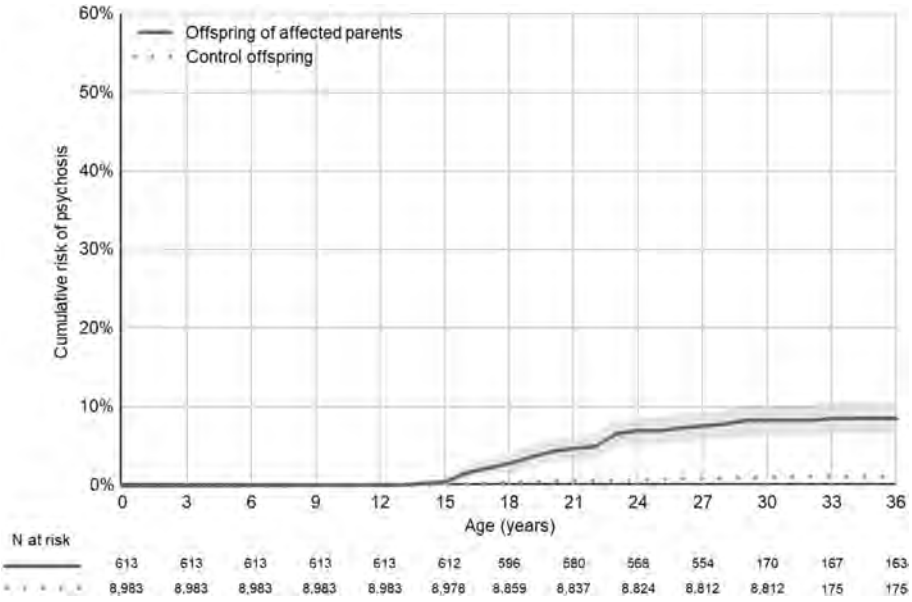

Figure 2 Meta-analytic Kaplan-Meier curve summarizing the cumulative incidence of DSM/ICD psychotic disorders in offspring of parents affected with those disorders (n=4) and control offspring (n=3). The shade in the curve represents 95% CI.

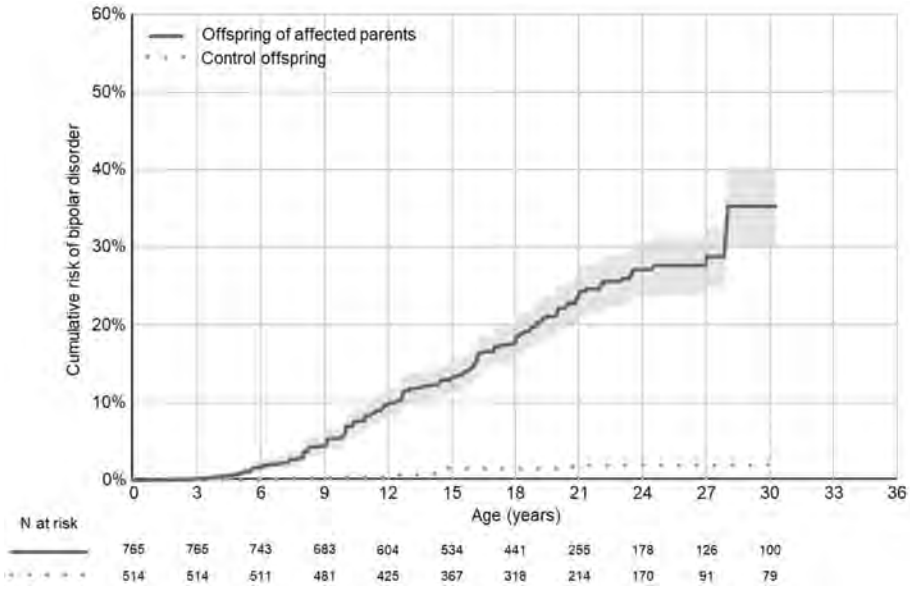

Figure 3 Meta-analytic Kaplan-Meier curve summarizing the cumulative incidence of DSM/ICD bipolar disorder in offspring of parents affected with that disorder (n=4) and control offspring (n=4). The shade in the curve represents 95% CI.

mental disorder was 5 times smaller in the former than in the latter. Of the specific mental disorders, the risks of bipolar disorder, depressive disorders, anxiety disorders, substance use disorders, borderline personality disorder, and ADHD were between 3 and 10 times lower in registry than in family high-risk studies (see Figure 5).

What is offspring's risk of developing the same mental disorder as the parent compared to the risk of developing any other mental disorder?

Across all examined mental disorders, the offspring of affected parents were 3-fold more likely to develop the same disorder as the parent and 2-fold more likely to develop a mental disorder other than that diagnosed in the parent, with little difference between family high-risk and registry studies (see Table 5).

DISCUSSION

The body of evidence on the risk of developing mental disorders in offspring of affected parents has increased dramatically over the past decade. The present meta-analysis synthesizes data from 6 times more studies than the most inclusive prior analysis[18]. We present estimates of relative and absolute risks for 90 parent-offspring disorder combinations, based on over 3 million offspring of affected parents and 20 million control offspring, originating from 211 family high-risk (prospective, cross-sectional) and registry studies. This data synthesis shows that the offspring of affected parents have strongly elevated relative and absolute risk of developing any mental disorder, as well as the same mental disorder that was diagnosed in the parent. In addition, the offspring of affected parents have moderately elevated transdiagnostic risk of most other disorders. We provide tables allowing clinicians to reference relative and absolute risks for parent-offspring disorder combinations as well as meta-analytic cumulative incidence by offspring age to inform clinical practice and prevention.

By systematically searching the global literature and summarizing evidence, this study has identified offspring who are at highest risk for mental disorders. We found that approximately one-in-two offspring of parents with anxiety, bipolar and depressive disorders will develop a mental disorder. Similarly, more than one third of offspring of parents with substance use disorder and one sixth of offspring of parents with psychosis will develop a mental disorder. Notably, offspring of parents with ADHD have 8-fold increased risk of developing the same disorder; offspring of parents with psychotic and bipolar disorders have a 5-fold increased risk; and offspring of parents with substance use, depressive and anxiety disorders about a 2-fold increased risk.

Prospective studies reveal that the lifetime risk of offspring to develop the same disorder of parent is substantial, cumulating to 34% for offspring of parents affected with depressive disorder, 21% for offspring of parents with psychosis, and 13% for offspring of parents with bipolar disorder. These estimates are important for clinical practice, including genetic counselling and prevention in psychiatry. The results align with independent twin-study literature showing that twin heritability is 77% for psychotic, 76% for bipolar, 40% for anxiety and 34% for depressive disorders[56]. There is also evidence for a dose-response association in first-degree relatives for psychotic (one proband: OR=7.69; two probands: OR=11.11), bipolar (one proband: RR=6.10, two probands: RR=29.1) and depressive (one proband: OR=2.14; two

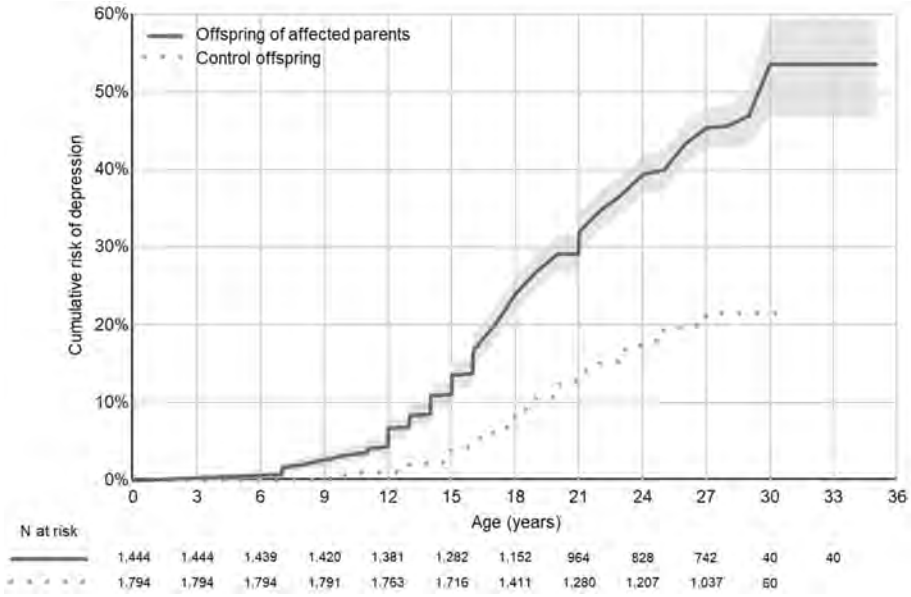

Figure 4 Meta-analytic Kaplan-Meier curve summarizing the cumulative incidence of DSM/ICD depressive disorders in offspring of parents affected with those disorders (n=5) and control offspring (n=6). The shade in the curve represents 95% CI.

probands: OR=3.23) disorders[2,57-59].

The magnitude of the meta-analytic risks designates offspring of parents affected with psychotic, mood (bipolar and depressive), anxiety, substance use disorders and ADHD as a population that should be prioritized for systematic screening, monitoring and preventive interventions. To date, these efforts have been largely limited to young people at clinical high risk for psychotic, and more recently bipolar disorders[3,4,60,61]. While the clinical high-risk paradigms include a subgroup of individuals with affected first-degree relatives, screening of relatives is not routinely implemented[2]. Our meta-analytic data urge professionals to systematically assess and address the mental health of offspring of patients affected with psychotic, mood, anxiety, substance use disorders and ADHD.

Based on the substantial risk, mental health screening of these offspring would be supported by sufficient evidence. A next step could involve the implementation of a periodic monitoring for additional risk indicators over time, coupled with targeted preventive approaches[62]. Emerging preventive approaches include needs-based interventions; psychotherapy for offspring at risk of psychotic or anxiety disorders; physical activity for offspring at risk of depressive disorders; and genetic counselling for offspring at risk for bipolar or depressive disorders, and their parents[5,45,63-67].

These interventions are not effective when administered to the whole population (universal prevention). For example, school-based interventions designed to prevent anxiety and depressive disorders are ineffective[68] and may even cause harm to some adolescents[69]. However, interventions targeted to youth with a specific risk profile can have beneficial effects, including reduction in the risk of depressive disorder onset[70,71]. Preventive interventions may target symptomatic offspring of affected parents[72], and include optimized treatment of parents[73], both of which can reduce the risk of onset and burden of mental disorders in offspring.

The present report is also the most comprehensive summary of the transdiagnostic risk of developing mental disorders in offspring of affected parents. It has been debated whether the risk to offspring is specific to the disorder diagnosed in a parent or whether it extends transdiagnostically to most or all mental disorders. Typically, family high-risk studies focus on disorder-specific relationships[15,16], but studies of national registries highlighted extensive transdiagnostic risks[10,17]. The present synthesis of family high-risk and registry studies suggests broad transdiagnostic risks, although the magnitude of transdiagnostic RRs was smaller than for disorder-specific estimates. Overall, the offspring of affected parents were 3 times more likely to develop the same disorder as their parent and, in addition, were 2 times more likely to develop a different disorder. These results were consistent across family high-risk and registry studies, suggesting that discrepancies in prior literature might have been the result of limited statistical power.

The most robust transdiagnostic risk was observed for psychosis in offspring of parents with substance use disorder. There was substantial variation in transdiagnostic effect sizes and some indications of limited specificity. For example, the relative risk of anxiety disorders is elevated in offspring of parents with bipolar, depressive and substance use disorders, but not in offspring of parents with psychosis. On the other hand, the relative risk of ADHD is elevated in offspring of parents with bipolar disorder, depressive disorders, borderline personality disorder and psychosis, but not in offspring of parents with anxiety disorders. These variations to the broad transdiagnostic familial risks deserve attention, as they may hold clues to the structure of risks for mental

Table 4 Cumulative incidence by age of psychotic, bipolar and depressive disorders in offspring of parents affected with the same disorder

Age (years)	Risk of mental disorder in offspring of parents with that disorder		
	Psychosis	Bipolar disorder	Depressive disorders
4	0% (0-0)	0% (0-1)	0% (0-1)
6	0% (0-0)	1% (1-2)	1% (0-1)
8	0% (0-0)	4% (2-5)	2% (1-3)
10	0% (0-0)	6% (4-8)	3% (2-4)
12	0% (0-0)	9% (7-11)	7% (5-8)
14	0% (0-0)	11% (9-14)	11% (9-13)
16	2% (1-3)	15% (12-18)	17% (15-19)
18	3% (2-5)	19% (16-22)	24% (22-26)
20	5% (3-7)	23% (19-26)	29% (27-31)
22	6% (4-7)	26% (22-29)	35% (32-37)
24	7% (5-9)	28% (24-32)	39% (37-42)
26	7% (6-9)	28% (24-31)	43% (41-46)
28	8% (6-10)	36% (30-41)	46% (43-48)
30	9% (6-11)	36% (30-41)	54% (47-59)

Estimates (with 95% CIs) are based on meta-analytic Kaplan-Meier curves

disorders.

In the context of precision psychiatry, these findings can inform the development of new algorithms that can predict the transdiagnostic risk of onset across mental disorders[74,75]. In the context of genetic counseling, the provision of absolute risk estimates helps counter the common overestimation of familial risk and related fatalism among potential parents living with mental disorders[7]. In the context of public health, the common element in familial risk suggests that transdiagnostic approaches to targeted prevention can be more advantageous, as multiple outcomes can be potentially prevented with the same intervention.

The risk of mental disorders is age dependent. Information on the development of risk over age is essential to time-targeted prevention efforts in clinical practice and to adjust risk information to the client's current age (for example, when providing genetic counselling)[76]. In this respect, longitudinal family high-risk studies provide unique information on prospectively ascertained onsets over long developmental periods, that complements clinical high-risk studies focused on individuals at an age close to the typical onset of major mental disorders. Our meta-analyses of cumulative incidence show a rapid accumulation of onsets through adolescence and into mid-to-late twenties, aligning with a recent meta-analysis which indicated that the peak age of onset of any mental disorder worldwide is of 14.5 years[77]. By age 28, just under one-in-ten offspring of parents with psychotic disorders, one-in-three offspring of parents with bipolar disorder, and one-in-two offspring of parents with depressive disorders will develop the same disorder themselves.

These cumulative incidence estimates exceed the absolute lifetime risk estimates derived from family high-risk and registry studies. In line with the known differences in prevalence between prospective and retrospective ascertainment of mental disorders[78], this discrepancy suggests that the actual risk of mental disorders in offspring of affected parents may be even higher than what is expected based on current family high-risk literature. The relatively low incidence of psychosis onset in offspring aligns with the existing meta-analytic evidence in samples at clinical high-risk for psychosis, which indicates that the genetic risk and deterioration syndrome subgroup, which includes first-degree relatives, has a lower short-term risk of transitioning to psychosis than other clinical high-risk groups[79].

Our meta-analytic cumulative incidence data are clinically in-

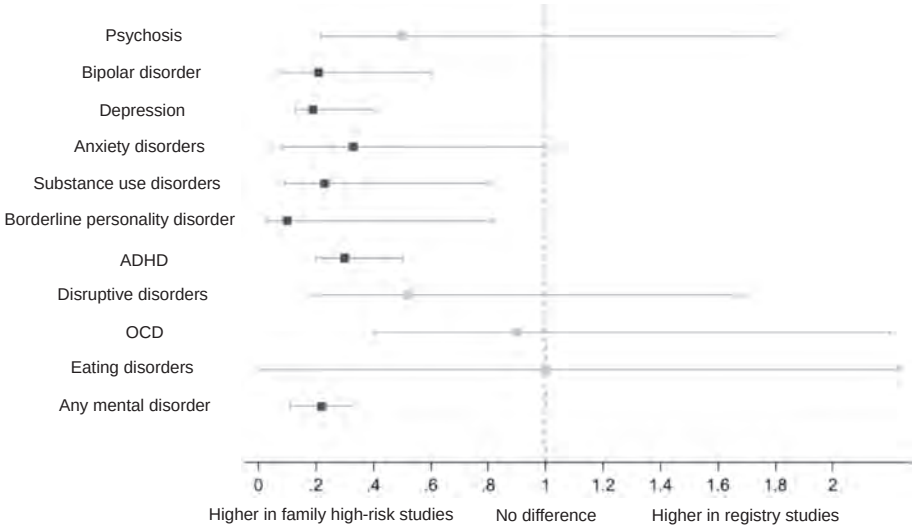

Figure 5 Comparison of the risk of mental disorders reported in registry studies vs. family high-risk studies. For each mental disorder in offspring, the square shows the estimate and the horizontal line the 95% CI of the registry to family high-risk ratio. Significant ratios are shown in dark grey squares; non-significant ratios in pale grey squares. ADHD – attention-deficit/hyperactivity disorder, OCD – obsessive-compulsive disorder.

Table 5 Relative risk (with 95% CI) of same or different mental disorder in offspring of parents with a mental disorder across family high-risk and registry studies

	Same disorder in offspring		Different disorder in offspring	
Disorder in parents	**Family high-risk studies**	**Registry studies**	**Family high-risk studies**	**Registry studies**
Psychosis	4.4 (2.8-6.8) (n=12, N=2,506)	6.1 (4.1-9.1) (n=9, N=7,542,868)	1.9 (1.2-3.1) (n=42, N=2,302)	1.7 (0.9-3.0) (n=23, N=11,553,211)
Bipolar disorder	5.4 (3.5-8.4) (n=28, N=5,234)	4.4 (1.2-16.9) (n=5, N=11,555,792)	2.2 (1.9-2.6) (n=70, N=6,698)	1.2 (0.5-2.8) (n=9, N=14,805,882)
Depressive disorders	2.3 (2.0-2.8) (n=47, N=22,121)	2.1 (1.7-2.6) (n=6, N=11,873,567)	2.7 (2.1-3.5) (n=26, N=6,682)	1.3 (0.5-3.2) (n=7, N=10,952,304)
Anxiety disorders	2.1 (1.8-2.6) (n=19, N=13,575)	2.3 (2.0-2.7) (n=3, N=1,967,517)	1.3 (1.0-1.7) (n=10, N=4,345)	*1.8 (1.7-2.0)* *(n=2, N=6,356,323)*
Substance use disorders	3.0 (2.2-4.2) (n=19, N=10,680)	2.1 (1.3-3.5) (n=4, N=674,572)	*9.4 (2.9-30.1)* *(n=2, N=1,328)*	2.2 (2.0-2.4) (n=3, N=2.151.844)
Overall	3.1 (2.2-4.4) (n=125, N=54,116)	2.9 (1.8-4.6) (n=27, N=33.614.316)	2.2 (1.5-3.3) (n=150, N=21,355)	1.9 (1.6-2.3) (n=44, N=45,819,564)

Low-confidence estimates based on fewer than three studies are shown in italics

formative. For example, a general practitioner might use them to predict the 5-year likelihood of developing bipolar disorder in a 16 year-old who has a parent affected with the same condition. However, the decision to communicate such information to individuals or families should take into account their preferences and priorities, as well as the availability of interventions and tools that can modify the risk. A clinician should explore existing perceptions of risk before providing new information, provide absolute rather than relative risks, contextualize the numbers provided, check understanding and emotional impact so as to promote positive outcomes (e.g., appropriate preventive intervention to mitigate risk for developing the condition) and avoid the potential for harms associated with this type of information (e.g., increasing stigma, or fatalism)[7,80-84].

Although based on a vast body of literature, the present study has some limitations. First, there are considerable differences in the estimates reported by family high-risk vs. registry studies. Since these two study designs are prone to different sources of selection and information bias, it may not be appropriate to declare one set of results as superior to the other. Accordingly, we gave family high-risk and registry studies equal weight in our primary analyses and we qualified the estimates in sensitivity analyses. For several mental disorders, registry studies report absolute risks between 5 and 10 times lower than those seen in family high-risk studies that systematically assess participants with diagnostic interviews. This difference is probably due to the fact that, in registry studies, diagnosis depends upon treatment seeking. Prospective studies suggest that the offspring of parents with psychotic, bipolar and depressive disorders have substantially elevated rates of mental disorders, that are discernable on repeated active inquiry even when some of them do not present for treatment. The clinical and societal significance of such undertreated disorders remains to be established.

Second, although we referred to a lifetime absolute risk of developing mental disorder, this estimate indexes the risk measured at the assessment point. The latter could widely vary from cross-sectional to prospective studies. However, we have performed a meta-analytic Kaplan-Meier assessment that provides fine-grained cumulative incidence of mental disorders by offspring age.

Third, the geographic distribution of available evidence is imbalanced: of the 211 eligible studies, only three originated from low- or middle-income countries. Intensive work is needed to establish the global invariance or heterogeneity of familial risk. Fourth, the distribution of evidence over various mental disorders is uneven, and several comparisons were underpowered (i.e., less than three independent studies available). While extensive efforts have been dedicated to examining familial risk for psychotic and mood (bipolar, depressive) disorders, less evidence is available for anxiety and substance use disorders, and most of the other mental disorders remain unexplored. Fifth, we have not identified enough relevant data to examine the effects of having both parents affected with mental disorders[85]. With evidence of assortative mating[86] suggesting that cumulation of risk from two affected parents is common, targeted efforts are warranted to prospectively study the offspring of two parents with mental disorders.

Although the current study primarily informs clinical practice, especially in prevention and genetic counselling, it additionally paves the way for future research in this field. Research may next focus on filling the gaps in existing evidence, particularly relating to familial risk for borderline personality disorder, ADHD, disruptive disorders, eating disorders and OCD. The empty or low-count cells in our tables highlight the specific parent-offspring combinations that should be prioritized by future studies. Transdiagnostic risks to offspring growing up in low- or middle-income countries also need to be determined. Although well-designed prospective studies require substantial resources, recent interest in epidemiological research by several European funders, international research networks, and methodological innovation may facilitate this type of research[87].

Examining mixed diagnostic groups of parents without diagnostic exclusions may prove particularly important. Additionally,

potential sex-specific patterns of transgenerational transmission of mental disorders – which have been reported for anxiety disorders, psychosis and ADHD[88-91] – should be examined transdiagnostically. A further research priority is better characterizing differences between family high-risk and registry studies. This would benefit from validation of registry diagnoses that extends to "controls" without registry-identified disorder and examines multiple comorbid mental disorders[37]. Future research may take advantage of family high-risk studies nested within registries to understand the sources of information in national and health-provider registries[50]. Only a few studies have been able to combine the advantages of the different study designs, through using a national registry as a basis for comprehensive recruitment into a prospective family high-risk study[50,92]. These exceptionally well-designed studies allow mapping the sources of selection and information bias to improve the interpretation of broader literature[93].

In conclusion, this large meta-analytic synthesis documents elevated risks for a range of mental disorders, including transdiagnostic risks, in offspring of parents affected with psychotic, mood (bipolar and depressive), anxiety and substance use disorders, as well as ADHD. While gaps in evidence motivate future research, the present knowledge robustly supports systematic screening in offspring of parents affected with these conditions. Urgent research is needed to identify effective targeted interventions to reduce risk for offspring of parents with these mental disorders, and to deliver them without exacerbating fatalism or stigma.

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World Health Organization's low-intensity psychosocial interventions: a systematic review and meta-analysis of the effects of Problem Management Plus and Step-by-Step

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Many societies have been recently exposed to humanitarian and health emergencies, which have resulted in a large number of people experiencing significant distress and being at risk to develop mental disorders such as depression, anxiety and post-traumatic stress disorder. The World Health Organization has released a series of scalable psychosocial interventions for people impaired by distress in communities exposed to adversities. Prominent among these is a low-intensity transdiagnostic psychosocial intervention, Problem Management Plus (PM+), and its digital adaptation Step-by-Step (SbS). This systematic review is the first to summarize the available evidence on the effects of PM+ and SbS. Up to March 8, 2023, five databases were searched for randomized controlled trials examining the effects of PM+ or SbS on distress indicators (i.e., general distress; anxiety, depressive or post-traumatic stress disorder symptoms; functional impairment, self-identified problems) and positive mental health outcomes (i.e., well-being, quality of life, social support/relationships). We performed random-effects multilevel meta-analyses on standardized mean differences (SMDs) at post-intervention and short-term follow-up assessments. Our search yielded 23 eligible studies, including 5,298 participants. We found a small to medium favorable effect on distress indicators (SMD=–0.45, 95% CI: –0.56 to –0.34) and a small beneficial effect on positive mental health outcomes (SMD=0.31, 95% CI: 0.14-0.47), which both remained significant at follow-up assessment and were robust in sensitivity analyses. However, our analyses pointed to substantial between-study heterogeneity, which was only partially explained by moderators, and the certainty of evidence was very low across all outcomes. These results provide evidence for the effectiveness of PM+ and SbS in reducing distress indicators and promoting positive mental health in populations exposed to adversities, but a larger high-quality evidence base is needed, as well as research on participant-level moderators of the effects of these interventions, their suitability for stepped-care programs, and their cost-effectiveness.

Key words: Psychosocial interventions, mental distress, mental health promotion, Problem Management Plus, Step-by-Step, humanitarian emergencies, depressive symptoms, anxiety symptoms, post-traumatic stress disorder

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In recent years, almost all societies have been exposed to an increasing number of crises (e.g., humanitarian and health emergencies), with low- and middle-income countries often being hit harder. This has resulted in a large number of people experiencing significant distress and being at risk to develop mental disorders such as depression, anxiety and post-traumatic stress disorder (PTSD)[1-3]. Thus, developing and evaluating interventions to prevent and treat mental distress and to promote positive mental health in populations exposed to adversities is recognized as a priority for global health research[4].

The World Health Organization (WHO) has developed a series of scalable psychosocial interventions for adults impaired by distress in communities exposed to adversities, with a special focus on low-and middle-income countries[5]. In 2015, Problem Management Plus (PM+) has been proposed as a low-intensity transdiagnostic intervention for adults suffering from mental distress and self-identified practical problems[6]. Being transdiagnostic in nature, PM+ aims at targeting the shared underlying factors of mental disorders (e.g., deficits in stress management, low use of social resources)[7] and promoting general strategies relevant for the prevention and treatment of these disorders (e.g., problem management, behavioral activation, use of social support)[6,8]. The five-session program, with approximately 90 min per session, can be delivered by trained non-specialist helpers in individual or group face-to-face settings.

Step-by-Step (SbS) was initially developed as a guided online self-help version of PM+[9]. However, as the problem management component of PM+ could not be adapted successfully for the online version, SbS specifically focuses on behavioral activation as a core strategy to reduce depressive symptoms. Consequently, SbS is not transdiagnostic as PM+. Behavioral activation, however, is supplemented by other strategies also included in PM+, such as stress management and promotion of social support, which are effective to reduce depressive symptoms. The five-session online intervention uses a narrative with a customizable character who visits a health professional to seek help for depression. Each session lasts 20 to 30 min and is guided by a trained non-specialist e-helper who supports the engagement with self-help materials.

Since the WHO has released these interventions[6,9], many trials have been performed to examine their effects in the context of heterogeneous situations of high and prolonged stress (e.g., involuntary displacement[10], armed conflicts and war[11], natural disasters[12], health stressors such as the COVID-19 pandemic[13]). The STRENGTHS project, an international research network which received funding from the European Union, worked on scaling up PM+ programs and examining their effectiveness for refugee populations[14].

To date, there is only one individual participant data meta-analysis on PM+[15], which examined the effects of the intervention on PTSD symptoms, reporting that PM+ reduced re-experiencing and avoidance, while effects were smaller for hyperarousal. However, this analysis only included three trials and solely focused on PTSD symptoms. A systematic review of the effects of PM+ and SbS, summarizing the whole body of evidence and potentially

moderating factors, is still missing. The current study aimed to address this gap.

METHODS

This systematic review adheres to the standards of the Cochrane Collaboration[16], and its results are reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[17]. The review was pre-registered (ID: CRD42022367698) and the protocol was made available in the Open Science Framework (no. 10.17605/OSF.IO/4Q53C).

Search strategy and data extraction

As PM+ was introduced in 2015, databases were searched from January 1, 2014, with the search being lastly updated on March 8, 2023. Searches were performed in the American Psychological Association (APA) PsycNET (including PsycInfo, PsycArticles, PsycExtra), the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Scopus and Web of Science.

Search terms comprised two clusters: those related to PM+ and SbS as interventions of interest, and those related to study design. If applicable, we used Cochrane high-sensitive search filters for the identification of randomized controlled trials[18], as well as Medical Subject Headings and Emtree terms (see also supplementary information). Additionally, we checked the reference lists of included studies, reports citing studies included in our review based on Google Scholar citation tracking, and the website of the STRENGTHS project[19].

Eligible studies were (cluster) randomized controlled trials (RCTs) examining the effects of PM+ or SbS in stress-exposed populations of all ages. Studies were eligible if PM+ or SbS was delivered as initially proposed[6,9] or amended with additional components (e.g., targeting alcohol consumption[20] or emotion processing[21]), but ineligible if they examined stepped-care programs employing PM+/SbS as second step. All comparators were eligible, including waitlist, (enhanced) care-as-usual, and active control conditions.

Eligible studies assessed at least one of the following outcomes: distress (i.e., general distress; anxiety, depressive or PTSD symptoms; functional impairment, self-identified problems); positive mental health (i.e., well-being, quality of life, social support/relationships); somatic symptoms; family distress/functioning (e.g., child mental distress), and health care costs/use.

After de-duplication in Zotero, titles, abstracts and full texts were assessed by two reviewers independently in Rayyan[22]. Inter-rater reliability was almost perfect at title/abstract level (kappa = .97) and substantial at full text level (kappa = .78). At both stages of screening, disagreements were resolved through discussion or by consulting a third reviewer.

We developed a customized data extraction sheet for this review. All descriptive data of eligible primary studies were extracted by one reviewer and checked by a second. Any disagreements were resolved through discussion or consultation of a third reviewer.

Quality appraisal

Two team members independently evaluated the risk of bias of primary studies using the Cochrane risk-of-bias tool for randomized trials (RoB 2)[23], which assesses the following bias domains: randomization process; deviations from the intended intervention; missing outcome data; outcome measurement; and selection of reported results. For cluster RCTs, we additionally assessed risk of bias due to identification/recruitment of participants. Bias ratings were assessed at single outcome and overall study levels. Judgements could be "low", "high", or express "some concerns".

We examined a potential publication bias statistically by approximating rank correlation tests[24] and using visual inspections of contour-enhanced funnel plots. Rank correlation tests are available for multilevel models by including sampling error as moderator[25]. If the sampling error significantly predicts effect sizes, this can be interpreted as evidence for a publication bias.

Data synthesis

Eligible studies were summarized narratively and in tabular form. Pairwise meta-analyses were performed for primary outcomes if more than two effect estimates were available per outcome type (e.g., PTSD symptoms) and assessments were sufficiently homogeneous. For other outcomes, we provided a brief qualitative summary. In cases where data needed for effect size calculation were missing or unclear, primary study authors were contacted by the review team via email (see supplementary information).

Meta-analyses were performed in *R* version 4.2.3[26] using the packages *metafor*[27] and *clubSandwich*[28]. All analyses used random-effects models and maximum likelihood estimations with an inverse variance method. Standardized mean differences (SMDs, Hedges' g) at post-intervention and follow-up assessments were used as effect estimates, and their 95% confidence intervals (CIs) as indicators of significance. SMDs were calculated based on means and standard deviations, with positive SMDs indicating unfavorable intervention effects for distress indicators, but favorable intervention effects for positive mental health outcomes. To account for uncertainty of meta-analytical findings, we calculated 95% prediction intervals (PIs) as an estimate of the range in which 95% of future observations will fall[29]. In cluster RCTs, effect sizes were corrected for clustering effects[16] (see supplementary information).

We calculated separate models for distress indicators and positive mental health outcomes, as well as for post-intervention and follow-up assessments. Exploratively, we examined the stability of intervention effects between post-intervention and follow-up assessments by means of two-way random-effects intra-class correlations (ICCs). We used multivariate multilevel models nesting effect estimates within studies (outer factor) and outcome types

(inner factor)[30]. Cluster-robust tests and CIs were used to account for non-independent effect estimates.

As little information was available on between-outcome correlations within studies, covariances were imputed based on a correlation of ρ=0.60, with other correlation estimates being used for sensitivity analyses[31]. For each model, we examined whether the use of an unstructured variance-covariance matrix improved model fit. As this was not the case for any model, symmetric matrices were assumed. Moreover, the specification of multilevel models was examined by calculating profiles of the log-likelihood, which should show single peaks. In case of evidence for over-parameterization, standard univariate meta-analyses were performed. As effects of PM+ and SbS on depressive symptoms were of particular interest, they were examined in additional univariate models for illustrative purposes.

Statistical heterogeneity was assessed using Cochran's Q[32], with a significant Q indicating the presence of heterogeneity. To quantify the amount of heterogeneity in our analyses, we used the I^2 statistic (range: 0-100%) at single outcome level, with values of 50% and above indicating substantial heterogeneity[16].

Due to the substantial heterogeneity in our primary analyses, moderator analyses were performed on distress indicators and positive mental health outcomes (at post-intervention assessment). For categorical variables (e.g., intervention type) we used subgroup analyses, while meta-regressions were used for omnibus moderation tests and continuous moderators (e.g., age), with a significant QM test indicating the presence of a moderator effect. All analyses used cluster robust estimations. First, we examined whether intervention effects differed between PM+ delivered in individual settings, PM+ delivered in group settings, and SbS. As we found no evidence for such a difference, additional moderator analyses were performed for all studies. We examined sociodemographic sample characteristics (i.e., age, gender balance per sample), stressor type (i.e., gender-based violence vs. health stressors vs. humanitarian disasters vs. war or armed conflict), stressor level (i.e., individual vs. collective), duration of intervention (in weeks and minutes), intervention setting (i.e., low- or middle-income vs. high-income country), and intervention providers (i.e., professionals vs. lay staff) as moderators.

Sensitivity analyses were performed for between-outcome correlations (ρ=.40, ρ=.80), risk of bias, inclusion of outliers, and context of evaluation (i.e., STRENGTHS project vs. other trials).

The certainty of evidence for specific outcome types (e.g., depressive symptoms) at post-intervention and follow-up assessments was evaluated in duplicate using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)[33].

RESULTS

Search outcome and study characteristics

Our search for primary studies in electronic databases yielded 2,902 eligible records, with 805 duplicates being removed. Of 2,097 records screened at title/abstract level, 97 were assessed at full text level. Five additional eligible records were identified by our searches on websites, citation searching, and Google Scholar citation tracking. Taken together, this resulted in 23 eligible primary studies (from 55 reports) for synthesis (see Figure 1).

Table 1 presents the characteristics of the 23 studies, comprising 5,298 participants (range of sample sizes: 8 to 680), included in our review[10-13,34-53]. These were performed in Pakistan (four studies); Lebanon, Kenya (three studies each); Jordan, The Netherlands, Nepal (two studies each); Australia, Austria, China, Colombia, Switzerland, Turkey and the UK (one study each). Seventeen studies (73.9%) were conducted in low-to-middle income countries. Fifteen studies included follow-up assessments between 3 and 6 months; a longer follow-up interval of 12 months was only reported for one study[37]. Six studies (26.1%) were performed within the STRENGTHS project and examined effects of PM+ in refugee populations[10,34,35,37,38,42,52].

The mean age of participants was 34.9±8.33 years (range: 21.3-63.2), and 73% of the participants were women (range: 33-100%). Most populations were exposed to war or armed conflicts (11 studies), followed by humanitarian crises (seven studies), health stressors (three studies, with one study on COVID-19), and gender-based interpersonal violence (two studies).

Thirteen studies (56.5%) reported on PM+ in individual settings, seven (30.4%) examined the group version of PM+, and three (13.0%) investigated the SbS intervention. The duration of the intervention ranged between 5 and 26 weeks (average: 6.4±4.5) and 100 and 750 min (average: 501±156), with SbS being shorter than (group) PM+ (about 100 min). Twenty-two studies (95.7%) used (enhanced) care-as-usual, and one[49] employed a waitlist control.

Quality appraisal

Only one study[12] had an overall low risk of bias rating, while risk of bias was high for the remaining 22 studies (95.6%). The main flaws (some concerns or high risk) were found for outcome measurement (post-intervention: 95.6%; follow-up: 100%), selection of reported results (post-intervention: 43.4%; follow-up: 32.5%), deviations from the intended intervention (post-intervention: 35.2%; follow-up: 32.5%), and missing outcome data (post-intervention: 30.8%; follow-up: 24.1%). In most cluster RCTs, identification/recruitment of participants was sufficiently described (see also supplementary information).

Meta-regression models provided no evidence for an association of standard errors and effect estimates at post-intervention for distress indicators (QM=1.81, p=0.178) and positive mental health outcomes (QM=3.23, p=0.110). However, the visual inspection of contour-enhanced funnel plots indicated that more effect estimates fell into the significance border areas of the plots (see supplementary information). At follow-up assessments, regression models provided evidence for a publication bias in the analysis on distress indicators (QM=4.61, p=0.032), but not for positive mental health outcomes (p≥0.657). The contour-enhanced funnel plots for distress indicators and well-being or quality of life suggested that more effect estimates fell into the signif-

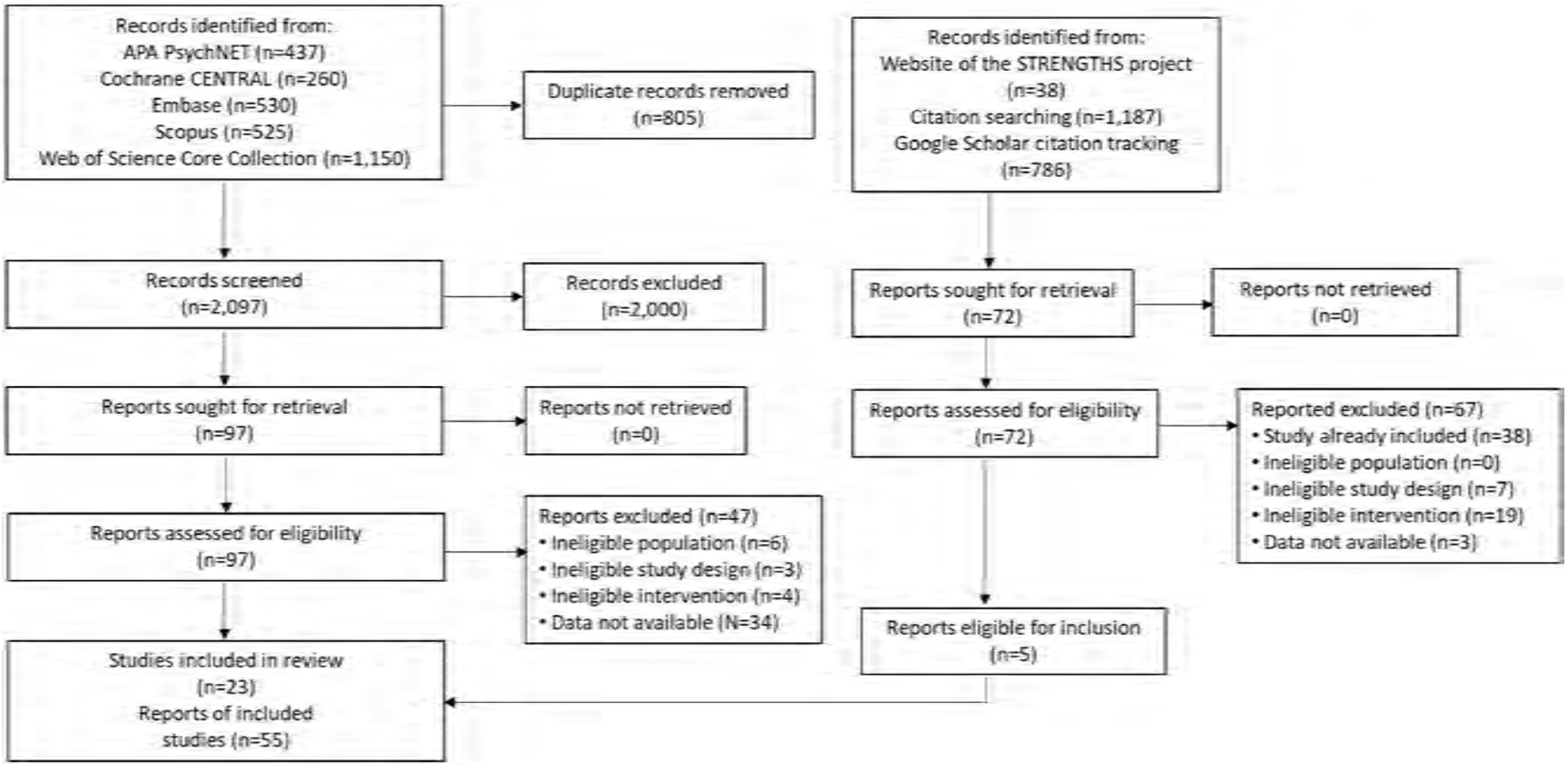

Figure 1 PRISMA flow chart. APA – American Psychological Association

Table 1 Characteristics of included studies

Study	Country	Stressor	Population	N	Intervention	Providers	Comparator	Outcomes
Acarturk et al[34]	Turkey	Syrian civil war	Syrian refugees (% female: 66.7% in IG, 68.2% in CG)	IG: 24, CG: 22	Group PM+ (+ECAU)	Peer-/lay-guided	ECAU	General distress, PTSD symptoms, self-identified problems
Akhtar et al[35]	Jordan	Syrian civil war	Syrian refugees (% female: 68.6% in IG, 72.4% in CG)	IG: 35, CG: 29	Group PM+	Professional guided and/or related educational background	ECAU	Anxiety symptoms, depressive symptoms, general distress, PTSD symptoms, self-identified problems
Bryant et al[36]	Kenya	Gender-based violence	Women with experience of gender-based violence	IG: 209, CG: 212	PM+	Peer-/lay-guided	ECAU	Functional impairment, general distress, PTSD symptoms, self-identified problems
Bryant et al[13]	Australia	COVID-19 pandemic	People residing in Australia (% female: 84.2% in IG, 83.3% in CG)	IG: 120, CG: 120	PM+ (adapted to pandemic context)	Professional guided and/or related educational background	ECAU	Anxiety symptoms, depressive symptoms
Bryant et al[37,38]	Jordan	Syrian civil war	Syrian refugees (% female: 71.1% in IG, 75.2% in CG)	IG: 204, CG: 206	Group PM+	Professional guided and/or related educational background	ECAU	Anxiety symptoms, depressive symptoms, functional impairment, PTSD symptoms, self-identified problems
Cuijpers et al[39]	Lebanon	Humanitarian crises (mixed stressors)	People residing in Lebanon (% female: 72.5% in IG, 67.3% in CG)	IG: 331, CG: 349	SbS	Minimally guided by e-helpers	ECAU	Anxiety symptoms, depressive symptoms, functional impairment, PTSD symptoms, self-identified problems, well-being
Cuijpers et al[40]	Lebanon	Syrian civil war	Syrian refugees (% female: 61.7% in IG, CG 55.2% in CG)	IG: 283, CG: 286	SbS	Minimally guided by e-helpers	ECAU	Anxiety symptoms, depressive symptoms, functional impairment, PTSD symptoms, self-identified problems, well-being
Dawson et al[41]	Kenya	Urban adversity, gender-based violence	Women residing in Kenya	IG: 35, CG: 35	PM+	Peer-/lay-guided	ECAU	Functional impairment, general distress, PTSD symptoms
De Graaff et al[10]	The Netherlands	Syrian civil war	Syrian refugees (% female: 60.0% in IG, 60.0% in CG)	IG: 30, CG: 30	PM+ (+CAU)	Professional guided and/or related educational background	CAU	Anxiety symptoms, depressive symptoms, functional impairment, general distress, PTSD symptoms, self-identified problems
De Graaff et al[42]	The Netherlands	Syrian civil war	Syrian refugees (% female: 29.1% in IG, 47.6% in CG)	IG: 103, CG: 103	PM+	Professional guided and/or related educational background	CAU	Anxiety symptoms, depressive symptoms, functional impairment, general distress, PTSD symptoms, self-identified problems

Table 1 Characteristics of included studies *(continued)*

Study	Country	Stressor	Population	N	Intervention	Providers	Comparator	Outcomes
Dowrick et al[43]	UK	Humanitarian crises (mixed stressors)	Refugees/asylum seekers (% female: 100% in IG, 50.0% in CG)	IG: 4, CG: 4	PM+	Peer-/lay-guided	CAU	Anxiety symptoms, depressive symptoms, functional impairment, general distress, PTSD symptoms, self-identified problems, well-being
Hamdani et al[44]	Pakistan	Humanitarian crises (mixed stressors)	People residing in Pakistan (% female: 64.6% in IG, 68.8% in CG)	IG: 96, CG: 96	PM+	Professional guided and/or related educational background	CAU	Anxiety symptoms, depressive symptoms, functional impairment, general distress, perceived social support, PTSD symptoms, self-identified problems
Heim et al[45]	Lebanon	Humanitarian crises (mixed stressors)	Syrian refugees, people residing in Lebanon (% female: 67.2% in IG, 67.6% in CG)	IG: 67, CG: 71	SbS	Minimally guided by e-helpers	ECAU	Anxiety symptoms, depressive symptoms, functional impairment, PTSD symptoms, self-identified problems, well-being
Jordans et al[46]	Nepal	Humanitarian crises (mixed stressors)	People residing in Nepal (% female: 82.3% in IG, 82.0% in CG)	IG: 306, CG: 305	Group PM+	Peer-/lay-guided	ECAU	Depressive symptoms, functional impairment, general distress, perceived social support, PTSD symptoms
Khan et al[11]	Pakistan	Armed conflicts	Women residing in Pakistan	IG: 59, CG: 60	Group PM+	Peer-/lay-guided	ECAU	Anxiety symptoms, depressive symptoms, functional impairment, general distress, PTSD symptoms, self-identified problems
Knefel et al[47]	Austria	Humanitarian crises (mixed stressors) in Afghanistan	Afghan refugees/asylum seekers (% female: 38.5% in IG, 60% in CG)	IG: 49, CG: 39	PM+ (adapted)	Professional guided and/or related educational background	CAU	Anxiety symptoms, depressive symptoms, general distress, PTSD symptoms, quality of life, social relationships, self-identified problems
Nyongesa et al[48]	Kenya	Human immuno-deficiency virus (HIV)	Young people residing in Kenya (% female: 62.9% in IG, 68.6% in CG)	IG: 35, CG: 35	PM+ (adapted)	Peer-/lay-guided	ECAU	Anxiety symptoms, depressive symptoms, perceived social support, quality of life
Perera et al[49]	Colombia	Humanitarian crises (mixed stressors) in Venezuela	Venezuelan refugees/ migrants (% female: 48.7% in IG, 21.2% in CG)	IG: 40, CG: 39	PM+	Peer-/lay-guided	Waitlist	Self-identified problems, quality of life, social relationships, well-being
Rahman et al[50]	Pakistan	Armed conflict	People residing in Pakistan (% female: 75.0% in IG, 82.8% in CG)	IG: 172, CG: 174	PM+	Peer-/lay-guided	ECAU	Anxiety symptoms, depressive symptoms, functional impairment, general distress, PTSD symptoms, self-identified problems

Table 1 Characteristics of included studies *(continued)*

Study	Country	Stressor	Population	N	Intervention	Providers	Comparator	Outcomes
Rahman et al[51]	Pakistan	Armed conflicts	Women residing in Pakistan	IG: 306, CG: 306	Group PM+	Peer-/lay-guided	ECAU	Anxiety symptoms, depressive symptoms, functional impairment, general distress, perceived social support, PTSD symptoms, self-identified problems
Sangraula et al[12]	Nepal	Earthquakes	People residing in Nepal (% female: 83% in IG, 84% in CG)	IG: 66, CG: 64	Group PM+	Peer-/lay-guided	ECAU	Depressive symptoms, functional impairment, general distress, perceived social support, PTSD symptoms
Spaaij et al[52]	Switzerland	Syrian civil war	Syrian refugees/asylum seekers (% female: 45.2% in IG, 57.1% in CG)	IG: 31, CG: 28	PM+	Peer-/lay-guided	ECAU	Anxiety symptoms, depressive symptoms, functional impairment, PTSD symptoms
Zhang et at[53]	China	Multiple myeloma	People living with multiple myeloma (% female: 32.5% in IG, 37.5% in CG)	IG: 40, CG: 40	PM+	Professional guided and/or related educational background	CAU	Anxiety symptoms, depressive symptoms, functional impairment, self-identified problems

PM+ - Problem Management Plus, SbS - Step-by-Step, (E)CAU - (enhanced) care-as-usual, PTSD – post-traumatic stress disorder, IG – intervention group, CG – control group

icance border areas (see supplementary information). Thus, our analyses are potentially impacted by publication bias.

Main analysis

Data preparation

Preliminary analyses pointed to considerably larger effect estimates for positive mental health outcomes (SMD ≥ 2.00) in two studies[49,53]. As those findings biased our results, the respective effect estimates were excluded from further quantitative synthesis.

Effects at post-intervention

Twenty-two studies were included in our analysis on distress indicators (see Table 2 and Figure 2). Across all indicators, we found evidence for a small to moderate favorable effect of PM+/SbS over (enhanced) care-as-usual (SMD=–0.45, 95% CI: –0.56 to –0.34), with substantial correlations of outcomes within studies (ρ=0.74). Between-outcome differences were rather small, but accounted for heterogeneity in effect estimates (QM=18.90, p< 0.001).

For all outcome types, we found evidence for small to moderate favorable effects: SMD=–0.51 (95% CI: –0.63 to –0.39) for anxiety symptoms; SMD=–0.46 (95% CI: –0.62 to –0.30) for depressive symptoms; SMD=–0.36 (95% CI: –0.48 to –0.23) for functional impairment; SMD=–0.55 (95% CI: –0.68 to –0.41) for general distress; SMD=–0.34 (95% CI: –0.47 to –0.22) for PTSD symptoms; and SMD=–0.51 (95% CI: –0.70 to –0.32) for self-identified problems.

Only the PIs for functional impairment and PTSD symptoms included zero. After accounting for between-outcome differences, there was still evidence for residual heterogeneity (Q=155.08, p<0.001), which was substantial for all outcome types ($58.2 \leq I^2 \geq 62.6$). Favorable effects on depressive symptoms were larger for SbS (SMD=–0.60, 95% CI: –0.81 to –0.39) than for (group) PM+ (SMD=–0.46, 95% CI: –0.64 to –0.29).

Ten studies were included in our analysis on positive mental health outcomes (see Table 2 and Figure 3). Those provided evidence for a small favorable effect of PM+/SbS over (enhanced) care-as-usual (SMD=0.31, 95% CI: 0.14-0.47), with only moderate heterogeneity (Q=18.08, p=0.080), and no significant between-outcome differences (QM=2.04, p=0.191). For well-being and quality of life, there was evidence for small to moderate favorable effects of PM+/SbS over (enhanced) care-as-usual (SMD=0.37, 95% CI: 0.15-0.59). Effect estimates for social support/relationships were favorable but small (SMD=0.26, 95% CI: 0.12-0.40). Heterogeneity at single outcome level was moderate ($I^2 \leq 41.2$), and overall non-significant (Q=15.77, p=0.106).

Based on GRADE, the certainty of evidence was very low for all outcome types (see supplementary information).

Effects at follow-up assessment

Sixteen studies reported on follow-up data for distress indicators, finding a small favorable effect of PM+/SbS over (enhanced) care-as-usual (SMD=–0.33, 95% CI: –0.46 to –0.21) (see Table 3). Again, between-outcome differences were small, but accounted for a relevant proportion of between-study heterogeneity (QM= 9.19, p=0.001).

For all outcome types, we found evidence for small to moderate favorable effects: SMD=–0.40 (95% CI: –0.54 to –0.25) for anxiety symptoms; SMD=–0.36 (95% CI: –0.58 to –0.14) for depressive symptoms; SMD=–0.27 (95% CI: –0.44 to –0.10) for functional

Table 2 Results of analyses comparing Problem Management Plus (PM+) and Step-by-Step (SbS) with (enhanced) care-as-usual at post-intervention

	n	SMD	95% CI	95% PI	p	Q	p(Q)	I^2
Distress indicators	22	–0.45	–0.56, –0.34	–0.87, –0.03	<0.001	206.01	<0.001	
Anxiety symptoms	16	–0.51	–0.63, –0.39	–0.92, –0.10	<0.001			58.8
Depressive symptoms	18	–0.46	–0.62, –0.30	–0.88, –0.04	<0.001			61.3
Only (group) PM+	15	–0.46	–0.64, –0.29	–1.02, 0.09	<0.001			71.2
Only SbS	3	–0.60	–0.81, –0.39		<0.001			28.9
Functional impairment	16	–0.36	–0.48, –0.23	–0.76, 0.05	<0.001			62.6
General distress	14	–0.55	–0.68, –0.41	–0.96, –0.14	<0.001			58.2
PTSD symptoms	19	–0.34	–0.47, –0.22	–0.75, 0.06	<0.001			62.5
Self-identified problems	13	–0.51	–0.70, –0.32	–0.94, –0.08	<0.001			59.4
Positive mental health outcomes	10	0.31	0.14, 0.47	–0.07, –0.69	0.003	18.08	0.080	
Well-being and quality of life	6	0.37	0.15, 0.59		0.005			41.2
Social support/relationships	6	0.26	0.12, 0.40		0.002			39.1

SMD – standardized mean difference, 95% PI – 95% prediction interval, PTSD – post-traumatic stress disorder

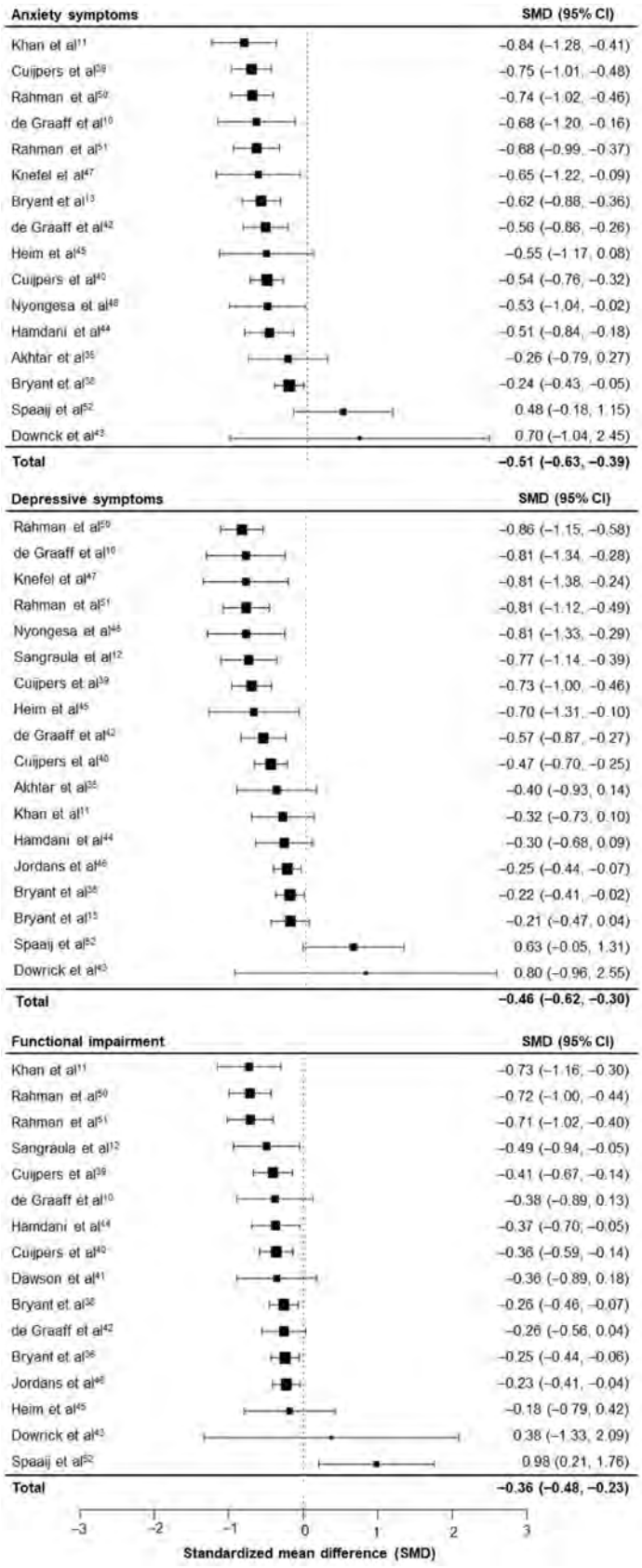

Figure 2 Forest plots of the meta-analysis on distress indicators at post-intervention assessment. Negative estimates indicate an effect favoring PM+/SbS over (enhanced) care-as-usual. PTSD – post-traumatic stress disorder.

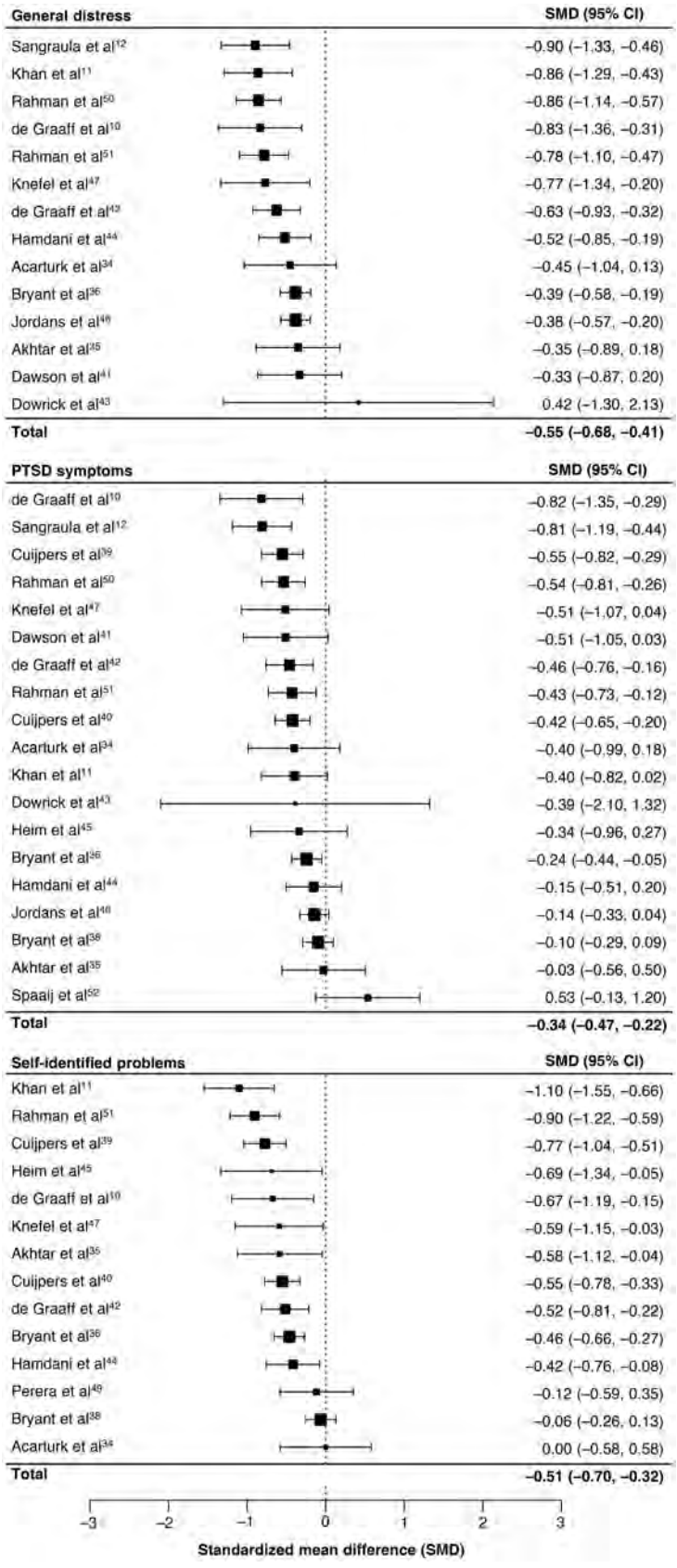

Figure 2 Forest plots of the meta-analysis on distress indicators at post-intervention assessment. Negative estimates indicate an effect favoring PM+/SbS over (enhanced) care-as-usual. PTSD – post-traumatic stress disorder *(continued).*

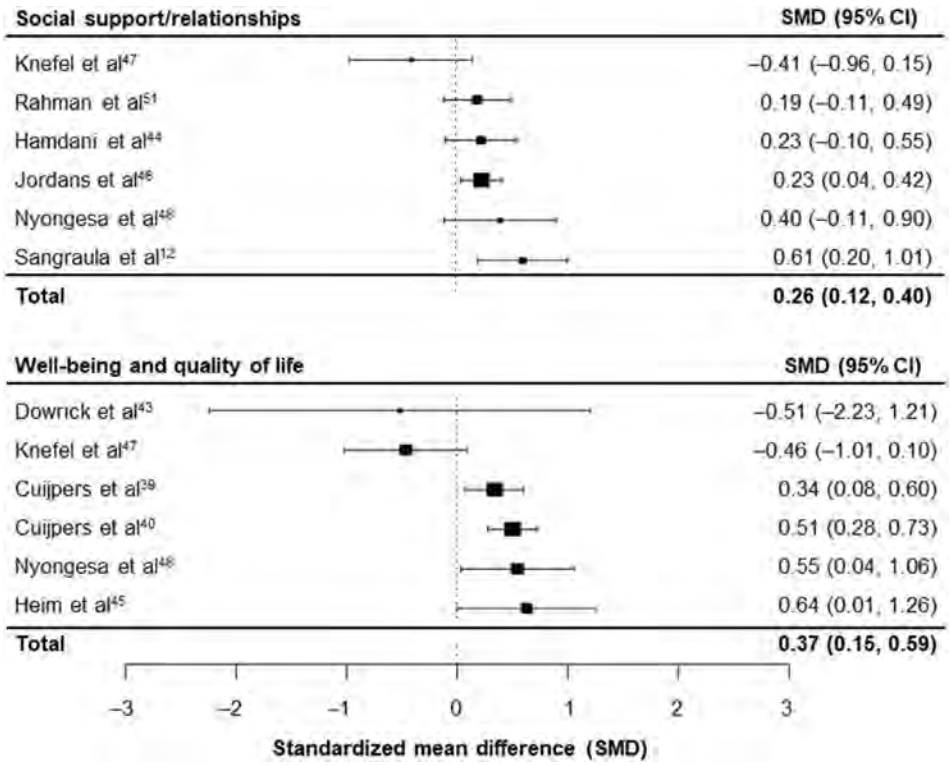

Figure 3 Forest plots of the meta-analysis on positive mental health outcomes at post-intervention assessment. Positive estimates indicate an effect favoring PM+/SbS over (enhanced) care-as-usual.

impairment; SMD=–0.44 (95% CI: –0.63 to –0.25) for general distress; SMD=–0.29 (95% CI: –0.47 to –0.11) for PTSD symptoms; and SMD=–0.27 (95% CI: –0.43 to –0.10) for self-identified problems.

After accounting for between-outcome differences, there was evidence for residual heterogeneity (Q=133.35, p<0.001), which was substantial for all outcome types ($64.0 \leq I^2 \geq 67.5$). Effect estimates were strongly correlated within studies (ρ=0.78). Beneficial effects on depressive symptoms were larger for SbS (SMD=–0.58, 95% CI: –0.76 to –0.40) than for (group) PM+ (SMD=–0.33, 95% CI: –0.54 to –0.13).

Findings on positive mental health outcomes at follow-up assessment were reported in eight studies (see Table 3). Separate univariate models were calculated, as multilevel models showed inacceptable fit. In absence of between-study heterogeneity, there was evidence for small to moderate favorable effects of PM+/SbS over (enhanced) care-as-usual for quality of life and well-being (SMD=0.52, 95% CI: 0.35-0.69). Effect estimates for social support/relationships were favorable but small (SMD=0.22, 95% CI: 0.08-0.36).

The GRADE assessment indicated an overall very low certainty of evidence for all outcome types (see supplementary information).

ICCs indicated substantial stability of intervention effects from post-intervention to follow-up assessments for both outcome categories: ICC=0.85 (95% CI: 0.77-0.90) for distress indicators; ICC=0.88 (95% CI: 0.53-0.98) for positive mental health outcomes.

Moderator analyses

Moderator analyses were performed for distress indicators at both timepoints and for positive mental health outcomes at post-intervention assessment, as our models indicated no heterogeneity at follow-up assessment.

At post-intervention assessment, we did not find evidence for overall differences between PM+, group PM+ and SbS for either distress indicators (QM=1.33, p=0.287) or positive mental health outcomes (QM=2.37, p=0.306). For distress indicators, interventions with longer duration (in weeks) showed larger favorable effects (QM=5.82, p=0.026). However, this finding was mainly driven by one study[48] extending the delivery from mostly 5 to 10 weeks, which reported large favorable effects. We found no evidence for other moderator effects (see supplementary information).

At follow-up assessment, we found no differences between PM+, group PM+ and SbS for distress indicators (QM=2.38, p=0.132). We found a moderator effect of age, with older age being associated with less favorable effects of PM+/SbS (QM=12.24, p=0.004). Interventions with longer duration (in minutes) had smaller favorable effects at follow-up assessments (QM=7.37, p=0.022). There was no evidence for other moderator effects (see supplementary information).

Table 3 Results of analyses comparing Problem Management Plus (PM+) and Step-by-Step (SbS) with (enhanced) care-as-usual at follow-up (3-6 months)

	n	SMD	95% CI	95% PI	p	Q	p(Q)	I^2
Distress indicators	16	–0.33	–0.46, –0.21	–0.77, 0.10	<0.001	163.93	<0.001	
Anxiety symptoms	13	–0.40	–0.54, –0.25	–0.84, 0.05	<0.001			64.0
Depressive symptoms	14	–0.36	–0.58, –0.14	–0.83, 0.11	0.005			66.3
Only (group) PM+	11	–0.33	–0.54, –0.13	–0.92, –0.25	0.001			76.7
Only SbS	3	–0.58	–0.76, –0.40		<0.001			0
Functional impairment	13	–0.27	–0.44, –0.10	–0.72, 0.18	0.005			67.5
General distress	9	–0.44	–0.63, –0.25		<0.001			64.6
PTSD symptoms	14	–0.29	–0.47, –0.11	–0.74, 0.17	0.006			67.4
Self-identified problems	10	–0.27	–0.43, –0.10	–0.72, 0.18	0.005			65.9
Positive mental health outcomes								
Well-being and quality of life	5	0.52	0.35, 0.69		<0.001	1.03	0.906	0
Social support/relationships	4	0.22	0.08, 0.36		0.002	0.77	0.857	0

SMD – standardized mean difference, 95% PI – 95% prediction interval, PTSD – post-traumatic stress disorder

Sensitivity analyses

Sensitivity analyses on between-outcome correlations showed that the use of weaker or stronger correlations (ρ=.40, ρ=.80) had no impact on our conclusions (see supplementary information).

To account for a potential impact of risk of bias within studies, we re-ran all analyses limited to the studies at low risk of bias for the respective bias domain. Neither at post-intervention nor at follow-up assessments, results were significantly different (see supplementary information).

Including effect estimates identified as outliers[49,53] increased the range of CIs and PIs, but did not change our overall conclusions. Studies conducted within the STRENGTHS project did not differ from the others (see supplementary information).

Effects on other outcomes

Seventeen studies examined adverse events, with nine reporting no adverse events during (group) PM+ or SbS, six reporting events unlikely to be related to the intervention (e.g., hospitalization due to physical illness), and two[12,42] reporting adverse events in the intervention group (i.e., hospitalizations, suicide ideation), which, however, were equally likely in the (enhanced) care-as-usual arm (see supplementary information).

Other outcome categories were only examined in a small number of studies. Two studies[35,37,38] investigated effects of group PM+ on child mental distress, with heterogeneous results. However, one study[38] found favorable symptom changes in children to be associated with more consistent disciplinary behavior in parents who received group PM+. Two studies[46,47] investigated effects on somatic symptoms, both finding no evidence for favorable effects of (group) PM+. Health care costs and health care utilization were examined in three studies[10,36,52], with none of them finding evidence for favorable effects. Hamdani et al[54] examined the cost-effectiveness of PM+ for reducing mood and anxiety disorders in Pakistan, based on data from Rahman et al[50], and found PM+ to be more effective but also more costly than (enhanced) care-as-usual.

DISCUSSION

This is the first systematic review and meta-analysis of the effects of the scalable psychosocial interventions PM+ and SbS, that were developed by the WHO to address an increasing need for mental health care in times of intensified humanitarian crises, especially in low- and middle-income countries. Based on 23 studies, including 5,298 participants, we found evidence for small to moderate favorable effects of these interventions, compared with (enhanced) care-as-usual, on distress indicators and positive mental health outcomes. These effects remained significant across all outcome types at short-term follow-up 3 to 6 months after the end of the intervention, and were robust in sensitivity analyses.

Even though favorable effects of PM+ and SbS were found consistently across all outcome types, effect estimates were the largest for general distress at both timepoints (SMD=–0.55 to –0.44), which is in line with other transdiagnostic interventions[55] and may support the transdiagnostic nature of PM+. We found no evidence for overall differences between PM+, group PM+ and SbS; however, only three studies[39,40,45] (with 1,387 participants) delivered SbS. Future reviews will have to examine whether SbS more specifically targets depressive symptoms, as proposed by primary studies on SbS[39,40] and differences from (group) PM+ at both timepoints in our analyses.

Effects for PTSD symptoms were smaller (SMD=–0.34 to –0.29), which may suggest that more specific interventions (e.g., targeting core symptoms of PTSD such as intrusive memory[56]) might be more suitable to reduce post-traumatic stress. However, as studies examined heterogeneous stressors (including wars/armed conflicts[34] and health stressors such as the COVID-19 pandemic[13]), not all stressors may have evoked PTSD symptoms, which may also account for smaller effect sizes.

Based on a smaller number of studies that examined positive mental health outcomes, there was a trend towards lower effect estimates for these outcomes, especially for social support and social relationships. Given the importance of positive mental health[57], future studies on PM+/SbS should include such measures and may answer the question of whether effects on these outcomes emerge over longer time periods, or remain small as many people continue to live under adverse circumstances during PM+/SbS delivery (e.g., in refugee camps[35]).

Overall, intervention effects were small to moderate and tended to be smaller at follow-up assessments. Given the high symptom burden after exposure to severe stressors such as humanitarian crises, wars or armed conflicts[1,58,59], at least a proportion of the affected people will need additional mental health care. In line with this, PM+ and SbS have been proposed as components of stepped-care approaches that provide effective evidence-based treatments with the least resources[60]. Our review shows that PM+ and SbS have the potential to constitute effective components of such programs. However, future studies will have to examine the combination of PM+ and SbS with less intensive self-help programs (e.g., Doing What Matters in Times of Stress[61] by the WHO) and more intensive standard care[60]. Together with further research on the cost-effectiveness of PM+ and SbS, such studies can pave the way for establishing PM+ and SbS as basic interventions for stress-exposed populations.

The results of this review should be considered in the light of some limitations. First, we found moderate to considerable heterogeneity in all analyses, except for positive mental health outcomes at follow-up assessment, which could not be fully accounted for by study-level moderators. Second, we found evidence for a potential impact of publication bias; the overall risk of bias was high; and the certainty of evidence was very low for all outcomes. Our results remained robust in sensitivity analyses, but we cannot exclude that future studies may change effect sizes. Third, although a systematic review was highly needed at this time, the literature search showed that about 23 trials are still ongoing. Based on our sensitivity analyses, we believe that these trials are unlikely to change substantially the scenario we described. However, this systematic review should be updated when a larger high-quality evidence base becomes available. Fourth, for some moderator levels, only a small number of effect estimates was available, and some analyses provided inconsistent findings (e.g., age, duration of intervention), which need further replication.

Based on all available evidence so far, we conclude that PM+ and SbS are effective programs to reduce distress and promote positive mental health in populations exposed to adversities. Favorable intervention effects remain significant during short-term follow-up periods. Future individual participant data meta-analyses[62] may shed light on participant-level moderators of intervention effects and help to clarify for whom PM+ and SbS are most effective. If further research provides support for the cost-effectiveness of PM+ and SbS, and their suitability for stepped-care programs, both WHO interventions can help to reduce the negative mental health consequences of current and future global crises.

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Adverse childhood experiences: a meta-analysis of prevalence and moderators among half a million adults in 206 studies

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Exposure to adverse childhood experiences (ACEs), including maltreatment and family dysfunction, is a major contributor to the global burden of disease and disability. With a large body of international literature on ACEs having emerged over the past 25 years, it is timely to now synthetize the available evidence to estimate the global prevalence of ACEs and, through a series of moderator analyses, determine which populations are at higher risk. We searched studies published between January 1, 1998 and August 5, 2021 in Medline, PsycINFO and Embase. Study inclusion criteria were using the 8- or 10-item ACE Questionnaire (±2 items), reporting the prevalence of ACEs in population samples of adults, and being published in English. The review protocol was registered with PROSPERO (CRD42022348429). In total, 206 studies (208 sample estimates) from 22 countries, with 546,458 adult participants, were included. The pooled prevalence of the five levels of ACEs was: 39.9% (95% CI: 29.8-49.2) for no ACE; 22.4% (95% CI: 14.1-30.6) for one ACE; 13.0% (95% CI: 6.5-19.8) for two ACEs; 8.7% (95% CI: 3.4-14.5) for three ACEs, and 16.1% (95% CI: 8.9-23.5) for four or more ACEs. In subsequent moderation analyses, there was strong evidence that the prevalence of 4+ ACEs was higher in populations with a history of a mental health condition (47.5%; 95% CI: 34.4-60.7) and with substance abuse or addiction (55.2%; 95% CI: 45.5-64.8), as well as in individuals from low-income households (40.5%; 95% CI: 32.9-48.4) and unhoused individuals (59.7%; 95% CI: 56.8-62.4). There was also good evidence that the prevalence of 4+ ACEs was larger in minoritized racial/ethnic groups, particularly when comparing study estimates in populations identifying as Indigenous/Native American (40.8%; 95% CI: 23.1-59.8) to those identifying as White (12.1%; 95% CI: 10.2-14.2) and Asian (5.6%; 95% CI: 2.4-10.2). Thus, ACEs are common in the general population, but there are disparities in their prevalence. They are among the principal antecedent threats to individual well-being and, as such, constitute a pressing social issue globally. Both prevention strategies and downstream interventions are needed to reduce the prevalence and mitigate the severity of the effects of ACEs and thereby reduce their deleterious health consequences on future generations.

Key words: Adverse childhood experiences, mental health conditions, substance abuse, low-income households, unhoused individuals, racial/ethnic minorities

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Research on the impacts of child maltreatment spans over half a century. However, the publication of the Adverse Childhood Experience (ACE) Questionnaire[1] 25 years ago – which is designed to document exposure to severe and stressful adversities related to maltreatment and household dysfunction experienced prior to age 18 – spurred a considerable body of research in this field.

Research has shown that ACEs have cascading life-course effects on health-harming behaviors (e.g., early substance use, smoking), mental health (e.g., depression, anxiety), physical health (e.g., cardiovascular disease, obesity, cancer), and relational functioning (e.g., intimate partner violence)[2]. A dose-response association is often evident: as the number of ACEs increases, so too do the rates of the various unfavourable outcomes.

Through various mechanisms (e.g., neurodevelopmental disruption, epigenetic changes, and reprogramming of stress regulatory systems), exposure to ACEs is thus believed to increase the risk of cognitive challenges, lifelong disease and premature mortality, psychopathology, and social problems in adulthood.

In addition to the individual toll of ACEs, existing evidence also links substantial financial costs to such childhood adversity. Costs include loss of economic opportunity and productivity among individuals affected by ACEs and their families, legal and judicial costs associated with criminal offenses, as well as substantial lifetime medical costs associated with management of chronic disease and disability. The financial costs attributable to ACEs have been estimated to represent an average of 3% and as much as 6% of a country's annual gross domestic product[3]. Accordingly, ACEs have been identified by health agencies and institutions globally as one of the principal antecedent threats to individual well-being, and an urgent social issue[3].

The ACE Questionnaire asks respondents if they experienced any of the following events prior to the age of 18: sexual abuse, physical abuse, emotional abuse, physical or emotional neglect, growing up in a home where one or both parents were affected by mental illness or substance abuse, were incarcerated or separated, and/or were perpetrators or victims of domestic violence. Adversities that were in the original 8-item version of the questionnaire included physical abuse, sexual abuse, emotional abuse, parent substance use, parent incarceration, parent mental health problems, and exposure to domestic violence. In 2001, an expanded 10-item version was published that included two additional categories: physical/emotional neglect and parent divorce/separation. Otherwise, the questionnaire has remained remarkably consistent since its introduction. This consistency is critical as it allows for the development of a coherent evidence base, valid replication across time and geographical contexts, as well as comparisons between groups with different sociodemographic, economic and medical-clinical characteristics, as well as risk profiles.

In 2018, Merrick et al[4] published the largest (N=248,934) ACE study to date, based on a representative US sample telephone survey, reporting a prevalence of 38.5% of people with no ACE, 23.5% of those with one ACE, 13.4% of those with two ACEs, 8.8% of those with three ACEs, and 15.8% of those with four or more ACEs. Research also shows that the prevalence of ACEs is higher in samples of individuals in socially and/or economically disadvantaged contexts, including groups that experience marginalization[5-7]. For example, in a meta-analysis of the prevalence of ACEs in unhoused individuals, an average of 53.9% reported having 4+ ACEs[8].

To our knowledge, no systematic review or meta-analysis exists on the prevalence of ACEs in the general population globally, and, to date, there has been limited cross-study moderation analysis examining whether the prevalence of ACEs differs between racial/ethnic, sex, sociodemographic and economic characteristics or profiles, or across geographical regions[5-7].

With the widespread adoption of the ACE Questionnaire in public health research, and considering the individual, social and economic toll of ACEs, it is timely to synthetize the literature to establish a cross-study and multi-country distribution of these experiences. Systematic reviews and meta-analyses are recognized as important resources for informing decision-making in public health and clinical practice, because they summarize and quantify existing evidence across multiple, often heterogeneous, studies.

The objectives of the present systematic review and meta-analysis were to estimate the distribution of ACEs across adult samples; the geographic differences in distribution of ACEs; and the differences in the distribution of ACEs among samples with different individual, social, demographic, economic and clinical characteristics.

METHODS

Search strategy

Studies published between January 1, 1998 and August 5, 2021 were searched in Medline, Embase and PsycINFO. Text word fields were searched with the phrase "adverse childhood experience or event", as well as the acronym "ACEs". We used both truncation symbols and adjacency operators to capture variations in phrasing. No language restrictions were applied (see also supplementary information).

This study followed the PRISMA guidelines[9]. The protocol was registered with PROSPERO (CRD42022348429).

Selection criteria

All titles/abstracts were independently double-coded by five coders in Covidence according to the following inclusion criteria: using the 8- or 10-item ACE Questionnaire (±2 items), reporting the prevalence of ACEs in population samples of adults, and being published in English. Studies were excluded if the ACE Questionnaire had <6 or >12 items.

Full-text articles were reviewed by two independent coders (agreement probability: 84%). Discrepancies were resolved via consensus.

Data extraction

We applied a standardized protocol to extract the following study and sample characteristics: authors and publication date, country from which participants were sampled, method of data collection, sample size, counts for each category of ACEs, mean or median age, proportion of females and racially/ethnically minoritized individuals, socioeconomic profile (categorized as low, mixed or mid-to-high levels of household income), sociodemographic and health-related characteristics (e.g., whether the sample included persons who were homeless, or with a history of mental health conditions or offending/criminality), and other study design and methodological characteristics to assess study quality (see also supplementary information).

Data extraction was conducted independently by two trained coders. Twenty percent of studies were randomly selected to estimate reliability among coders; intercoder agreement was 95%. Discrepancies were resolved through consensus.

Study quality assessment

Study quality was evaluated using an adapted version of the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[10]. Two coders evaluated all studies for study quality (see also supplementary information). Intercoder agreement was 81%. Discrepancies were resolved through consensus.

Data preparation and analysis

Prevalence proportions for each of the five levels of ACEs (0, 1, 2, 3, 4+) were calculated by dividing the sample count for the given category of ACE by the overall study sample size. To stabilize the variances to properly weight prevalence proportions at the extreme ends of the range (e.g., where there was a 0 count for a given category of ACE), we applied the Freeman-Tukey double arcsine transformation to each of the study estimates and standard errors prior to conducting the meta-analysis[11].

To estimate the prevalence proportions for each of the five levels of ACEs, a single multicategory prevalence meta-analysis was performed in MetaXL (Version 5.3)[12]. The inverse of the average of the five levels of ACE variances was used to weigh the meta-analysis, and between-study heterogeneity was estimated and assessed using the tau (τ) statistic, which represents the average difference in the prevalence proportion between studies[13].

Further subgroup and moderator analyses were conducted using the 'regress' command in Stata (Version 17), wherein ro-

bust (i.e., Huber-Eicker-White-sandwich) error variances were applied[12]. Subgroup analysis of categorical moderators was conducted by calculating the ratio of the prevalence of a given category of ACE between different categories of the moderator (e.g., prevalence of 4+ ACEs in samples of Indigenous persons divided by the corresponding prevalence for samples of White or Asian persons). Analysis of continuous moderators was conducted by calculating the ratio between below (mean: –1 standard deviation, SD) and above (mean: +1 SD) average values for the moderator (e.g., prevalence of 4+ ACEs in studies with above average quality scores divided by the corresponding prevalence in studies with below average quality scores)[14].

The magnitudes of the ratio representing a moderating association were interpreted using the following scale for increases in the prevalence proportion: slight: <1.11; small: 1.11-1.43; moderate: 1.44-2.00; large: >2.00. The inverses of these thresholds for interpreting decreases were: slight: >0.90; small: 0.90-0.70; moderate: 0.71-0.50; large: <0.50. The choice of such thresholds was guided by the scale of magnitudes for evaluating the effect size of a correlation coefficient devised by Cohen[15] (see also supplementary information). Thresholds for interpreting the magnitude of between-study heterogeneity (τ) were the square root of the thresholds for ratio increases above[16].

Sampling uncertainty was expressed as 95% confidence intervals (CI), and a precision of estimation approach was used to assess the level of evidence for or against the magnitude of a moderating association[17-19]. The extent of overlap of the 95% CI with slight and/or substantial (i.e., small, moderate and large) values was used to assess the level of evidence for or against the magnitude[18] (see supplementary information). Precision of estimation was deemed inadequate when the 95% CI included both substantial increases and decreases (i.e., ratios <0.90 and >1.11)[18].

Assessment of publication bias, outliers, and influential cases

Publication bias was assessed by visually inspecting funnel plots of the double arcsine prevalence versus the standard error of the study-estimate prevalence proportion for each category of ACE[12]. Sequential "leave-one-out" analysis (i.e., recalculating prevalence proportions with one study estimate omitted at a time) was conducted to identify outliers and influential cases[20].

RESULTS

A total of 11,920 non-duplicate records were identified by our search, of which 4,656 full-text articles were screened for inclusion. Two hundred and six studies met the full inclusion criteria (see Figure 1), from which 208 multi-category prevalence proportions were extracted for use in this review.

The characteristics of included studies are detailed in the supplementary information. Across the 206 studies, 546,458 adults were represented. One hundred and seventy-two studies reported data from North America (83.5%), 20 from Europe (9.7%), six from Asia (2.9%), four from Australia and New Zealand (1.9%), two from South America (1.0%), and one each from Africa (0.5%) and the Caribbean (0.5%). The average age of study samples was 33.9±11.7 years, and the average proportion of females was 35.5%. The racial/ethnic profile of the sample of included studies was as follows (as some studies allowed participants to indicate >1 category, percentages do not add to 100%): White (58.3%), Black (26.1%), Latinx (17.6%), Asian (13.3%), Indigenous/Native American (12.1%), mixed (8.3%), other unspecified (11.1%). The mean study quality score was 7.4 (range 3-11; see also supplementary information).

Inspection of funnel plots only revealed evidence of publication bias for the category 0 ACE (see supplementary information). Sensitivity analysis of bias (i.e., "leave-one-out") revealed limited evidence of influential cases; therefore, all study estimates were retained for the final meta-analysis and moderation analyses.

The overall mean meta-analyzed prevalence proportions for the five levels of ACEs, as well as the predicted mean prevalence proportions for ACEs at different levels of categorical and continuous moderators, are displayed in Table 1. The corresponding forest plots for each category of ACE are displayed in Figure 2 (0 ACE) and 3 (4+ ACE) and in the supplementary information.

The pooled prevalence of the five levels of ACEs was derived from 208 unique samples of adults and can be summarized as follows: 39.9% (95% CI: 29.8-49.2) for no ACE; 22.4% (95% CI: 14.1-30.6) for one ACE; 13.0% (95% CI: 6.5-19.8) for two ACEs; 8.7% (95% CI: 3.4-14.5) for three ACEs; and 16.1% (95% CI: 8.9-23.5) for four or more ACEs.

Between-study heterogeneity was moderate in magnitude for the prevalence of no ACE (τ=24.3%; 95% CI: 21.9-27.2) and four or more ACEs (τ=23.4%; 95% CI: 21.1-26.2), whereas it was small in magnitude for the prevalence of one ACE (τ=10.9%; 95% CI: 9.9-12.2), two ACEs (τ=7.8%; 95% CI: 7.1-8.7), and three ACEs (τ=9.5%; 95% CI: 8.6-10.6).

Ratios of prevalence proportions for the five levels of ACEs between different values of the categorical and continuous moderators are displayed in Table 2. There was strong evidence that the prevalence of 4+ ACEs was substantially larger in populations from low vs. mid-to-high income households (ratio: 1.21; 95% CI: 1.15-1.28); unhoused individuals (ratio: 1.38; 95% CI: 1.35-1.41); and people with a history of a mental health condition (ratio: 1.27; 95% CI: 1.17-1.39), or with substance abuse or addiction (ratio: 1.34; 95% CI: 1.26-1.43). There was also strong evidence that the prevalence of 0 ACE was substantially lower for persons from low-income households (ratio: 0.85; 95% CI: 0.82-0.88), unhoused individuals (ratio: 0.80; 95% CI: 0.78-0.82), and people with a history of a mental health condition (ratio: 0.82; 95% CI: 0.79-0.86), or with substance abuse or addiction (ratio: 0.83; 95% CI: 0.80-0.86).

There was good evidence that the prevalence of 4+ ACEs was higher in racially-ethnically minoritized groups, particularly when comparing study estimates for people identifying as Indigenous/Native American to those identifying as White or Asian (ratio: 1.20; 95% CI: 1.05-1.37). There was also good evidence that the preva-

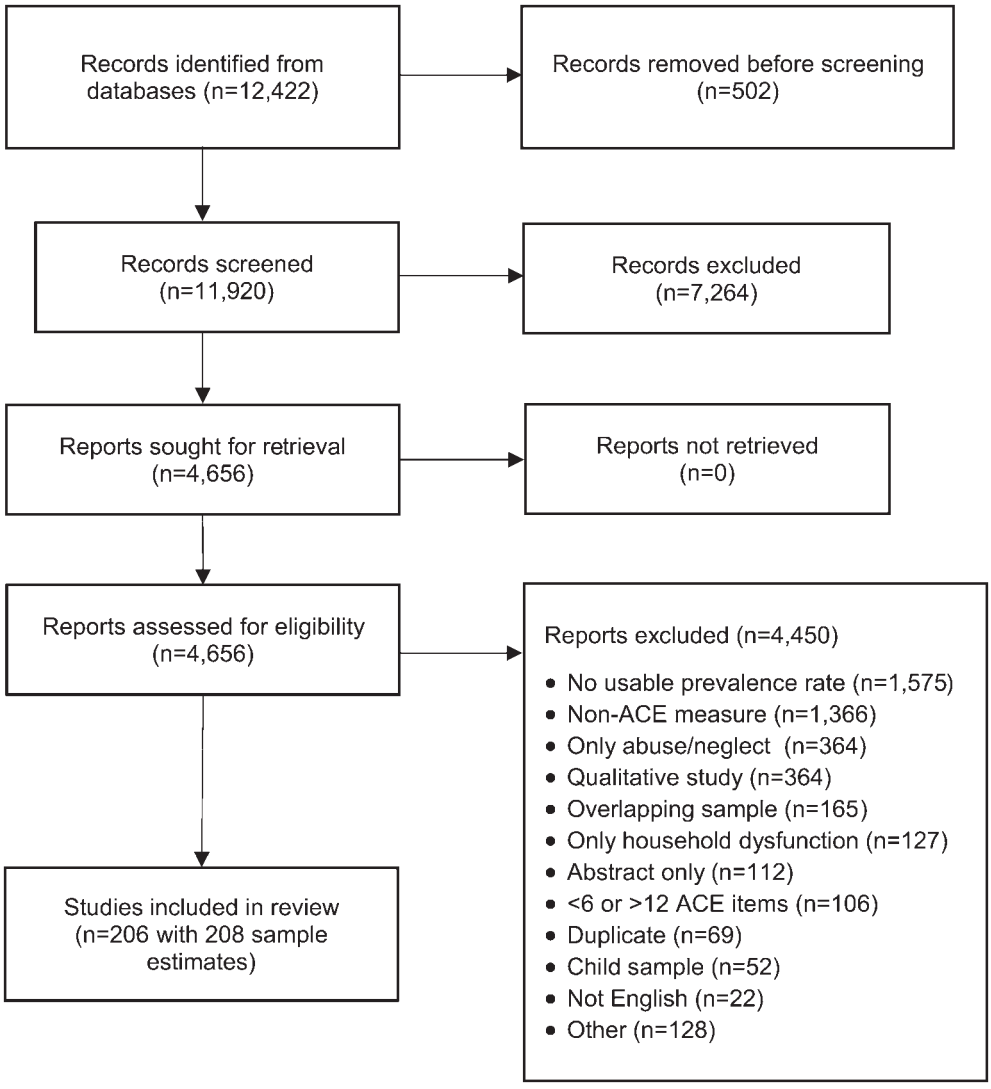

Figure 1 PRISMA flow diagram. ACE – adverse childhood experience

lence of 0 ACE was lower for samples of individuals involved in the criminal justice system (ratio: 0.88; 95% CI: 0.80-0.96). There was some evidence that the prevalence of 4+ ACEs was higher for Latinx persons (vs. persons of Caucasian heritage) and those with a history of offending or criminality. Finally, there was some evidence that the prevalence of 0 ACE was higher among males (vs. females), and lower in samples from Europe compared to North America.

There was weak evidence to suggest that the prevalence of 0 or 4+ ACEs differed between assessment methods. There was strong evidence that age- and study quality-related differences in the prevalence of each ACE category were only slight.

DISCUSSION

In this meta-analysis of 206 studies (208 prevalence estimates), representing 546,458 adult participants across 22 countries, the prevalence of ACEs was 39.9% for no ACE, 22.4% for one ACE, 13.0% for two ACEs, 8.7% for three ACEs, and 16.1% for four or more ACEs. Thus, six out of ten adults report having experienced at least one ACE, and one in six report exposure to four or more ACEs prior to age 18.

Although these data suggest that ACEs are common, we also found considerable disparities across the population. Specifically, there was strong evidence of differences in the prevalence of 4+ ACEs across samples with different sociodemographic, economic and health-related profiles (in particular, racial/ethnic features, household income, and history of a mental health condition or substance abuse/addiction).

Exposure to ACEs can lead to intense and prolonged activation of the stress response, which can impact brain development, as well as cognitive, social and emotional functioning in childhood. Adoption of risky behaviours, such as substance misuse, can then occur, which can exacerbate later-life health problems (e.g., cardiovascular, lung, liver and respiratory diseases; cancer, hypertension, diabetes), leading to premature death. In

Table 1 Prevalence of the five levels of adverse childhood experiences (ACEs)

		Prevalence, % (95% CI)				
Moderators	**n**	**0 ACE**	**1 ACE**	**2 ACEs**	**3 ACEs**	**4+ ACEs**
Overall mean	208	39.9 (29.8-49.2)	22.4 (14.1-30.6)	13.0 (6.5-19.8)	8.7 (3.4-14.5)	16.1 (8.9-23.5)
Sex at birth						
Female	190	34.6 (29.7-39.8)	23.6 (21.5-25.8)	14.1 (12.8-15.5)	9.1 (8.1-10.2)	17.5 (14.7-20.6)
Male	163	45.1 (34.5-56.6)	20.3 (16.0-25.0)	11.2 (8.5-14.3)	7.8 (6.0-9.7)	14.3 (12.0-16.6)
Age						
Below average (mean: –1 SD)	170	33.4 (27.5-39.6)	21.2 (19.6-22.9)	14.1 (13.2-15.1)	10.5 (8.6-12.6)	18.1 (13.3-23.5)
Above average (mean: +1 SD)	170	38.0 (35.1-40.9)	23.1 (21.9-24.3)	13.2 (12.3-14.2)	9.5 (8.4-10.6)	14.9 (12.3-17.7)
Region						
North America	173	38.7 (34.9-42.6)	21.8 (19.6-24.1)	12.8 (11.6-14.1)	8.7 (8.0-9.4)	16.9 (15.4-18.6)
Europe	21	46.7 (39.9-53.7)	25.4 (22.4-28.5)	12.0 (10.3-13.7)	7.2 (4.5-10.6)	5.6 (2.9-9.0)
Other	14	43.7 (23.2-62.7)	23.2 (7.1-40.5)	13.6 (1.5-28.3)	8.2 (0.0-20.6)	11.3 (0.5-25.2)
Racial-ethnic group						
White	149	43.4 (38.7-48.0)	23.7 (21.3-26.1)	13.2 (11.9-14.5)	8.1 (7.3-9.1)	12.1 (10.2-14.2)
Black	112	33.2 (25.7-41.1)	20.3 (17.5-23.3)	13.3 (11.2-15.7)	9.3 (7.2-11.6)	21.5 (16.2-27.5)
Latinx	113	28.6 (21.6-36.2)	20.3 (17.0-23.8)	13.3 (11.5-15.3)	10.7 (9.0-12.6)	25.6 (20.7-30.8)
Asian	73	51.3 (43.0-59.6)	24.7 (22.3-27.3)	11.1 (8.3-14.2)	6.5 (4.7-8.5)	5.6 (2.4-10.2)
Indigenous/Native American	61	20.6 (10.7-32.7)	11.3 (4.5-20.8)	13.3 (9.6-17.7)	12.9 (8.7-17.9)	40.8 (23.1-59.8)
Any minoritized group	148	31.2 (22.8-40.3)	18.5 (15.4-22.0)	12.2 (10.1-14.5)	9.60 (7.7-11.7)	26.6 (21.0-32.6)
Household income						
Low	32	17.4 (13.3-21.9)	15.7 (12.6-19.0)	13.3 (11.9-14.7)	11.3 (9.9-12.8)	40.5 (32.9-48.4)
Mid-to-high	15	38.2 (37.6-38.8)	23.4 (23.1-23.7)	13.4 (13.4-13.4)	8.9 (8.8-9.0)	16.0 (15.4-16.7)
Sociodemographic and health-related variables						
Unhoused	7	11.6 (10.2-13.1)	9.1 (7.8-10.5)	10.0 (9.3-10.8)	9.6 (8.0-11.2)	59.7 (56.8-62.4)
Substance abuse/addiction	11	15.8 (13.5-18.3)	13.0 (11.4-14.8)	12.7 (1.6-13.7)	11.1 (10.1-12.1)	55.2 (45.5-64.8)
History of offending/criminality	13	22.1 (12.5-33.5)	19.7 (14.6-25.4)	13.3 (11.9-14.7)	10.2 (8.4-12.1)	31.8 (17.0-48.8)
History of a mental health condition	10	15.0 (11.0-19.4)	12.6 (8.4-17.5)	12.2 (9.4-15.3)	11.0 (10.0-12.0)	47.5 (34.4-60.7)
Assessment method						
Questionnaire	186	39.9 (35.8-43.1)	22.1 (20.1-24.1)	12.8 (11.7-14.0)	8.6 (7.9-9.2)	15.8 (14.5-17.1)
Other methodologies	15	34.3 (21.2-48.7)	20.5 (18.2-23.0)	13.1 (11.0-15.3)	9.5 (7.1-12.2)	19.8 (11.1-30.2)
Study quality						
Below average (mean: –1 SD)	208	38.5 (37.1-39.9)	22.9 (21.7-24.1)	13.1 (12.4-13.7)	8.6 (8.2-9.1)	16.3 (15.1-17.6)
Above average (mean: +1 SD)	208	40.5 (34.0-47.2)	21.0 (18.2-24.1)	12.4 (10.6-14.4)	8.5 (7.2-9.8)	15.3 (12.8-17.9)

addition, research suggests that ACEs can "get under the skin" and be transmitted to the next generation, thereby perpetuating intergenerational cycles of risk[21].

However, the occurrence of ACEs does not necessarily predict problematic outcomes for all victims, especially if they experience safe, stable and nurturing relationships at the family or community levels[22]. For example, neighbourhood collective efficacy has been shown to moderate the association between ACEs and marital discord, whereby individuals with high ACE scores had lower levels of marital discord when exposed to high levels of neighbourhood social cohesion and support[23]. Thus, protective factors can reduce or even offset the consequences of ACEs.

Our moderation analysis demonstrated that the prevalence of 4+ ACEs was greater among individuals with a history of a mental health condition, and with substance abuse or addiction. For example, we found that 55.2% of individuals with substance abuse or addiction had 4+ ACEs, whereas the prevalence of 4+ ACEs in the general population was 16.1%. The association between ACEs and risky substance use or addiction may be mediated by emotional dysregulation[24]. Further, substance abuse and addiction are known behavioural mechanisms by which ACEs precipitate involvement in the criminal justice system[25]. In gen-

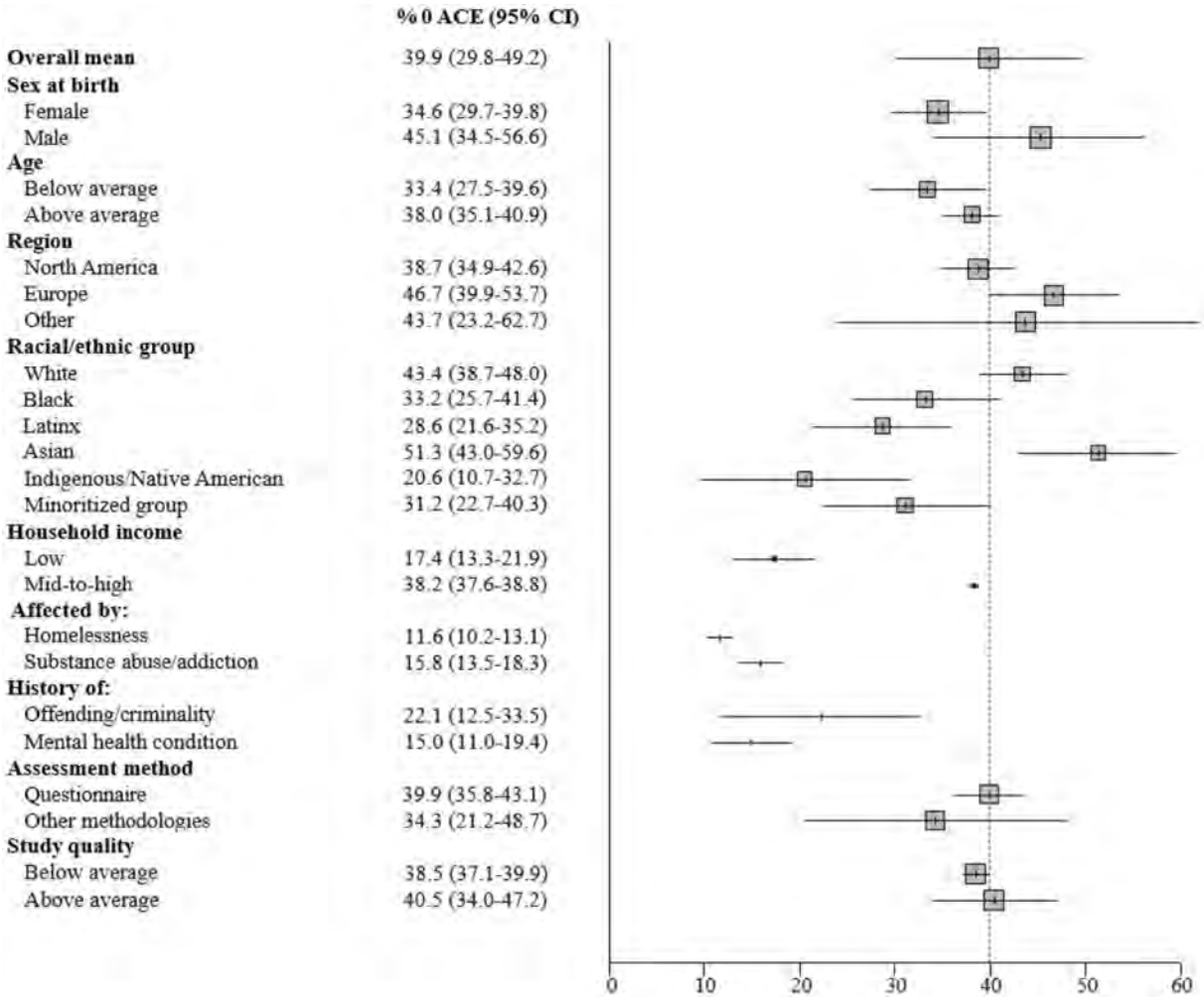

Figure 2 Forest plot of the prevalence of no adverse childhood experience (ACE). The overall mean prevalence of 0 ACE is displayed alongside the mean prevalence of 0 ACE for different levels of categorical moderators, and below and above average values for continuous moderators. Error bars represent 95% CIs.

eral, there are both direct and indirect pathways by which early adversity can contribute to mental health and social challenges in adulthood. More research focused on these developmental pathways is critical to identify opportunities for intervention leading to better-than-expected outcomes.

Our moderation analysis also showed that the prevalence of 4+ ACEs was higher in samples of unhoused individuals (59.7%), which is consistent with the recent findings by Liu et al[8]. Moreover, on average, the prevalence of 4+ ACEs in samples of White persons was 12.1%, whereas the corresponding prevalence for samples of Black (21.5%), Latinx (25.6%), and Indigenous/Native American (40.8%) persons was substantially higher. Beyond ACEs, minoritized groups in Western countries have also experienced historical, structural and economic inequalities, oppression, discrimination and poverty, that could perpetuate ACEs and initiate intergenerational cycles of adversity[7]. Future research should focus on such disparities in ACEs, which could add valuable insight into population health.

Consistency of instrumentation in the measurement of ACEs was a requirement and is a strength of this systematic review and meta-analysis. Such consistency underpinned a valid quantitative synthesis and robust estimation of the prevalence of ACEs across many studies, in addition to an extensive set of moderation analyses. However, to ensure consistency, only studies that used the 8- or 10-item ACE Questionnaire (±2 items) were included in our analysis. Although the vast majority of ACE studies employed these two versions, excluding studies using <6- or >12-item versions was methodologically necessary, but is still a limitation of this systematic review.

Further limitations relating to representativeness should be mentioned. Although included studies were from 22 countries across all continents, most were from North America and Europe (>90%). Thus, further studies in Asia, Australia/New Zealand, South America, the Caribbean and Africa are needed to ensure better generalizability of ACE prevalence estimates. Moreover, few studies have been conducted in low- and middle-income

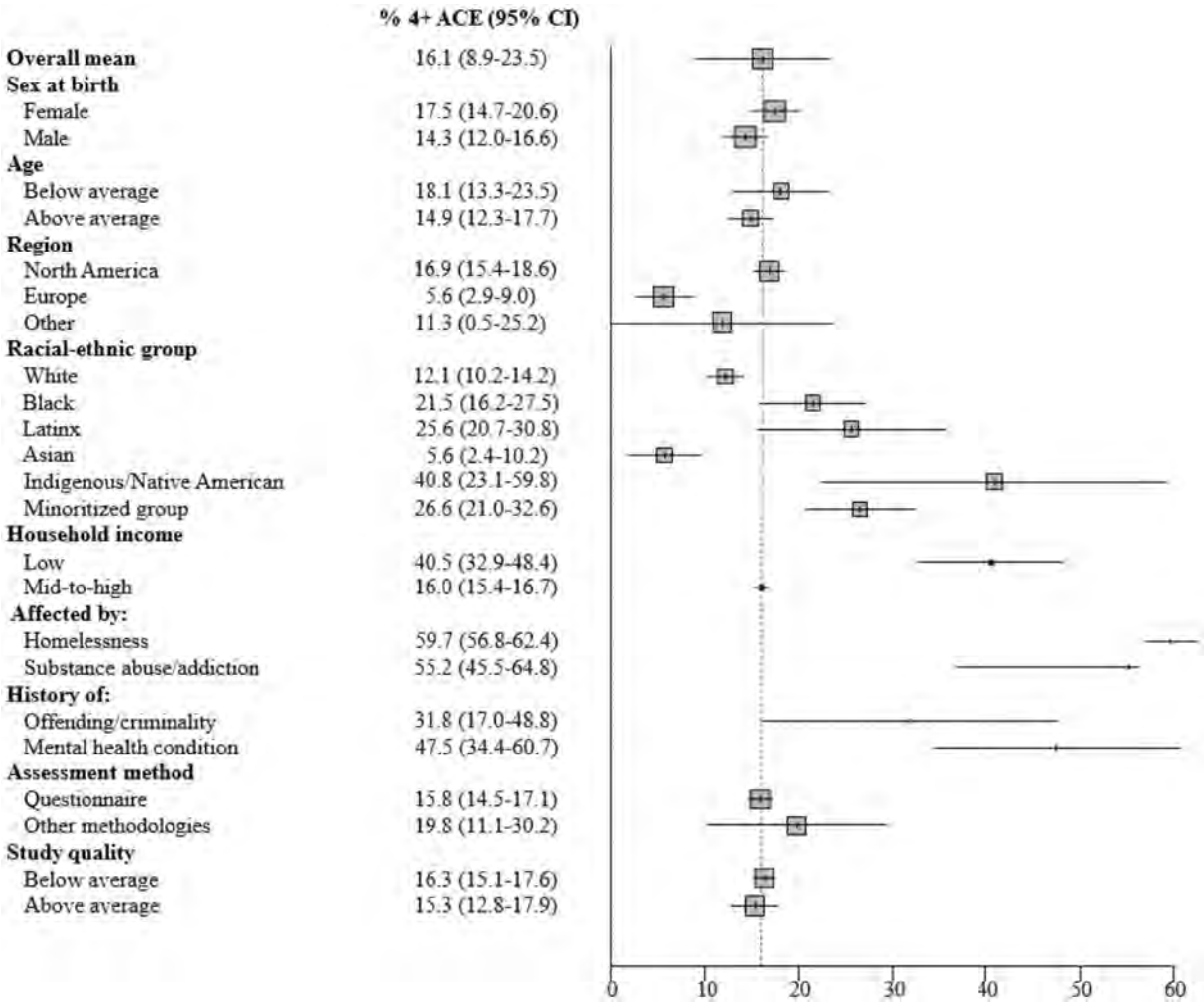

Figure 3 Forest plot of the prevalence of 4+ adverse childhood experiences (ACEs). The overall mean prevalence of 4+ ACEs is displayed alongside the mean prevalence of 4+ ACEs for different levels of categorical moderators, and below and above average values for continuous moderators. Error bars represent 95% CIs.

countries, with a very high variability observed in the prevalence of 4+ ACEs (from 6.75% to 88.31%). More studies on ACEs are needed in these countries, and their consequences should be investigated in the context of global health research.

There were also too few studies with ACE prevalence estimates in samples representing the lesbian, gay, bisexual, transgender, queer, intersexual, asexual and two-spirited (LGBTQIA2+) community. Therefore, new studies of ACEs in this community, such as the one recently published in this journal[26], should be encouraged and welcomed to enable further exploration of gender and sexual identity as potential moderators of the impact of childhood adversity.

Efforts to mitigate the impact of ACEs are focused on screening for these experiences when interfacing with patients as part of routine care. However, there are cautions around ACE screening, especially when encounters with patients are brief and few resources are available following disclosure[27]. Specifically, it is recommended that ACE screening be optional, to give patients choice on what they discuss and disclose, and that screening only occurs in combination with trauma-informed practice[28].

Trauma-informed practice requires having personnel who are sensitive to the impacts of adversity, recognize how the signs and symptoms of toxic stress manifest in individuals, integrate knowledge of ACEs and their impacts into their work practice, and can actively resist harm or re-traumatization (e.g., having trust violated, or experiences minimized)[28]. Clinicians need to be particularly aware of the complex issues that may surround trauma-informed care, including systemic oppression, racism, and intersecting identities[29]. A recent study[30] showed that the adoption of trauma-informed practice in a maternity clinic was associated with fewer infant delivery complications and health risks at birth. However, future research is needed to determine the effectiveness of trauma-informed approaches across various contexts, such as paediatric settings, schools, and justice systems.

In conclusion, ACEs are common, represent a threat to individual well-being and societal prosperity, and should be a key public

Table 2 Moderation of prevalence of the five levels of adverse childhood experiences (ACEs)

	Ratio (95% CI)				
Moderators	**0 ACE**	**1 ACE**	**2 ACEs**	**3 ACEs**	**4+ ACEs**
Sex at birth	1.08 (0.99-1.17) ↑	0.97 (0.93-1.01)	0.97 (0.95-1.00)	0.99 (0.97-1.01)	1.03 (1.00-1.06)
Age	1.03 (0.98-1.09)	1.02 (1.00-1.03)	0.99 (0.98-1.00)	0.99 (0.97-1.01)	0.97 (0.93-1.02)
Region					
North America	0.97 (0.91-1.04)	0.99 (0.96-1.02)	1.00 (0.98-1.01)	1.01 (0.99-1.02)	1.05 (1.02-1.09)
Europe	1.03 (0.95-1.12)	1.02 (0.99-1.06)	0.99 (0.97-1.01)	0.99 (0.96-1.03)	0.95 (0.91-0.99)
Europe/North America	1.06 (1.00-1.12)	1.03 (1.00-1.06)	0.99 (0.97-1.01)	0.99 (0.96-1.02)	0.90 (0.87-0.93) ↓
Racially/ethnically minoritized					
Black	0.95 (0.89-1.02)	0.99 (0.96-1.02)	1.01 (0.98-1.03)	1.01 (0.99-1.03)	1.05 (1.00-1.10)
Latinx	0.91 (0.85-0.97) ↓	0.99 (0.95-1.03)	1.01 (0.99-1.03)	1.02 (1.01-1.04)	1.09 (1.04-1.14) ↑
Asian	1.07 (0.97-1.18) ↑	1.05 (1.01-1.09)	1.00 (0.96-1.03)	0.98 (0.96-1.01)	0.89 (0.85-0.94) ↓
Indigenous/Native American	0.88 (0.80-0.96) ↓	0.91 (0.84-0.98) ↓	1.00 (0.94-1.04)	1.04 (1.00-1.08)	1.20 (1.05-1.37) ↑
Any minoritized group	0.92 (0.85-0.99) ↓	0.96 (0.93-0.99)	0.99 (0.97-1.01)	1.01 (0.99-1.03)	1.13 (1.08-1.19) ↑
Household income	**0.85 (0.82-0.88) ↓**	0.94 (0.91-0.96)	1.00 (0.99-1.01)	1.02 (1.01-1.04)	**1.21 (1.15-1.28) ↑**
Sociodemographic and health-related variables					
Unhoused	**0.80 (0.78-0.82) ↓**	**0.89 (0.88-0.91) ↓**	0.98 (0.96-0.99)	1.01 (0.99-1.03)	**1.38 (1.35-1.41) ↑**
Substance abuse/addiction	**0.83 (0.80-0.86) ↓**	0.93 (0.91-0.95)	1.00 (0.99-1.01)	1.02 (1.01-1.03)	**1.34 (1.26-1.43) ↑**
History of offending/criminality	0.88 (0.80-0.96) ↓	0.98 (0.94-1.03)	1.00 (0.99-1.02)	1.02 (1.00-1.03)	1.14 (1.01-1.28) ↑
History of a mental health condition	**0.82 (0.79-0.86) ↓**	0.92 (0.88-0.96) ↓	0.99 (0.97-1.02)	1.02 (1.01-1.03)	**1.27 (1.17-1.39) ↑**
Assessment method	1.04 (0.93-1.15)	1.01 (0.99-1.04)	1.00 (0.98-1.02)	0.99 (0.97-1.02)	0.97 (0.89-1.05)
Study quality	1.01 (0.97-1.06)	0.99 (0.96-1.01)	0.99 (0.98-1.01)	1.00 (0.99-1.01)	0.99 (0.97-1.02)

Arrows indicate effects where the chances of a substantial and slight moderating association were respectively >25% and <95%. Bold prints indicate effects where the chances of a substantial and slight moderating association were respectively >95% and <5%. Concerning sex, the prevalence for males was divided by that for females. As to age, the prevalence for studies with above average values (mean: +1 SD) was divided by that for studies with below average values (mean: –1 SD). Concerning region, the prevalence for studies from North America or Europe was divided by that for studies from other regions, and the prevalence for studies from Europe was divided by that for studies from North America. The prevalence for each minoritized group was divided by that for people identifying as White. The prevalence for samples from low-income households was divided by that for samples from mid-to-high income households. The prevalence for samples of persons with homelessness, substance abuse or addiction, or a history of a mental health condition or offending/criminality was divided by that for samples of persons without such profiles. The prevalence for studies of ACEs collected using a questionnaire was divided by that for studies using other methodologies. As to study quality, the prevalence for studies with above average values (mean: +1 SD) was divided by that for studies with below average values (mean: –1 SD).

health priority. Several efforts are underway globally to mitigate ACEs and their impacts. Their prevention through universal and targeted policies that optimize early child development is critical.

It has been documented that fewer social and material resources within families are among the strongest predictors of childhood maltreatment[31]. As such, social policies that reduce income inequalities and increase social welfare, access to affordable education, higher-paying employment opportunities, and supportive parenting policies (i.e., paid parental leave, supportive family work policies), are likely to help mitigate collective exposure to childhood adversity.

With regard to targeted prevention, the implementation and scaling up of evidence-based interventions for preventing exposure to childhood maltreatment are needed. Home visitation programs and parent coaching interventions – particularly in families at high risk – have been identified as effective deterrents of abuse at home and child maltreatment[31].

A multi-pronged strategy using universal and targeted approaches to prevent maltreatment has the greatest chance to improve long-term outcomes.

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How computational psychiatry can advance the understanding and treatment of obsessive-compulsive disorder

The behavioral repertoires of patients with obsessive-compulsive disorder (OCD) often appear puzzling and irrational. For example, an OCD patient who just locked a door might repeatedly return and check that it is locked. Similarly, a patient might continue washing and rewashing his hands, waiting for a vague "just-right" feeling before deciding to stop.

Numerous models have been proposed to explain such symptoms. Prominent theories argue that compulsions are driven by an attempt to reduce potential threat or anxiety. Such theories stem from patients' reports of obsessional preoccupations with catastrophic, even if improbable, scenarios. Other equally compelling theories argue that compulsions do not relate to attaining any instrumental goal but rather to difficulty stopping a repetitive, habitual behavior[1]. The latter accounts rely primarily on patients' habit-like performance on neuropsychological tasks, but their role in real-life symptoms and experiences is less well studied. Since these (and other) theories refer to different assumptions and methods, they are rarely formally evaluated against one another, let alone integrated. Furthermore, how such theoretical debates can constructively contribute to understanding and improving pharmacological and psychosocial treatments for OCD remains unclear.

One way to overcome these impasses is to specify *a mechanism* tying together symptoms, performance in neurocognitive tasks, and the mode of action of existing treatments. This is an overarching goal of the field of computational psychiatry[2]. A computational model of OCD might first ask[2,3]: what computations are normally performed by the brain to solve the everyday problems of deciding when to stop handwashing or checking that a door is locked? One class of models, relying on principles of Bayesian inference, highlights a prominent role of expectations and predictions[3,4]. For example, when locking your door, you rely not only on sensory information (seeing, hearing, and feeling a click), but also on a prediction that locking the door determines that it is locked and will remain that way unless someone unlocks it. This necessity to infer the actual consequences of an action from its expected outcomes is even more evident in the case of handwashing. Given that we have no reliable sensory evidence for the absence (or presence) of germs, we nevertheless infer that our hands are clean and disinfected from the mere fact that we have just washed them.

The consequences of an inability to rely on such "top-down" predictions is likely to include an exaggerated need to repeatedly verify that the goals of such actions have actually been attained. Furthermore, it can naturally lead to an experience of the world as unstable and unpredictable, thereby also explaining OCD patients' excessive preoccupation with catastrophic scenarios. This mechanistic perspective also allows linking such symptoms and experiences to patients' behavior in neurocognitive tasks requiring the integration of predictions and sensory evidence[3,5,6].

In addition to explaining how people in general integrate predictions and sensory information to plan and infer the consequences of their behavior, a Bayesian framework also offers insight into why people sometimes persist in doing what they are used to, regardless of consequences[4], and why OCD patients seem more prone to this[1,3]. The basic idea is that people rely on habits especially when they cannot reliably predict the outcomes of an action[4]. Thus, the repetitive, habitual nature of some compulsions (and of some behaviors that patients exhibit in neurocognitive tasks) might reflect a compensatory mechanism, allowing patients to avoid uncertainty and indecision[3].

This mechanistic, computational perspective allows us to integrate different, ostensibly inconsistent, explanations of OCD. Compulsions can be both attempts to reduce overestimated threat, and expressions of inflexible habits. Both proximal causes stem from the same core impairment (unreliable predictive models), and differentiating them becomes a question of context (e.g., some contexts encourage habit formation more than others), rather than a theoretical stance.

This perspective also has important treatment implications. In principle, it can allow clinicians to go beyond the classical question of what works for whom, to ask what works for whom, *for what*, and *when*. For example, a recent study suggested that selective serotonin reuptake inhibitors (SSRIs) reduce patients' difficulties in maintaining a predictive model of their actions and outcomes[7]. A computational model can explain how this helps reduce obsessions and compulsions. However, after sufficient time and repetitions, some compulsions may reach a tipping point rendering them so deeply ingrained that they are no longer maintained by this core impairment alone. Such compulsions may also be less sensitive to cognitive interventions that aspire to convince a patient that no harm will accrue if a compulsive act is not executed. Since habit-based and non-habit-based compulsions may co-occur within the same patient, such interventions might alleviate some symptoms but not others. A behavioral "outcome devaluation" test[1] can help with differentiation: for example, an urge to check a door persisting even when seeing that it is locked might imply a habit-based compulsion. This dynamic conceptualization of compulsions also highlights the importance of early interventions aimed at preventing the conversion of goal-directed compulsions into habitual compulsions. Overall, these considerations serve to highlight a need for more research examining how effective different therapeutic interventions are for compulsions arising out of different putative proximal causes.

A computational approach also has the benefit of allowing researchers to perform computer simulations that can examine how a manipulation of key factors might affect specific pathological dynamics; this, in turn, can suggest a focus for novel, targeted interventions. For example, stopping compulsions completely can be intolerable for many patients. Simulations can be used to examine whether nudging a patient to occasionally avoid a compulsion[3], or to perform it in a constantly changing manner, helps reduce the emergence of habitual dominance and improves behavioral flexibility. Similarly, the clinical practice of stressing the harm caused

by certain compulsive behaviors is also supported by simulations[3]. Thus, computational simulations can efficiently reveal effects and mechanisms for various potential interventions. These predictions can then be examined in controlled experimental environments (e.g., by introducing different micro-interventions in simple decision-making tasks) and subsequently converted into personalized *in vivo* interventions, paving the way for a precision psychiatry approach to the management of OCD.

More generally, a computational psychiatry perspective helps promote greater integration of the perspectives of clinicians and basic researchers, allowing the common clinical intuition that symptoms can change across time and context to be tested using well-specified, falsifiable models[2]. Ultimately, computational models aspire to advance diagnosis and treatment.

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Attentional biases in anxiety and depression: current status and clinical considerations

Cognitive models of anxiety and depression postulate that these conditions are marked by negative attentional biases, i.e. increased or exaggerated attention to disorder-relevant negative information. These biases are not regarded as mere correlates of these disorders, but are thought to play a major role in their development and maintenance.

Temperamental factors such as neuroticism are thought to bias cognitive processes (e.g., attention, interpretation and memory) in such a way that negative information is prioritized, which can heighten the risk for anxiety disorders[e.g.,1]. Likewise, depression is thought to be associated with difficulty to disengage attention from negative information and thoughts, which can play a key role in persistent negative thinking and sustained negative affect[e.g.,2]. Based on these ideas, procedures have been developed to assess attentional biases and their role in psychopathology and, more recently, to correct these biases.

The most commonly adopted assessment procedures are cognitive-experimental tasks in which behavioral data (e.g., reaction times) are used to infer whether participants preferentially allocate attention to negative information as compared to neutral or positive one. In the dot probe task, for instance, individuals are presented with two spatially separated stimuli for a brief period of time (500 ms). One of these stimuli is negative (a negative word or picture), while the other is neutral. After offset of these stimuli, a small probe immediately appears on the location previously occupied by the negative or neutral stimulus. The speed of detection of the probe allows to infer where individuals allocated attention (e.g., faster response to probes replacing negative stimuli indicates a bias towards those stimuli).

Meta-analytic evidence supports the association between attentional biases and levels of anxiety and depression[e.g.,3]. However, there are some inconsistencies in this empirical work[e.g.,4], in part due to the problematic psychometric properties of several frequently used behavioral tasks. This has led to the development of studies in which either eye-tracking data are collected (e.g., gaze fixation and duration) or psychophysiological markers of attention (e.g., event-related potentials) are examined. These measures allow to capture attention more reliably and can more easily evaluate attentional processes as they develop over time.

Despite this extensive research, there is still disagreement on the precise nature of attentional biases, as well as debate about whether the most frequently used measures adequately capture the dynamic nature of these biases (e.g., fluctuations between orienting towards and away from disorder-relevant information[5]). Progress has also been hampered by a predominant focus on visual attention to external stimuli, whereas many of the relevant stimuli for anxiety and depression may be internal (feelings and thoughts).

There is also a substantive literature on the mechanisms through which attentional biases could contribute to the development of anxiety and depression. For instance, in prospective studies, higher levels of attentional bias to negative information predicted increased stress reactivity, sustained negative mood, and higher levels of persistent negative thinking[2], which could in turn give rise to symptoms of anxiety and depression. As such, attentional bias could be a central driver of the Research Domain Criteria (RDoC) constructs of sustained threat and loss, which are of key relevance in anxiety and depression[6].

Debates about the causal impact of attentional biases on psychopathology have also been fueled by studies using attentional bias modification (ABM) procedures, that is, procedures designed

to correct attentional biases. The most frequently used procedure is a modified dot probe task where the task-relevant probe almost always follows the neutral information and rarely the negative one. In order to respond quickly to the probe, one thus has to learn to inhibit the tendency to orient to negative information. If this training generalizes to real life situations, it could in principle help reduce anxiety or depression. Despite initial encouraging findings, meta-analyses have shown that these procedures have only a limited and inconsistent impact on attentional biases and symptomatology[7].

In response to these disappointing findings, novel procedures are being developed that try to correct attentional biases in methodologically as well as conceptually different ways. In these approaches, participants are made aware of their attentional bias, for instance, by using gaze-contingent feedback. More specifically, individuals are presented with displays in which both positive and negative information is presented, such as scrambled sentences (e.g., "life/my/a/party/is/mess") that can be unscrambled in a positive ("my life is a party") or negative way ("my life is a mess"). Eye-tracking methodology allows to detect when individuals allocate attention disproportionally to negative words in the scrambled sentences, which is then signaled back to them. Hence, they are trained to regulate their attention in more adaptive ways.

In laboratory studies, these procedures are effective in modifying attentional bias, which subsequently reduces rumination and increases positive reappraisal. There is also initial evidence for the efficacy of online and app-based versions of these procedures, which is important for dissemination purposes[8]. Yet, rigorous evaluation of clinical efficacy is required before clinical application is warranted.

Computer-based ABM tasks are only one way of targeting attentional biases for clinical purposes. There are in fact a host of clinical interventions that may be effective by targeting disorder-relevant attentional processes. For instance, mindfulness-based cognitive therapy for depression and metacognitive therapy for anxiety and depression contain exercises to correct attentional biases for negative information. Moreover, some theories on the impact of antidepressant medication and neurostimulation suggest that reductions in negative processing biases could be among the key mechanisms of change in these treatments[9].

In summary, there is an increasing interest in clinical interventions targeting attentional biases in anxiety and depression, given their role in the maintenance and exacerbation of these conditions. Yet, further progress can be made in terms of conceptual precision and ecological validity. The term "attentional bias" is still used to refer to markedly different phenomena, such as shifting, maintaining or redirecting attention towards and/or away from disorder-related stimuli. These conceptual problems restrict our ability to precisely measure and train attentional biases and hampers the study of the underlying (neural) mechanisms.

Moreover, there can be substantial discrepancies in laboratory versus real-world assessment of social attention. Thus, if researchers wish to capture clinically relevant aspects of attentional biases and determine their influence on psychopathology, the step to the real word, using portable eye-trackers and virtual reality, seems crucial.

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Progress in understanding functional somatic symptoms and syndromes in light of the ICD-11 and DSM-5

It is over a decade since the new diagnosis of Somatic Symptom Disorder (SSD) was introduced in the DSM-5, and Bodily Distress Disorder was proposed for inclusion in the ICD-11. These new diagnoses were introduced to move away from the terms "somatoform" and "somatization", which were thought to be unhelpful to patients and doctors.

It was also thought necessary to define these disorders in a positive way rather than as "medically unexplained" symptoms, an unsatisfactory term as doctors frequently disagree about whether or not a symptom is explained by a medical disorder. The new classifications aimed to rely more on the presence of definite psychological and behavioral features.

The mode of working of the DSM-5 and ICD-11 relevant committees differed considerably. The DSM-5 group held monthly meetings by conference call and annual face-to-face meetings over a period of five years. This process was described as "not a dry scholarly debate but one marked by disputation and passion, yet thankfully also informed by data"[1]. By contrast, the ICD-11 group held very few formal meetings, with most work done by editing drafts of the diagnostic requirements.

Bodily Distress Disorder appeared in a descriptive form, whereas the DSM-5 developed specific criteria for SSD that were more readily operationalized. This may partly explain the remarkable research activity concerning SSD over the last decade. Empirical

work has found evidence of good reliability, validity and clinical utility of SSD, which were improvements on previous diagnoses[2]. No such body of literature has been published yet concerning Bodily Distress Disorder.

The prevalence of SSD in the general population has yet to be established. This requires a new measurement tool to detect the condition accurately in large surveys. A questionnaire has been developed to measure the cognitive, affective and behavioral aspects of the B criteria (excessive thoughts, feelings or behaviors related to somatic symptoms, with disproportionate thoughts about their seriousness; high health anxiety or excessive time and energy devoted to them). This work has shown, for example, that some people with SSD spend up to four hours per day concerned with somatic symptoms[3]. Interestingly, time dedicated to somatic symptoms proved to be an independent predictor of physical health-related quality of life and health care utilization. The other independent predictors were number of somatic symptoms, the other SSD B criteria, anxiety/depression, and age[3].

It was feared that SSD would be overinclusive, because criterion A requires only one distressing or disruptive somatic symptom. The evidence to date suggests otherwise; the B criteria limit the number of patients who are diagnosed with SSD. There is some evidence that the SSD criteria are associated with higher symptom severity and more impaired physical functioning than the corresponding DSM-IV criteria for somatoform disorders.

The B criteria chosen for the definition of SSD have been criticized as "not a reliable guide" by the EUROSOMA group, which has proposed a new classification of "functional somatic disorders" based solely on somatic symptoms and not at all on their cause[4]. These disorders are conceptualized as "occupying a neutral space within disease classifications, favouring neither somatic disease aetiology, nor mental disorder"[4]. This suggestion is supported by recent work showing that a high number of somatic symptoms should not be regarded primarily as a psychiatric problem; stressful life events, general medical illnesses and neuroticism are stronger predictors than psychiatric disorders[5].

The main difficulty with the "functional somatic disorders" classification is that it conflates two distinct, but overlapping, sets of disorders: one is characterized by a high number of troublesome somatic symptoms, and the other by a cluster of specific symptoms which fulfil the diagnostic criteria for one or more functional somatic syndromes (e.g., irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia). Most people with functional somatic syndromes do not have symptoms which fulfil the criteria for SSD. Even in severe irritable bowel syndrome, only about half of people report a high number of somatic symptoms, and they are those who benefit most from psychotherapy or antidepressants. About half of new onsets of self-reported fibromyalgia occur in participants who have a low somatic symptom count; those with and without multiple somatic symptoms appear to have different risk factors[6].

Recent research has emphasized differences in symptom perception in the different disorders. The findings are consistent with predictive coding theory, which highlights a decoupling of somatosensory input and the perception of body sensations[7]. For example, interoceptive inaccuracy appears to be a feature of the functional somatic syndromes, whereas a more liberal response bias has been observed in SSD[7]. Such research may lead to improved classifications in the future, and is important in developing specific treatments.

Several recent epidemiological studies suggest that the risk factors for functional somatic syndromes can be best understood by examining specific syndromes, or even subgroups of them, rather than lumping them together. Patients with fibromyalgia have been found to carry substantial genetic risks for pain syndromes and internalizing, autoimmune and sleep disorders; this pattern was quite different from that seen in chronic fatigue syndrome and irritable bowel syndrome[8]. Another study found that the predictors of self-reported irritable bowel syndrome, chronic fatigue syndrome and fibromyalgia were mostly syndrome-specific, with only four predictors common to all three syndromes[9]. In that study, psychiatric disorder was a predictor of irritable bowel syndrome, but not of the other two syndromes. Further analysis suggests that there is a subgroup of self-reported irritable bowel syndrome preceded by psychiatric disorder, which appears to have somewhat different risk factors from the remainder. Examining the mechanisms of symptom development in these subgroups may be more rewarding than doing so in the entire syndromes.

In conclusion, the new diagnostic entities introduced by the DSM-5 and ICD-11 (SSD and Bodily Distress Disorder) have successfully moved away from definitions based on "medically unexplained symptoms". The inclusion of specific psychological and behavioral features appears to be useful for both clinical and research purposes. The move from cross-sectional clinical studies to population-based cohort ones has been particularly informative concerning risk factors for this group of disorders, confirming that SSD and functional somatic syndromes are different sets of disorders, and that there are differences in risk factors both between and within functional somatic syndromes. Smaller psychological and physiological studies are becoming more productive now that they are focusing on specific patient groups. It is reasonable to expect that our knowledge of somatic symptoms and syndromes will develop greatly over the next decade.

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F. Creed has been a member of both the DSM-5 Somatic Symptoms Work Group and the ICD-11 Working Group on Bodily Distress Disorder. Additional references relevant to this paper can be found at www.interfacefhc.co.uk.

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Catatonia and its varieties: an update

Catatonia is being increasingly recognized in both clinical practice and ongoing research. Although originally described as a unique syndrome by Kahlbaum in 1874, it was associated with schizophrenia by Kraepelin and Bleuler in the early 1900s, and this nosological oversight was reflected in the first three editions of the DSM[1]. Fink and Taylor supported its separate categorization as a syndrome in 1991, prior to publication of the DSM-IV. They argued that catatonia occurs in many illnesses and is not simply a subtype of schizophrenia[1]. In the DSM-IV, "catatonia due to a general medical condition" was added, and "catatonic features" became a specifier for major depressive, manic and mixed episodes, although a "catatonic type" was still included for schizophrenia.

Further classification progress was made in the DSM-5, influenced by a group of scholars who advocated the recognition of catatonia as a unique syndrome that warranted a single defined class[2]. Although the manual does not establish catatonia as a truly independent class, it lists "catatonia associated with another mental disorder" (i.e., a neurodevelopmental, psychotic, bipolar, depressive or other mental disorder), as well as "catatonic disorder due to another medical condition" and "unspecified catatonia".

Significant progress has also been made with the recent transition from the ICD-10 to the ICD-11[3]. The ICD-10 coded catatonia as either "catatonia due to a known physiological condition" or "catatonic schizophrenia". The ICD-11 explicitly conceptualizes catatonia as an independent syndrome, with the subtypes of "catatonia associated with another mental disorder" (emphasizing that the syndrome can occur "especially" in the context of autism spectrum disorder), "catatonia induced by substances or medications", and "secondary catatonia syndrome" (when symptoms are judged to be the direct pathophysiological consequence of a medical condition). Specifiers for autonomic abnormalities in catatonia (including tachycardia or bradycardia, hypertension or hypotension, and hyperthermia or hypothermia) are also introduced.

Diagnosing catatonia can be challenging, as operational definitions for catatonic signs, although available, are not well known by clinicians. Additionally, there is debate in the research literature about the number of signs necessary to diagnose the condition[4]. Two widely utilized symptom lists are the one included in the DSM-5 and the Bush-Francis Catatonia Rating Scale (BFCRS).

The DSM-5 requires at least three out of a total of 12 signs (an incomplete list including stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerism, stereotypy, agitation, grimacing, echolalia and echopraxia). The manual does not define these signs well and lacks guidelines for severity. A study showed that, out of 232 cases of catatonia validated using a standardized rating scale and treatment response, only 73% met DSM-5 criteria[5].

The BFCRS contains 23 items, all operationally defined. It identifies a case by the presence of at least two of the first 14 items (immobility/stupor, mutism, staring, posturing/catalepsy, grimacing, echopraxia/echolalia, stereotypy, mannerism, stereotyped and meaningless repetition of words and phrases, rigidity, negativism, waxy flexibility, withdrawal, and excitement). The severity of catatonia is defined by rating all 23 items on a three-point scale. A standardized examination procedure is provided. The scale has been found to be highly reliable and sensitive to clinical change[6].

A problem with the DSM-5 is that the diagnosis of catatonia is disallowed in the presence of delirium. The empirical basis for this exclusion is not provided, and systematic reports of catatonia co-existing with delirium continue to emerge in the literature. Perhaps the best example is a study that prospectively assessed 136 critically ill patients[7], finding that 31% of them fulfilled criteria for both catatonia and delirium using DSM-5 criteria, while 43% had delirium alone. No treatment interventions were reported. This study also helped to address the dilemma of the number of signs necessary to diagnose catatonia: sensitivity and specificity were 91% after increasing the screening threshold to four signs rather than two on the BFCRS. This is an important diagnostic consideration, as there is potential for reduced specificity in such medically complex populations.

Delirious mania is a syndrome (unrecognized by the DSM and ICD systems) that adds to the nosological dilemma of co-existing delirium and catatonia. This is a syndrome of catatonic excitement, delirium and psychosis, first described in 1849 by Bell and repopularized by Fink in 1999[4]. There are no formal diagnostic criteria for this syndrome, as the literature on diagnosis and treatment is sparse. It may be worsened by antipsychotic medications and, despite the presence of delirium, benzodiazepines are effective and treatment with electroconvulsive therapy (ECT) typically results in resolution of the syndrome[4]. Consensus is lacking as to whether delirious mania is best classified as a feature of bipolar spectrum illness, a severe form of catatonia, or another clinical syndrome altogether.

There is further nosological confusion at the interface of neuroleptic malignant syndrome (NMS) and catatonia. Neither DSM nor ICD systems recognize NMS as a subtype or variant of catatonia; however, many catatonia scholars view NMS as another prototype of malignant catatonia, differing only in its precipitation by dopamine antagonists. NMS cases score on catatonia rating scales and respond to benzodiazepines and ECT[4]. Rather than being a distinct entity, it seems more likely that NMS lies on the same spectrum of illness as catatonia.

As alluded to in the ICD-11, catatonia is being increasingly recognized in people with autism spectrum disorder, with a recent meta-analysis reporting that the syndrome is present in 10.4% of these patients[8]. Catatonia is often undiagnosed in this population, as certain catatonic signs – such as repetitive speech and behaviors, purposeless agitation, self-injury, and stereotyped motor movements – are usually explained as inherent manifestations of autism itself. Indeed, the differential diagnosis may be difficult. Although there are no prospective studies, case reports and clinical reviews indicate that catatonia in these patients can be effectively treated with ECT[4].

Anti-N-methyl-d-aspartate (NMDA) receptor encephalitis is another syndrome where catatonia is being increasingly recog-

nized, which again presents nosological implications, as many of these patients are also delirious. In a recent prospective study of over 600 patients with the above diagnosis, catatonia was identified in 59% of the cases, and catatonia with delirium in 58% of them[9]. Proper identification of catatonia associated with this complex neuropsychiatric syndrome is important, as 12% of patients from this study developed NMS after administration of antipsychotic medication. ECT seems to be safe and effective in these patients, occasionally even without immune modulating treatment[9].

Despite these many varieties, catatonia remains a recognizable and treatable syndrome across the many psychiatric and medical conditions where it is seen. The nosological implications of the emerging research evidence are clear. This evidence suggests that catatonia lies on a spectrum of illness interfacing with mood disorder, psychotic disorder, delirium, neurological illness and other medical conditions. All psychiatrists should become familiar with the detection and treatment of this syndrome, as well as with its multiple varieties.

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The Hikikomori Diagnostic Evaluation (HiDE): a proposal for a structured assessment of pathological social withdrawal

Our social ties underpin the substance of our daily lives and exert a strong influence on our individual mental health and collective well-being. While these connections often imbue our lives with meaning and positive feelings, they can for some people go terribly awry. One of the more striking manifestations of this is called hikikomori.

Hikikomori has been an emerging topic of study in psychiatry since the 1990s, and is characterized by physical isolation in one's home, compounded by significant functional impairment or distress related to this isolation, and a sustained duration of symptoms for at least six months[1,2]. While patients with hikikomori require unique consideration, studies spanning the globe have revealed that comorbidity of hikikomori with various other psychiatric disorders, such as autism spectrum disorder and major depressive disorder, is common[1].

Having conducted research and provided clinical care for individuals with hikikomori for more than 25 years, our group has contributed significantly to the steady growth of popular interest[3] and scholarly study of this condition across countries and cultures. To help standardize what is meant by the term "hikikomori", we introduced an updated definition in 2020[4]. More recently, hikikomori has been included in the section "Culture and Psychiatric Diagnosis" of the DSM-5-TR[5], presumably because it was first described in Japan. While these have been steps in the right direction, we believe that there is now a pressing need for a transcultural tool which can help clinicians and researchers to understand and assess individuals for hikikomori. Here we introduce a structured diagnostic interview called Hikikomori Diagnostic Evaluation (HiDE), providing a practical guidance on how to collect information and assess individuals for this condition.

There is a long history of structured diagnostic interviews in psychiatry, which might lead one to wonder why one is particularly needed for hikikomori. The most obvious reason is that social withdrawal is scarcely considered within existing tools such as the Structured Clinical Interview for DSM-5 (SCID-5), the Composite International Diagnostic Interview (CIDI) and the Mini-International Neuropsychiatric Interview (MINI). Unless reliable and standardized tools are employed in studies purporting to examine hikikomori, advancement of this field of research will be stifled. Furthermore, we regularly encounter well-meaning individuals who seek to self-diagnose (or conversely, rule out) hikikomori by simply filling out the 25-item Hikikomori Questionnaire (HQ-25), a self-report measure of symptoms of hikikomori that we developed to support (but not replace) the process of clinical diagnosis of the condition[6], similarly to the current use of other patient-reported measures such as the Patient Health Questionnaire-9 (PHQ-9) or the Generalized Anxiety Disorder-7 (GAD-7).

The HiDE is a clinician-administered tool that requires 5 to 20 min to complete, depending on the number of positive responses (see supplementary information for the full structured diagnostic interview form). We originally developed it for use in our research. Over the past two years, applying it to over 100 patients seen in our academic medical center clinic in Japan, we have continued to refine it. To minimize recall bias, most items in the HiDE focus on symptomatology during the past month.

The first section of the tool addresses the essential features required to establish a diagnosis of hikikomori. Items quantify the frequency of outings, the chronicity of social withdrawal, and the distress and functional impairment related to this withdrawal. We have found that some patients with hikikomori overemphasize non-social, brief outings (e.g., putting out the trash) as evidence of going outside the home, and we therefore carefully characterize the purpose and duration of outings. We have also found patients who deny distress or functional impairment, though they acknowledge significant concern by family members or others about their social withdrawal. For this reason, we incorporate *concern by others* as evidence of distress or functional impairment.

The next section of the tool aims to obtain supplemental details that are not strictly required for the diagnosis but do provide helpful context to patients' social withdrawal. These items cover social participation, including work and school, personal activities and interests, attending appointments for medical care or counseling, and in-person versus other interactions. Specific attention is paid to whether these social interactions rise to the level of having actual *conversation*, since in our clinical experience some patients (incorrectly) insist that exchanging greetings qualifies for meaningful social interaction.

Clinicians or researchers who lack the time to administer the HiDE to all patients may consider using a *screening form* that we have also developed (see supplementary information). We suggest that the full HiDE be administered to patients who respond that: a) they spend out of their home one hour or less per day at least three days a week, and b) they personally feel bothered by this, or their family or others they know feel bothered by this. It would also be reasonable for patients with a positive screen to complete the HQ-25 in order to provide supporting information on the severity of their symptoms of hikikomori.

The HiDE has proven an indispensable tool for the structured assessment of pathological social withdrawal in our clinical practice and ongoing research. However, we fully recognize the need for further empirical study of the tool to determine its validity and implications beyond our practice. We hereby call upon our colleagues around the globe to help assess its reliability and validity in their practice settings, examine aspects of its implementation (e.g., feasibility, acceptability, appropriateness, and clinical utility), and help refine the tool as appropriate. A collective effort in this direction will help move hikikomori into the mainstream of diagnostic assessment in psychiatry.

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The performance of ChatGPT in generating answers to clinical questions in psychiatry: a two-layer assessment

ChatGPT (Chat Generative Pretrained Performer), an artificial intelligence (AI) chatbot, was launched in 2022. It is trained on a large language model (LLM) consisting of text derived from websites, Internet forums, digital books, and subtitles of videos. After registration on openai.com, users can prompt ChatGPT on chat.openai.com to give answers to any questions.

Research and clinical communities are currently signaling opportunities and pitfalls when relying on ChatGPT to write scientific papers or provide information about clinical issues[1]. Importantly, few resources are available to guide the uptake of ChatGPT in health care education, e.g., concerning its performance in answering relevant clinical questions that professionals see themselves confronted with in everyday practice. Indeed, many researchers and clinicians are worried about incorrect content and lack of nuanced information generated by AI[2,3]. On the other hand, given large inequities in medical education opportunities and in the availability of medical knowledge and full text research publications across the globe[4], particularly low- and middle-income countries (LMICs) may benefit from AI, as Internet access on a device is the only prerequisite for free-to-use chatbots.

In order to address the current knowledge gap about the reliability of ChatGPT in answering questions about clinical psychiatry, we examined the accuracy, completeness and nuance of its answers to a diverse set of questions, as well as the speed at which it generates answers compared to other sources of information.

Our approach was divided into two layers: first, an author-rated analysis of the accuracy, completeness and nuance of ChatGPT's answers; second, an analysis comparing the accuracy, completeness, nuance and speed between answers provided by respondents using ChatGPT and respondents using other information sources.

In the first layer, two raters conceived 40 questions (20 questions each) representing a diversity of topics related to epidemiology, diagnosis and treatment in psychiatry (see supplementary information). Each rater assessed the accuracy, completeness and nuance of the answers given by ChatGPT (version 3; Dec. 15, 2022 release) to the questions conceived by the other rater. ChatGPT's answers were rated on a scale from 0 to 2 (0, insufficient; 1, reasonable to good; 2, very good to perfect) for each of the quality criteria (accuracy, completeness and nuance). Average scores and standard deviations (SDs) were computed.

In the second layer, 85 psychiatrists and psychiatry residents working in institutes in The Netherlands, Germany and the US, not including the raters, were asked to participate in an online survey. Participants were randomized either to ChatGPT or to any other source of information they preferred, except for other chatbots. After randomization, each participant was requested to answer 10 of the same questions as in the first layer, with all questions having the same number of respondents in the two groups. Then, two raters blindly (for group, i.e. ChatGPT vs. other) assessed the accuracy, completeness and nuance of each answer. Squared weighted kappas were computed to assess inter-rater reliability between the blinded raters. Times recorded to answer the questions were compared between the ChatGPT and the other group.

All analyses were performed using R version 4.2.3. The average of all accuracy, completeness and nuance scores was used as the main outcome measure in all analyses and is referred to as composite score. Additional outcomes included individual scores of accuracy, completeness and nuance, as well as response speed. For the composite score, means and SDs were divided by 6 (maximum score) and multiplied by 10, to translate the original 0-6 range to a 0-10 scale. To obtain mean and SD values for individual accuracy, completeness and nuance scores, original values were divided by 2 (maximum score) and multiplied by 10, to translate the 0-2 range to 0-10. Mann-Whitney U test was used to compare scores between the two groups (ChatGPT vs. other). Total response times for all questions were compared, also using the Mann-Whitney U test. Finally, odds ratios (ORs) with 95% confidence intervals (CIs) were computed to assess the chance of having the maximum composite, accuracy, completeness and nuance scores when using ChatGPT vs. when not using it. Statistical significance of the ORs was assessed using a Fisher's exact test. The threshold for statistical significance was Bonferroni-corrected for multiple testing (dividing 0.05 by the number of tests performed).

In the first layer of the study, we found the following average 0-10 scale scores for ChatGPT: composite 8.0 (SD=2.8), accuracy 8.4 (SD=2.9), completeness 7.6 (SD=3.0), and nuance 8.1

(SD=3.3). In the answers to the 40 questions, we detected 4 erroneous information units (average of 0.1 per question).

In the second layer of the study, 38 respondents participated (25 psychiatrists and 13 residents). The average weighted kappa across raters was 0.65. For participants using ChatGPT, the average 0-10 scale scores were as follows: composite 7.6 (SD=2.9), accuracy 8.1 (SD=3.1), completeness 7.3 (SD=3.2), and nuance 7.2 (SD=3.5).

We detected significantly higher composite scores in ChatGPT users than in non-users (7.6 vs. 6.7, p=0.0016). ChatGPT users were on average 19% faster in completing the questionnaire than users of other sources, although this difference was non-significant. ChatGPT users had greater odds of maximum scores than non-ChatGPT users: ORs were 2.34 (composite), 1.96 (completeness) and 2.89 (nuance), with 95% CIs not encompassing 1, and corrected p values of 0.0037, 0.022, and 3.09×10^{-5}, respectively. The OR for accuracy was 1.33 (non-significant). ChatGPT answered questions about pharmacotherapy (particularly interactions and specific indications) less accurately than other questions, possibly due to the lack of reliable online information and reliance on textbooks for such questions.

In sum, in what we believe is the first study about the reliability of ChatGPT in answering questions about clinical psychiatry, we found that ChatGPT answered a 40-item test with high accuracy, completeness and nuance. Participants using ChatGPT performed better than those using other resources.

A strength of our study is that we employed a comprehensive, two-layered approach that goes beyond similar studies in other specialties by number of users, number of questions asked, numbers of outcomes, and the complementary use of two methods[5]. A limitation is the potential lack of power to detect significant differences in response speed between ChatGPT and non-ChatGPT users. In addition, improvement over time in the performance of ChatGPT may be examined using more longitudinal designs.

We conclude that ChatGPT scores well on accuracy, completeness, nuance and speed when generating answers to clinical questions in psychiatry. It may, therefore, represent a tool providing rapid access to reliable information about clinical psychiatry which is (at the time of writing) freely accessible to medical students, residents and physicians across the globe. It may thus also contribute to bridging gaps in health care education between richer countries and LMICs. However, we highlight the need for research into ethical issues when relying on medical knowledge derived from AI[6].

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Supplementary information on this study is available at https://github.com/flgerritse/ChatGPT_psychiatry/.

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The ICD-11 opens the door for overdue improved identification of depression in men

Population prevalence rates indicate that depression is twice as common in women as in men[1]. But, is this estimate an accurate reflection of men's mental health, or rather an artifact of diagnostic criteria favouring female-typical manifestations of depression[2]?

We and others would argue that the latter is, in fact, the case[2-6]. Indeed, results from decades of epidemiological and clinical studies point to the existence of a depressive syndrome with marked externalizing features (e.g., irritability, aggression, risk-taking and alcohol/substance misuse) which is particularly prevalent among males (especially younger ones) and likely related to an increased risk for suicide[2-6].

Yet, detecting and treating male depression is seriously complicated by the fact that the two major diagnostic manuals currently used in psychiatry, the DSM-5 and the ICD-10, do not consider these externalizing symptoms. Most importantly, the key role of irritability in male depression[4-6] is not reflected in the DSM-5 diagnostic criteria for major depression. According to these criteria, irritability can superseed depressed mood only in children and adolescents, but not in adults, which seems to be an arbitrary distinction.

In the recently introduced ICD-11[7], which is set to replace the ICD-10 over the course of the following years, both irritability and an absence of emotional experience ("emptiness") can replace depressed mood as the so-called affective component requirement for a depressive episode, irrespective of age[7]. This represents a substantial improvement with regard to the identification of depressive disorders in men who present with an externalizing phenotype[4].

Indeed, irritability is among the core symptoms included in male-specific inventories of depression[5,6], and likely underlies and relates to other symptoms that characterize male depression, such as

aggression, alcohol/substance misuse and risk-taking, all of which are also assessed in those inventories. Notably, according to one of these inventories, the Gotland Male Depression Rating Scale[5], feelings of emptiness are also a feature of male depression. Hence, by allowing for both irritability and absence of emotional experience (emptiness) to replace depressed mood in the symptom requirements for a depressive episode, a group of predominantly male individuals who did previously not meet criteria for depression will likely fulfill them with the introduction of the ICD-11[8].

While those with special interest in this topic will find the described change in the ICD-11 to be both substantial and important, this change may go unnoticed by most practitioners seeing the men who will benefit from being identified and treated. Therefore, information and training initiatives to raise awareness about this change and its implications for clinical practice will be required. Relatedly, health care systems will have to prepare for the increased demand for (specific) care caused by this diagnostic change.

Furthermore, the externalizing depression phenotype contributes to the help-seeking barrier experienced by men. To overcome this, screening initiatives may be needed within environments with predominant male representation and typical masculine values, such as military services, manual labor organizations, and sports clubs. There is a known relationship between the male depression phenotype and suicidality[3,4,8]. Assuming that the men affected can be treated successfully, these initiatives are likely to reduce the number of suicides among men. With approximately 700,000 suicides globally every year, the majority among men, even relatively minor improvements to detection rates could potentially save thousands of lives and improve the quality of even more lives.

The described changes to the ICD-11 will hopefully inspire the American Psychiatric Association (APA) to make analogue changes in the next edition of the DSM. Recently, the DSM-5-TR noted that "men with depression may be more likely than depressed women to report greater frequencies and intensities of maladaptive self-coping and problem-solving strategies, including alcohol or other drug misuse, risk taking, and poor impulse control"[9]. Thus, as the ICD-11 incorporates diagnostic changes in line with the evolving evidence base, it also seems that the door remains open for an (overdue) update of forthcoming DSM criteria for major depression.

Although supportive of the above changes, we are aware that they will not occur without associated challenges. Both the number of, and the symptom heterogeneity among, individuals meeting diagnostic criteria for depression will increase. This will, in turn, increase the need for treatment stratification by depressive subtypes. Relatedly, for individuals meeting depression criteria according to the ICD-11, but not according to the ICD-10 (or the DSM-IV and DSM-5), it can be argued that currently approved treatments may not be (equally) effective, as these individuals have not been adequately represented in the studies in which these treatments were tested. Therefore, changes to the diagnostic requirements for depression must spur research initiatives focusing on this specific group, including validation of the efficacy of available treatments.

In conclusion, we argue that the changes in the conceptualization of depression in the ICD-11 will open the door for an overdue improved identification of depression in men. If implemented wisely and integrated with appropriate information and screening initiatives, this may lead to reductions in the number of suicides and improved mental health among men. Hopefully, the benefits of this change to the diagnostic criteria for depression will be sufficiently evident to the APA for it to make analogue changes in the DSM system when due.

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Thoughts of self-harm in late adolescence as a risk indicator for mental disorders in early adulthood

Early intervention for youth mental disorders has received increasing attention in recent decades. For psychosis, this is exemplified by the clinical high-risk (CHR) paradigm, which has been highly successful in defining a subpopulation at enhanced risk. However, the subpopulation captured by CHR services represents a small proportion of all psychosis cases[1], highlighting the need for additional approaches to early detection of at-risk individuals.

Thoughts of self-harm are common in youth populations and are associated with several psychiatric outcomes. A recent Finnish registry study found that 18% of young people in Finland who presented to hospital with self-harm were diagnosed with a psychotic disorder by age 28[2], suggesting that hospital presentation with self-harm may be a system-based risk marker for psychosis. However, most individuals with self-injurious thoughts or behaviours do not present to hospital, and only a small proportion (4%) of future psychosis cases were captured in that study.

Expanding on this approach, we examined whether having thoughts of self-harm in late adolescence (irrespective of hospital

presentation) was a risk indicator for development of psychotic disorder, as well as depressive disorder and generalized anxiety disorder (GAD), in early adulthood. In exploratory secondary analyses, we also examined whether telling a general practitioner (GP) about thoughts of self-harm was a risk marker for these disorders.

The sample was drawn from the Avon Longitudinal Study of Parents and Children (ALSPAC)[3-5]. Pregnant women in Avon, UK with expected delivery dates between April 1, 1991 and December 31, 1992 were invited to participate. 14,541 pregnancies were enrolled (13,988 children alive at 1 year of age). When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who did not join originally. The total sample size for analyses using data collected after age 7 is 15,447 pregnancies (14,901 children alive at 1 year of age). Data were collected and managed using REDCap[6,7]. Ethical approval was obtained from ALSPAC Ethics and Law Committee and local research ethics committees. Informed consent for use of questionnaire and clinic data was obtained following recommendations of the above-mentioned Committee.

At age 17, participants completed the Clinical Interview Schedule Revised (CIS-R)[8]. This included a question asking whether the participant had thoughts of self-harm in the week prior to assessment. This was coded as a binary exposure variable (yes/no).

At age 24, participants completed the semi-structured Psychosis-Like Symptoms Interview (PLIKSi) to assess for psychotic experiences[9]. Psychotic disorder was defined as having at least one definite psychotic experience (not attributable to sleep or fever) which recurred at least once per month over the previous six months, and was associated with severe distress, or marked impairment of the participant's social or occupational functioning, or led him/her to seek professional help. We also examined outcomes of moderate/severe depressive disorder and GAD, defined according to the ICD-10, based on responses to the CIS-R completed at age 24.

At age 17, where participants reported thoughts of self-harm, they were also asked if they had spoken to their GP about their thoughts. This variable was coded with four categories: no thoughts of self-harm; told no-one; told someone other than their GP; told their GP.

Primary analyses used logistic regression to evaluate associations between thoughts of self-harm at age 17 and psychotic disorder, depressive disorder and GAD at age 24. Secondary analyses used logistic regression to evaluate associations between telling someone about thoughts of self-harm at age 17 and the same outcomes at age 24. For all analyses, "no thoughts of self-harm" was the reference category. For each analysis, participants who already met criteria for the relevant outcome at age 17 were excluded. In keeping with the predictive nature of this study, models were not adjusted for potential confounders. Analyses were performed using Stata 17 (StataCorp).

Participants assessed at age 17 and having data available on thoughts of self-harm were 4,563. Following exclusion of subjects who met outcomes criteria at age 17, the numbers of participants in each analytical sample were 2,591 for psychotic disorder; 2,622 for depressive disorder; and 2,628 for GAD. The numbers of participants who reported thoughts of self-harm at age 17 in each analytical sample were 267 (10.3%), 234 (8.9%), and 247 (9.4%), respectively (see also supplementary information).

Of the 18 participants who met criteria for psychotic disorder at age 24, 8 (44.4%) had reported thoughts of self-harm at age 17. The corresponding numbers were 34 of 157 (21.7%) among those with depressive disorder and 50 of 205 (24.4%) among those with GAD at age 24. On the other hand, the absolute risk of psychotic disorder by age 24 among those with thoughts of self-harm at age 17 was 3.0% (odds ratio, OR: 7.15, 95% CI: 2.80-18.27), while it was 14.5% for depressive disorder (OR: 3.19, 95% CI: 2.12-4.78); and 20.2% for GAD (OR: 3.64, 95% CI: 2.57-5.17).

Secondary analyses provided evidence of associations between telling a GP about thoughts of self-harm at age 17 and psychotic disorder (OR: 19.34, 95% CI: 5.11-73.24), depressive disorder (OR: 14.42, 95% CI: 6.20-33.53) and GAD (OR: 5.00, 95% CI: 2.20-11.35) at age 24 (see also supplementary information).

These results suggest that a large proportion of those who develop psychotic disorder (44.4%) may be captured through screening for thoughts of self-harm in late adolescence. On the other hand, of all those endorsing thoughts of self-harm at age 17, only 3% developed a psychotic disorder at age 24; 14.5% developed depressive disorder; and 20.2% developed GAD. The simplicity of this approach is that it is based on a single reported symptom. However, in isolation, its utility for defining an at-risk subgroup is limited, due to low positive predictive values. Nonetheless, the findings underscore the importance of appropriate long-term follow-up for young people with thoughts of self-harm in relation to distal mental health outcomes.

Secondary analyses indicated that presenting to a GP with thoughts of self-harm may be a particular indicator of risk for psychotic disorder in early adulthood, as well as for depressive disorder and GAD. This suggests a possible system-based approach for early detection in primary care. However, these results should be viewed as preliminary and interpreted with caution, given the small numbers of participants in the exposure category.

It is notable that effect estimates were highest for psychotic disorder compared to depressive disorder or GAD. However, confidence intervals overlapped, in keeping with the view that thoughts of self-harm in late adolescence may be a transdiagnostic risk marker.

One possible explanation of our findings is that endorsement of thoughts of self-harm in late adolescence captures young people exposed to known transdiagnostic risk factors for future mental disorders, such as bullying and other forms of childhood adversity, socio-economic disadvantage and substance use problems. However, the aims of this study were predictive rather than explanatory, and causal inferences cannot be drawn. If confirmed in further populations, these findings suggest novel opportunities for early detection of young people at risk of mental disorders in early adulthood.

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Labour market marginalization in children of persons with major psychiatric disorders: a Swedish national cohort study

Stable employment is consistently and strongly linked to key indicators of life quality and longevity, including physical and mental health, social integration, self-conception and self-fulfilment[1]. Involuntary exclusion, destabilization, or marginalization from the workforce has negative impacts across these same personal, social and economic domains. These effects may be further compounded by individual features (e.g., poor health, low education) or life stressors (e.g., low socioeconomic status, housing instability) associated with under- or un-employment[2].

Studies have highlighted a critical role for childhood adversity in influencing occupational trajectories. While the working definition has varied across investigations, there is a generally unified conception of "adversity" as encompassing both economic (e.g., low socioeconomic status) and emotional (e.g., chaotic environment) factors. In acknowledgement of its influence across these factors, it has been common for these definitions to include a measure of parental mental health.

Despite this, the relationship of parental mental illness to intergenerational occupational outcomes remains poorly delineated. Previous work has focused primarily on proxy-behaviors associated with parental psychiatric health (e.g., alcohol/drug abuse), and on early-life features associated with future work opportunity (e.g., personality formation, educational attainment)[3,4]. We are unaware of any work, to date, that has been powered to longitudinally dissect the relationship between established parental psychiatric diagnosis and objective occupational outcomes in offspring. Further, no work has considered the differential impact of parental diagnostic structure (e.g., mood vs. psychotic disorders; one vs. two affected parents) on these associations. Indeed, non-random mating is common in psychiatric populations[5,6], and likely to have a considerable impact on a range of offspring functional outcomes[7].

Here, we focused on the following questions: a) Is risk for receipt of disability pension and long-term unemployment increased among the offspring of persons with psychiatric disorders? b) Is this risk further increased if both biological parents have a psychiatric disorder? and c) What role do other individual (e.g., offspring's own mental health) and environmental (e.g., parent's level of education) factors have in this association? Ethical approval for this project was granted by the Regional Ethics Review Board in Stockholm, Sweden.

Leveraging linkage of key Swedish national registers, we assembled a cohort of 2,010,587 offspring (from 1,198,151 parental pairs) born in Sweden from January 1, 1973 to December 31, 1993. Using offspring of psychiatrically unaffected parents as a reference (selected in an "uncleaned" manner[8]), we compared the risks of receiving disability pension and long-term unemployment in offspring of single-affected parents (mother or father) and dual-affected parents (both mother and father) with any of the following eleven major psychiatric disorders: attention deficit/hyperactivity disorder, autism spectrum disorder, Tourette's/chronic tic disorder, substance use disorders, generalized anxiety disorder, major depressive disorder, agoraphobia, social phobia, obsessive-compulsive disorder, schizophrenia and bipolar disorder.

The disorders were then clustered into four operational groupings: neurodevelopmental disorders, substance use disorders, emotional disorders, and psychotic disorders (including schizophrenia and bipolar disorder). Within each disorder group, an exposure variable was created to distinguish dual-affected from single-affected pairs: for example, "dual-affected with psychotic disorders" indicates a pair in which both parents have schizophrenia or bipolar disorder (in any combination), while "single-affected with psychotic disorders" indicates a pair in which only one parent has a diagnosis within this disorder group.

For offspring outcomes, we estimated the incidence risk ratio (IRR) for disability pension and long-term unemployment across exposure groups. Several covariates were integrated in our models, including key demographic characteristics (base model), with further adjustment for offspring somatic disorders and highest educational level. A fully-adjusted model further controlled for parent's highest educational level and his/her receipt of disability pension/long-term unemployment. Most covariates were defined over the full study period (e.g., full length of follow-up), with a minority adapted to capture impacts at salient timepoints. In sensitivity analyses, we explored the impact of offspring's own psychiatric health by excluding offspring with any of the above-mentioned disorders. We also re-ran the main analyses using a "cleaned" comparison group, in which neither parent had any of the eleven relevant lifetime psychiatric diagnoses.

For each outcome, we fitted modified Poisson regression models with robust standard errors[9], using person-years as the offset term to address different follow-up times among participants, and clustering by family identification number to account for non-independence of repeated observations within families.

Compared to offspring of unaffected parents, individuals with one affected parent had a significantly increased risk of disability pension receipt, when accounting for demographic characteristics (IRR=1.88, 95% CI: 1.84-1.91, p<0.001; in 332,357 offspring of single-affected pairs vs. 1,641,244 offspring of unaffected pairs). The risk was doubled in offspring of dual-affected parents (IRR=2.84, 95% CI: 2.73-2.95, p<0.001; in 36,986 offspring of dual-affected pairs vs. 1,973,601 offspring of unaffected pairs). While all parental psychiatric disorders showed a significant association with offspring disability pension risk, the highest risk was observed in the offspring of parents affected with neurodevelopmental disorders (single-affected: IRR=3.36, 95% CI: 3.20-3.54, p<0.001; dual-affected: IRR=7.25, 95% CI: 5.68-9.26, p<0.001) and psychotic disorders (single-affected: IRR=2.11, 95% CI: 2.03-2.19, p<0.001; dual-affected: IRR=5.31, 95% CI: 4.33-6.52, p<0.001). Results were robust to further adjustment for offspring somatic disorders and education (single-affected with any disorders: IRR=1.73, 95% CI: 1.69-1.76, p<0.001; dual-affected with any disorders: IRR=2.38, 95% CI: 2.28-2.47, p<0.001) and for parental socioeconomic characteristics (IRR=1.40, 95% CI: 1.38-1.43, p<0.001; and IRR=1.60, 95% CI: 1.54-1.67, p<0.001, respectively). Results by parental disorder groups were also robust across models.

Offspring with one affected parent had a significantly increased risk of unemployment, compared to offspring of unaffected parents (IRR=1.46, 95% CI: 1.45-1.48, p<0.001). This risk was markedly raised among offspring of dual-affected pairs (IRR=1.92, 95% CI: 1.87-1.96, p<0.001). Offspring of parents single- and dual-affected by neurodevelopmental and substance use disorders showed the highest unemployment burden across both the base model and the model controlling for offspring somatic disorders and education. The fully-adjusted model resulted in significant, but attenuated, risks among offspring: IRR=1.21, 95% CI: 1.20-1.23, p<0.001 (single-affected with any disorders) and IRR=1.34, 95% CI: 1.30-1.38, p<0.001 (dual-affected with any disorders). Corresponding results by parental disorder groups were also attenuated, though the majority of them retained significance.

Repetition of analyses in a sub-cohort of offspring free from the diagnosis of interest produced comparable results for both outcomes. Likewise, the use of the "cleaned" comparison group in a sensitivity analysis did not alter the results.

Taken together, these results indicate a consistent and profound association between psychiatric history of parents and labour market marginalization in their offspring, which is particularly striking in dual-affected families. Though our primary finding is one of global, relative occupational adversity among the children of all affected parents, variation was further observed by parental diagnosis, with children of families impacted by neurodevelopmental, psychotic and substance use disorders having increased risk for adverse occupational outcomes.

Further work will be needed to gain nuanced insight into the mechanisms impeding labour market prospects in these populations, particularly given the limited impact of suspected determinant factors (e.g., child's own psychiatric health) on this association. Our findings suggest that such work should continue to extend consideration of differential risk dynamics by parent diagnosis and, particularly, parental diagnostic structure (e.g., single- vs. dual-affected families), in order to identify subgroups with particular need for preventive and early intervention strategies aimed to increase their chances of labour market participation.

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Is it possible to differentiate ICD-11 complex PTSD from symptoms of borderline personality disorder?

The introduction of complex post-traumatic stress disorder (CPTSD) and the revised descriptions of personality disorders in the ICD-11[1] is being accompanied by some uncertainty in clinical practice regarding the differentiation between the diagnostic profiles of CPTSD and borderline personality disorder (BPD).

The CPTSD diagnosis requires "exposure to an event or series of events of an extremely threatening or horrific nature, most commonly prolonged or repetitive events from which escape is difficult or impossible"[1]. Such events include, but are not limited to, torture, slavery, genocide campaigns and other forms of

organized violence, prolonged domestic violence, and repeated childhood sexual or physical abuse. At a symptom level, CPTSD includes the core PTSD symptoms of re-experiencing the traumatic event in the present, avoidance of traumatic reminders, and persistent perception of heightened current threat, along with the three symptom clusters of pervasive problems in affect regulation, negative self-concept, and relationship difficulties.

BPD has been reformulated in the ICD-11, due to the introduction of a fundamentally different approach to the classification of personality disorders[1]. Instead of diagnosing these disorders according to categorical types, the ICD-11 now requires impairments of the self (e.g., identity, self-worth, accuracy of self-view, self-direction) and interpersonal functioning as core features. A borderline pattern qualifier has been included, based on the nine DSM-5 diagnostic criteria for BPD, where the salient diagnostic features are instability in sense of self, relationships and affects, and the marked presence of impulsivity (e.g., unsafe sex, excessive drinking, reckless driving, uncontrollable eating). These diagnostic features represent some problems in the same general symptom domains as CPTSD, i.e. those related to affect dysregulation, identity, and relational capacities.

For several decades, the overlap between symptoms of BPD and various forms of CPTSD has been a subject of debate. There have been several studies exploring the association between these conditions using disorder-specific measures. These studies have been conducted in general population samples as well as in clinical samples of traumatized individuals, and they include factor analysis, latent class analysis and network analysis designs. All these studies concluded that there is a group of individuals who fulfil criteria for both disorders, but CPTSD and BPD were generally found to be distinguishable at the symptom and individual level.

There are several differences in the diagnostic criteria for the two disorders that are clinically informative in this respect.

While exposure to traumatic life events can precipitate both conditions, a history of trauma is not required for a diagnosis of BPD, while it is for CPTSD. Nevertheless, it is also important to highlight that a significant number of people with BPD report exposure to traumatic life events such as sexual abuse[2].

Diagnostic items related to affect dysregulation are often equally endorsed across the disorders, and in network analyses these symptoms appear to be common in both CPTSD and BPD[3]. However, BPD is associated with high rates of impulsivity and suicidal and self-injurious behaviours, while in CPTSD these characteristics may be present, but do not occur as frequently as other CPTSD symptoms, nor as often as in BPD[4]. Indeed, addressing suicidal and self-injurious behaviours has been viewed as the defining concern and primary treatment target in BPD.

Our clinical observations of people with CPTSD suggest that difficulties in affect regulation are ego-dystonic, stressor-specific and variable over time. In BPD, affect dysregulation and unstable mood seem to be ego-syntonic and persistent over time[5]. In BPD, self-concept difficulties reflect an unstable sense of self which includes changing goals and beliefs, whereas individuals with CPTSD have a consistent and stable negative sense of self. While it is frequently the case that individuals with CPTSD and BPD will both report feelings of low self-esteem, the additional presence of a changing view of self supports a BPD diagnosis.

Relational difficulties in BPD are characterized by unstable or volatile patterns of interactions, whereas in CPTSD they are defined by consistent difficulties in trusting others and avoidance of intimacy or closeness.

An important consideration in diagnosis is to avoid over-pathologizing the individual. For example, a symptom that is common to both disorders, such as emotional volatility, should be considered as part of each disorder when summing the totality of symptoms to determine whether the person meets criteria for a specific disorder. However, once a primary diagnosis has been made, the symptom should not be counted twice. The symptom should be counted once and designated to the diagnosis that been identified as primary, applying a "hierarchical" approach to diagnosis.

The clinical utility of formulating two diagnoses is primarily to guide treatment decisions and provide an intervention that optimizes outcomes by addressing the most impairing features associated with each disorder. Usually, BPD is likely the more severe disorder, with the greater impairment due to the presence of suicidality and self-injurious behaviours. We recommend that future research survey practitioners about what they find are the benefits and drawbacks of the current classification of these two conditions. In addition, the development of reliable and valid clinical interviews will further enable diagnostic accuracy.

There is a need to develop tailored treatments informed by the phenomenology and severity of the two conditions. A number of treatments with proven efficacy for PTSD, such as cognitive behavioural therapy or eye movement desensitization and reprocessing, might also be helpful for CPTSD[6]. It is also worth noting that dialectical behavioural therapy, a treatment that has been extensively used for people with BPD, has been modified and found effective for PTSD and comorbid BPD symptoms, BPD with comorbid PTSD, and BPD alone[7].

A trauma-informed modular approach has also been suggested for the treatment of CPTSD[8]. The modular approach proposes that symptom clusters of CPTSD should be targeted using a formulation-based model and based on a client's treatment goals and the severity of his/her symptoms. Modular approaches, such as skills training in affective and interpersonal regulation narrative therapy, have been found useful for those who have experienced PTSD related to childhood trauma[9] and have been adapted for CPTSD.

For those who meet the criteria for both conditions, a trauma-informed approach might still be the best treatment option. There is, however, an urgent need to explore the effectiveness of existing and new interventions for ICD-11 CPTSD, and for the new construct of personality disorder (including the new pattern qualifier for BPD).

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Promoting schizophrenia research in Europe: the contribution of the European Group for Research in Schizophrenia

The European Group for Research in Schizophrenia (EGRIS) was founded in the late 1990s to develop strategies for the promotion and coordination of schizophrenia research in Europe.

The founding members were W. Fleischhacker (Austria), J. Peuskens (Belgium), D. Naber (Germany), I. Bitter (Hungary), J. Gerlach (Denmark), J.-J. Lopez-Ibor (Spain), S. Galderisi (Italy), J. Libiger (Czech Republic), M. Paes de Sousa (Portugal) and T. Burns (UK). W. Fleischhacker was the chairperson of the group, and J. Peuskens the co-chair.

The primary aim of the group was to encourage independent collaboration in schizophrenia research across Europe, by identifying research gaps, exploring innovative approaches, and favoring "technology transfer" across centers joining the research projects designed by the group.

The group met two times per year. Open as well as in-depth scientific discussions, together with a friendly and pleasant atmosphere, characterized the meetings. The group discussed drafts of research protocols prepared and presented by one or more members, sometimes enriching them or, more often, after an in-depth discussion, either tabling them until the next meeting, with some suggestions for revision, or rejecting them.

Of the many protocols drafted and discussed during the meetings, very few survived the criticisms of the group members and were proposed to external bodies for funding. The first very successful initiative was the European First Episode Schizophrenia Trial (EUFEST), the largest randomized trial comparing the clinical effectiveness of second- vs. first-generation (haloperidol below 5 mg/day) antipsychotics in first-episode schizophrenia-spectrum patients[1].

This has been the first trial in a relatively unselected group of first-episode schizophrenia patients performed across a large number of European countries. Its focus was effectiveness of antipsychotic treatment, measured as retention of patients on treatment (non-retention can be the result of insufficient clinical efficacy and/or poor tolerability/acceptability). The primary outcome was the 1-year retention rate in first-episode patients treated with haloperidol, olanzapine, quetiapine, amisulpride or ziprasidone. Secondary objectives included the comparison of changes in various dimensions of psychopathology, social needs and quality of life, substance abuse and cognitive functions in response to treatment with the above antipsychotics, as well as the assessment of their side effects. The main paper was published in the Lancet[2]. The group discussed many proposals for secondary analyses and, for the approved ones, invited contributions by other group members, in addition to those who had presented the proposal.

The large database generated by the study resulted in over 40 papers, many by the EUFEST study group, and some by researchers who had not participated in the study, but later had shown interest in the study findings and conducted *post-hoc* analyses.

Through the EUFEST study, we learnt a lot about challenges and opportunities in running multicenter, multinational trials, and the EGRIS grew in terms of cohesion, skills and enthusiasm.

Over time, the composition of the group changed, with the admission of new members (based on the recommendations of existing ones), adopting a one country/one member policy. By 2009, for instance, the group had included five more members/countries, i.e., S. Dollfus (France), M. Davidson (Israel), R. Kahn (The Netherlands), W. Rössler (Switzerland) and J. Rybakowski (Poland); in addition, B. Glenthoj (Denmark) had joined the group, as J. Gerlach had retired.

While searching for innovative ideas, drafting new research protocols, and applying for funds, the group joined the European College of Neuropsychopharmacology (ECNP) Network Initiative, and created the ECNP Schizophrenia Network. However, after a couple of years, the EGRIS decided to return to its previous autonomy and working style. Part of the group also remained in the ECNP Schizophrenia Network, and, under my leadership, the Network included new members, who had never been EGRIS members, and focused on research on negative symptoms of schizophrenia[3,4].

In 2012, the EGRIS approved another large multicenter, multinational study, the European Long-acting Antipsychotics in Schizophrenia Trial (EULAST). The group moved from the evidence that discontinuation of antipsychotic medication is by far the most important reason for relapse, and concluded that a study comparing long-acting injectable antipsychotic drugs (LAIs) to corresponding oral formulations could shed some light on the ongoing discussion concerning the effectiveness of different formulations in reducing relapses[5].

It took a few years to design the study, identify participating centers and find the resources to conduct the study. Fifty psychiatric centers located in 15 European countries and Israel joined this large, pragmatic, open label, randomized clinical trial comparing LAIs with their oral equivalents in schizophrenia patients in the early phase of their illness. At the beginning of 2015, the study centers started the recruitment of patients, which ended in December 2018, with the final study visit taking place in August 2020. The paper reporting the study findings has been recently published[6].

The EGRIS has recently renewed its composition and leadership. I will lead the group in the role of chair, P. Falkai (Germany) in the role of co-chair; M. Weiser (Israel) will be the group treasurer; and I. Winter (The Netherlands) will support the group in the role of secretary. The other group members are C. Arango (Spain), I. Bitter (Hungary), P. Dazzan (UK), S. Dollfus (France), B. Glenthoj (Denmark), A. Hofer (Austria), P. Mohr (Czech Republic), N. Stefanis (Greece), J. Tiihonen (Sweden) and R. van Winkel (Belgium).

In its current composition, the group will further pursue the mission of identifying and targeting gaps in European research in schizophrenia, applying innovative approaches, and favoring translation of research findings into clinical practice across Europe.

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Improving mental health through fostering healthy lifestyles in young people: one of the targets in the WPA Action Plan 2023-2026

The life-course approach to health shows how early exposure to physical, environmental and psychosocial factors shapes future health and mental health. In particular, when this exposure occurs during critical life phases such as adolescence, it may cause shifts in health trajectories that become difficult to restore[1,2].

Future health and mental health patterns are established during youth. More than 80% of tobacco smokers start smoking between ages 14 and 25. In many countries, alcohol use starts before 15 years of age, with 13.6% of 15-19-year-olds reporting heavy episodic drinking. Heavy alcohol use during late adolescence tends to persist in adulthood and is associated with alcohol dependence. The onset of cannabis use often occurs around 18-19 years of age, and initiation at a younger age increases the risk to develop cannabis and other substance use disorders. Similarly, the peak age of onset of mental disorders is around 14 years[3].

Health and mental health are strictly interconnected. In young people, engaging in health risk behaviors – such as smoking, excessive alcohol consumption, risky sexual behaviors, as well as reduced sleep, sedentariness, and high media use – is significantly associated with high depression and anxiety symptoms as well as with suicidal ideation[4].

The WPA Planning Committee 2020-2023 strongly believes that there is "no health without mental health". We are convinced that we cannot help people achieve good mental health without improving their general health. Consequently, we wish to increase the contribution of the WPA to the achievement of the third United Nations (UN) Sustainable Development Goal: "Ensure healthy lives and promote well-being for all at all ages". Early health promotion and prevention are important to achieve good results during the life course. We recognize that physical and mental health go hand in hand, and are both influenced by early life experiences. Thus, focusing efforts and resources on prevention becomes the most effective way to reduce the burden of mental disorders[3].

More than 248 million adolescents live with a mental disorder, corresponding to 14% of the global adolescent population. Anxiety disorders (4.31%), depressive disorders (2.61%), and attention-deficit/hyperactivity disorder (2.39%) are the most common diagnoses in this age group. Indeed, self-harm, depressive disorders and anxiety disorders are respectively the third, fourth and sixth leading causes of disability among youth, while suicide represents the fourth leading cause of death in 15-19-year-olds[5]. The UN International Children's Emergency Fund (UNICEF) estimated that the annual loss in human capital due to children's mental health conditions is equivalent to US$ 340.2 billion, with an additional US$ 47 billion loss caused by intentional self-harm. Besides the huge burden posed by diagnosed mental disorders, around 30% of the youth population experience sub-threshold anxiety and depressive symptoms which are associated with functional impairment and suicidality.

Geopolitical and ecological crises highly impact youth mental health. The COVID-19 pandemic likely doubled the prevalence of youth mental health difficulties. Globally, 1 in 4 youth experienced clinically elevated depression symptoms, and 1 in 5 experienced clinically elevated anxiety symptoms, with girls and older adolescents being the most affected[6]. Furthermore, when people were adjusting to the new normality related to the ending phase of the pandemic, the escalation of the Russian-Ukrainian war emerged as another source of distress. One year after the Russian invasion, the UNICEF estimated that 1.5 million Ukrainian children are at risk of depression, anxiety, post-traumatic stress disorder, and other mental health issues.

Finally, natural disasters, noise and air pollution, overcrowding and poor housing conditions, migration, food insecurity, economic recession, and climate change can have major negative impacts on children and adolescents' emotions and mental health. It has been hypothesized that the risk of anxiety disorders and depression is reduced by the absence of noise and the restorative qualities of green spaces, since they promote mindfulness and interrupt rumination[7]. Furthermore, engaging in this and other positive leisure activities may reduce screen time and thus prevent its negative impact on mental health[8].

In order to decrease the burden of mental health in the youth, we need to address the problem at both the system and individual level. Evidence-based treatments for psychiatric disorders in children and adolescents do exist. Psychotherapies and pharmacotherapies, and their combination, are known to improve depressive and anxiety symptoms. Nevertheless, there are considerable gaps in the availability of mental health policies, resources and services both in low- and high-income countries. On average, countries devote globally only 2% of their health budget to mental health, and only 7.1% of mental health research expenditures are allocated to prevention. Additionally, limited mental health knowledge, perceived social stigma, and lack of trust in mental health professionals prevent young people and their parents from seeking help, further reducing access to services.

In this scenario, schools become essential settings for providing mental health interventions. Thanks to the role that schools play in the life of young people, barriers to accessing services – such as time, location, perceived stigma, and lack of trust – may be overcome. For every US dollar invested in school-based interventions that address anxiety, depression and suicide, a return of US$ 21.5 over the course of 80 years is expected[9].

Universally delivered psychosocial interventions, especially those based on interpersonal skills training, emotional regulation, alcohol, drug and lifestyle education, can improve youth mental health and reduce risky behaviors. Randomized controlled trials showed that, compared to control groups, school-based interventions have a significant positive effect on symptoms of depression and anxiety, suicide attempts, and suicidal ideation[10,11].

Interventions aimed to promote healthy lifestyles also improve youth mental well-being. Sleep is pivotal to youth mental health, cognitive functioning, and school performance. Nevertheless, up to 70% of youth report less than eight hours of sleep per night. School-based sleep education programs were found to significantly prolong weekday and weekend total sleep time and improve mood, and delayed school starting times were found to extend sleep duration and reduce daytime sleepiness[12,13].

Meeting the recommended level of physical activity is also crucial for achieving good health and mental health. Interventions aimed at enhancing levels of physical activity were found to reduce depression, anxiety and stress, while promoting resilience, well-being and self-esteem in young people[14]. The available evidence also supports a positive association between a healthy diet and better mental health in youth, although further studies are needed.

A limitation of universal youth mental health interventions is that their effects tend to fade over time. Positive mental health outcomes can be sustained only when the acquired awareness, coping strategies, lifestyle and social skills are internalized and become part of everyday life. Therefore, the WPA Action Plan 2023-2026 will be dedicated to promoting a life-course and holistic approach to improving mental health and preventing mental disorders by fostering the adoption and preservation of healthy lifestyle practices from an early age, spanning households, educational institutions, and health care facilities[15]. Previous WPA efforts in this area[16,17] are recognized, but the focus on fostering healthy lifestyles, complementary to existing treatments, will become an absolute priority in the new triennium.

Healthy lifestyles are an excellent addition to existing treatments for psychiatric disorders. They increase self-governance, decision latitude, and self-confidence. When they are performed in a group, the sense of loneliness diminishes and belongingness increases. Educational materials in the form of booklets and videos, currently in the production phase, will be disseminated, and their effectiveness will be investigated by the WPA[18]. Achieving this objective necessitates a multi-stakeholder partnerships involving families, education and social services, mental health agencies, and the research community.

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The WPA Expert International Advisory Panel for Early Intervention in Psychosis in Low- and Middle-Income Countries: an update on recent relevant activities

In 2019, the WPA set up an Expert International Advisory Panel for Early Intervention in Psychosis (EIP) in Low- and Middle-Income Countries (LMICs), as part of a presidential initiative[1] linked to the WPA Action Plan 2020-2023[2-4]. Here we present an update on recent activities related to that initiative.

The WPA has promoted several symposia and keynote/plenary lectures at international conferences on EIP models in LMICs, their clinical effectiveness, cultural contextualization, and implementation challenges. These conferences included the 21st World Congress of Psychiatry (virtual, October 2021); the WPA/UK National Institute for Health and Care Research (NIHR) Webinar on EIP in LMICs (December 2021); the WPA Thematic Conference "Public Health and Associated Opportunities" (Lahore, Pakistan, March 2022); the 22nd World Congress of Psychiatry (Bangkok, August 2022); and the WPA Thematic Conference "Early Intervention across the Lifespan" (Athens, June 2022).

Some recent examples (illustrative, not an exhaustive list) of EIP programmes in LMICs include the Schizophrenia Research Foundation (SCARF)'s dedicated EIP service in Chennai, India[5], developed in collaboration with the Prevention and Early Intervention Program for Psychosis in Montreal[6]; the University of Chile High-risk Intervention Program for Ultra-High-Risk Youth[7]; and a pilot EIP service in Malawi[8].

Understanding that inadequate mental health workforce, fragmented health care systems and scarcity of research and implementation capacity are significant barriers to introducing such programmes in LMICs, the Warwick-India-Canada (WIC) network was formed with a shared strategic vision to reduce the burden of psychotic disorders

in resource-poor settings[9]. This network brought together knowledge and expertise of four internationally recognized institutions: the University of Warwick, UK; the McGill University, Canada; the All India Institute of Medical Sciences (AIIMS), New Delhi, India; and the SCARF, Chennai, India. The largest cohort of first-episode psychosis cases in LMIC settings was recruited and followed through the WIC programme at SCARF and AIIMS. A comprehensive package of biopsychosocial care, ready to use in any LMIC setting, has been developed.

The integration of faith/traditional/indigenous healing with mental health services in LMICs appears a promising way for community detection of untreated psychosis, but there are significant challenges in such collaborations. Trusting relationships are difficult to build, ongoing training and supervision beyond the project timelines are hard to deliver, and sustainability is more easily promised than achieved. The COllaborative Shared care to IMprove Psychosis Outcome (COSIMPO) trial[10] assessed the effectiveness of a collaborative shared care (CSC) for psychosis delivered by traditional healers and primary health care providers, compared to enhanced care-as-usual, in Ghana and Nigeria. Participants randomized to the CSC model had significantly lower symptom scores at 6-month follow-up. CSC led to greater reductions in overall care costs. Such models offer the prospect of scaling up across LMICs. A new programme of such collaborations is under way in Nigeria and Bangladesh.

Digital technology can play a vital role in overcoming resource and infrastructure limitations in LMICs[11]. The WIC early psychosis study[9] co-designed the *Saksham* app for people with schizophrenia and their caregivers. The app is ready for public roll out in India. Telepsychiatry offers another innovative approach to reaching individuals in rural regions who may otherwise not have access to treatment. Several models of telepsychiatry have been launched in India: the SCARF STEP tele-psychiatry model[12]; *the psychiatristonweb* application[13]; the *Ganiyari* model; and the National Institute of Mental Health and Neurosciences (NIMHANS) hub-and-spoke model[14]. Emerging evidence suggests that these models improve medication and appointment adherence, and lead to reductions in relapses and fewer hospitalizations.

Our Panel will submit a detailed action plan with recommendations to the forthcoming WPA General Assembly, which will include the following principles:

- Early intervention should be the target of a WPA Scientific Section, to advance the field, facilitate sharing of expert contributions on the rapidly changing landscape of EIP in LMICs, and provide education and support for clinicians.
- In LMICs, EIP services should not focus only on first episodes, but rather provide good clinical care for early and established untreated or inadequately treated psychosis.
- Shared care models such as COSIMPO offer promise for scaling up EIP programmes in LMICs by drawing on local resources.
- Early intervention models in LMICs need to be co-designed with those with lived experience either as patients or carers.
- A public health approach is needed to increase mental health literacy and reduce stigma, in order to facilitate early access to care.
- There is a need for capacity building programmes at the clinical, research and implementation level.
- There is a need for regional and national meetings with stakeholder input to develop a network of collaboration that facilitates development and implementation of EIP.
- Telepsychiatry and leveraging digital approaches can help increase reach of services to individuals in rural areas and provide a more cost-effective approach.

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The World Psychiatry Exchange Program: expanding the world of early career psychiatrists

Global development seems to have openness to the world as a prerequisite. In psychiatry, this intercultural dialogue is particularly relevant, considering the diversity in illness manifestations and classifications[1] and the growing number of diasporas around the world[2]. Although early career psychiatrists have been calling for overseas training to acquire global health competencies, accessing such opportunities remains a challenge for many.

With this in mind, the WPA Section of Early Career Psychiatrists has proposed, in line with the WPA Action Plan 2020-2023[3-5], the organization of an exciting new ini-

tiative: the World Psychiatry Exchange Program[6]. This is an innovative project as there was not previously any worldwide exchange program for psychiatrists. The concept is straightforward: to offer early career psychiatrists worldwide free exchange programs overseas. At an early stage of their career, participants get valuable exposure to different mental health systems, illness manifestations and treatment options, and ways of working in mental health care. Participants are able to observe in clinics and attend educational meetings, teaching sessions or research activities, according to the plan offered by the host institution, and also have the opportunity to socialize with colleagues from another country. Hosts gain insights and perspectives from enthusiastic early career psychiatrists, eager to learn about different cultures and ways of practising psychiatry[7].

In October 2021, the Section opened the first call for applications. Further to the traveling restrictions imposed by the COVID-19 pandemic, we offered both options of face-to-face and remote exchanges. We started the first edition by announcing placements in different parts of the world, including Belgium, Brazil, Croatia, Iran, New Zealand, Tunisia and the UK. We received 49 applications from early career psychiatrists (age 25-44) based in Africa (N=28, 57%), Asia (N=11, 23%), Europe (N=9, 18%) and America (N=1, 2%), of which 61% were psychiatry trainees and 39% psychiatrists who had become specialists since no more than seven years.

A total of 10 early career psychiatrists completed exchanges in 2022 in Asia (N=4), Europe (N=3), Africa (N=2), and Oceania (N=1). We collected feedback from these participants. A vast majority (90%) "completely agreed" with the statements that the application process was easy, that it was easy to communicate with their host local coordinator, and that they enjoyed the site where they completed the exchange (if attended in person). Several participants highlighted the "great opportunity to improve knowledge and experience" and being involved in "all clinical activities of the hospital". Some also highlighted the opportunity to "discuss very interesting and complex cases" and the care of the hosts to translate patient interviews and seminar presentations to English when this was not the country's language. The academic experience, including networking opportunities, was highlighted for example as providing "magnificent interaction between neurology, cognitive sciences and psychiatry". Some participants wrote a manuscript during or after the exchange, which got published with them as first authors in scientific peer-reviewed academic journals[8,9]. Remarkably, all participants said that they were happy they had completed the exchange and would recommend it to a friend.

To prepare for the second edition of the World Psychiatry Exchange Program, we made an open call at the end of 2022 for members of the Section and reached out to more departments and countries interested to host placements for this program. We are delighted to have new countries, such as Australia, India and Spain, offering placements to host early career psychiatrists in 2023.

The success of the World Psychiatry Exchange Program documents the value of international exchange programs for early career psychiatrists. The first edition of the program had a very positive outcome, with participants reporting positive experiences and the opportunity to improve their knowledge and skills, and collaborative outputs for participants and hosts further to these exchanges. The program promoted the acquisition of transversal competencies and fostered the knowledge triangle of education, research and innovation. It was also a way of promoting formal and informal learning, encouraging networking, and establishing international partnerships[10].

As we move forward with the second edition, we are excited to expand the program to other countries, offering even more opportunities for early career psychiatrists to gain valuable insights and perspectives. We hope that the World Psychiatry Exchange Program will continue to inspire and support the next generation of psychiatrists to expand their horizons and build meaningful connections across borders.

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WPA Working Group on Medical Students: new accomplishments and online resources

As the COVID-19 pandemic persists and millions are impacted by war and economic unrest, it is critical that mental health services receive support[1-4]. Despite the pressing need, there remains a significant gap in access to services and an ongoing shortage of mental health workforce, especially in low- and middle-income countries[5]. In the WPA Action Plan 2020-2023, capac-

ity building and promotion of psychiatry among medical students has been an important pillar[6]. To this aim, a WPA Working Group on Medical Students was created and launched in December 2020, with the support and attendance of the WPA President and medical educators from Qatar, the US, Canada, Pakistan, India, Australia, Mexico and the UK.

The remit of this Working Group includes four components: to identify opportunities for promoting psychiatry as a career among medical students; to identify organizations and individuals interested in participating and promoting WPA's Action Plan in nurturing psychiatry among medical students; to liaise with other WPA Working Groups regarding medical students; and to support medical students around the world[7].

In order to address the growing needs for mental health workforce, educators must approach the stigma about becoming a mental health professional[8]. To this end, the Working Group produced a "Stigma" video featuring medical students from Australia, Brazil, Canada, Ecuador, Egypt, Ghana, Indonesia, Nepal, Portugal, Thailand, Turkey and South Africa, discussing the impact of stigma on pursuing a career in psychiatry. A central theme was the need to speak up to address myths about mental health and dismantle implicit or explicit bias against people with a mental health disorder. This video is available in English, French, Spanish and Russian on the WPA website, so that medical educators can share it with their trainees and medical students.

In addition to the video, the Working Group is continuing to develop free, open access online modules for psychiatric educators. E-learning has emerged as an increasingly important tool for medical student education during the COVID-19 pandemic, as it provides a flexible environment where students can learn at their own pace[9,10]. The topics covered by the modules are "Medical students wellbeing and selfcare", "Stigma in psychiatry – barriers and solutions", and "Introduction to psychiatry – what and why of psychiatry". These modules were developed by international teams of psychiatry faculty and medical students and are available on the WPA Education Portal[11].

The Working Group has organized several in-person events to promote psychiatry among medical students, foster discussions about well-being, and offer career mentorship. The Group visited the Siriraj Hospital faculty and medical students during the 2022 World Congress in Bangkok, Thailand, to share online resources and conduct a burnout exercise among the undergraduate medical students. Members of the Working Group also organized events for medical students at the Thematic and Regional WPA Conferences in Karachi, Pakistan, and Kolkata, India in 2023.

To complement the in-person conferences, the Working Group is fostering global engagement of medical students around the world through essay competitions, art competitions, and video competitions centered on psychiatry themes. Regarding the essay competition, the Working Group received more than 150 entries from 39 different countries on the topic of "Breaking the silence: how is stigma a barrier to mental health". The top 16 essays selected by an international panel of psychiatrists were published in a WPA e-book. An art competition was organized during the WPA Thematic Congress in Lahore, Pakistan, in March 2022, featuring undergraduate and postgraduate medical students and allied health students interested in psychiatry. Finally, at the WPA Regional Congress in Kolkata, India, in April 2023, a brief video competition was organized on the theme "The importance of psychiatry in the medical field". Twenty-seven videos were submitted by undergraduate medical students from the South Asian Association for Regional Cooperation (SAARC) countries: Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka.

The Working Group is also active in scholarship regarding undergraduate medical education and psychiatry. The activities are accessible on the dedicated section of the WPA website (www.wpanet.org/wg-on-medical students).

Future directions include: a) to organize additional essay competitions to promote psychiatry as a career; b) to publish a survey about psychiatry curriculum in medical education across medical schools in different countries; c) to engage in virtual and in-person activities to promote psychiatry among medical students and to address burnout among students; d) to liaison with regional and international organizations to promote psychiatry; e) to deliver presentations at WPA congresses and other national and international conferences; and f) to implement social media and video campaigns to promote psychiatry.

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Nurturing the next generation of clinician-scientists in child and adolescent psychiatry: recommendations from a WPA Presidential Task Force

Clinician-scientists are members of the health care workforce who devote at least half of their time to research[1]. There is a concern throughout medicine that the number of clinician-scientists is woefully insufficient to meet the needs of the population. For example, the number of clinician-scientists in the US declined by 22% from 1983 to 2003[1]. According to a 2012 report by the US National Institutes of Health[2], clinician-scientists comprised only 1.5% of the total physician workforce. We were not able to find data on the proportion of clinician-scientists in child and adolescent psychiatry, but we believe that it is even lower than for other medical specialties.

We are also not aware of any discussion of a human resource plan for child and adolescent psychiatry which includes an estimate of the number of clinician-scientists that the field needs and how this might be distributed across high- and low- or middle-income countries. Since the majority of the globe's children and youth live in low- or middle-income countries, the workforce needed to support mental health clinical innovation in these countries is a pressing human resource challenge.

Research from other disciplines suggests that the lack of mentors and organized research training programs plays an essential role in determining the scarcity of clinician-scientists[3]. Key issues in child and adolescent psychiatry appear to be the lack of protected time during training to learn research methodology, read the literature, conduct pilot studies, and participate in mentors' research.

Research training in child and adolescent psychiatry is in a crisis. The solution depends on our determination to focus on the mental health of today's children and youth while simultaneously developing the resources necessary to support the mental health and well-being of children and youth of the future. We can only do this using innovative evidence-based treatments, generated by clinician-scientists working today and in the near future.

There is evidence that clinician-scientist training programs are effective, at least in high-income countries, in medicine and surgery[4] as well as in adult or general psychiatry[5]. There is only one report of a successful training program in child and adolescent psychiatry[6]. Ingredients of successful training programs include a strong synergy between a trainee's clinical and research interests[7], an active support from department chairs and national policy makers, and availability of funds for the trainee to carry out initial, independent research separate from the mentor's scientific work.

Several key papers[8-10] have provided consensus recommendations on the training of clinician-scientists based on the above ingredients. The WPA Presidential Task Force on Child and Adolescent Psychiatry, established as part of the WPA Action Plan 2020-2023[11-14], revised and reconceptulized those contributions into a concise set of strategic recommendations specifically for the field. They are the following:

- Establish an international working group of child and adolescent psychiatrists from both high- and low- and middle-income countries to draw up best practices to support trainee and early career clinician-scientists.
- Invite global and national professional and regulatory bodies to support and monitor outcomes of clinician-scientist training programs to ensure the return on investment, especially in low- and middle-income countries.
- Develop a roadmap to identify the number of clinician-scientists that the field needs, reflecting the prevalence of mental health problems at the population level.
- Initiate a dialogue with national training regulatory bodies to implement "short track" clinical training options for those enrolled in research training programs.
- Vigorously promote the steps necessary to train clinician-scientists in a manner that reflects the diversity of the population and attends to special issues of discrimination and bias.

Our field is at a critical juncture. We fear that doing nothing will lead to the gradual "extinction" of clinician-scientists in child and adolescent psychiatry. By neglecting this priority, we will disadvantage the children who will need our services and our science in the decades to come.

The time has come to address the mental health needs of future generations of children and youth who will be the beneficiaries of clinical innovation based on the work done today by clinician-scientists. The effectiveness of our clinical interventions in child and adolescent psychiatry can be improved only by supporting and nurturing the next generation of clinician-scientists in this field.

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An update from the WPA Working Group on Digitalization in Mental Health and Care

The treatment gap for persons with mental disorders averages 50% in all countries of the world and rises to 90% in least-resourced countries[1]. The mental health care sector is increasingly adopting newer digital health options that may help to significantly reduce this gap. Although telemental health care has a long-standing history and compelling empirical evidence base, its implementation in routine mental health care conditions has remained scant for many years[2]. However, following the COVID-19 pandemic, it represents now a routine clinical activity, and newer opportunities (as well as challenges) are rapidly emerging[3].

Digital (mental) health offers several valuable options (ranging from digital therapies to digital phenotyping, augmented reality, social media, artificial intelligence)[4,5] that will contribute significantly to deliver, support and enhance mental health care globally over the coming years[6], being particularly appealing for younger generations[7-9]. However, the adoption of novel digital clinical options is occurring at different paces across countries, often with suboptimal implementation.

Many national and international initiatives have been set up to promote digital mental health and care. For example, in Europe, a six-nation project has been implemented with the support of the European Regional Development Fund to increase the dissemination and quality of e-mental health services in Belgium, France, Germany, Ireland, The Netherlands, and the UK (e-Mental Health Innovation and Transnational Implementation Platform North-West Europe project; eMEN)[10]. The European Psychiatric Association also launched a series of initiatives (e.g., scientific symposia at its annual congresses, a task force on e-mental health, a series of training courses and a training video toolkit) to ensure a more even spread of digital mental health across Europe[11]. According to recent evidence, digital mental health interventions in lower income countries may represent a valuable option, if adequately implemented and evaluated[12].

Thus, further action is required to ensure the equitable implementation and impact of digital mental health at a global scale. The WPA Working Group on Digitalization in Mental Health and Care is aiming at the improvement of global mental health and care by introducing digital tools and programs, thereby contributing to transforming health systems for universal health coverage. The Working Group, appointed in 2020[13] and chaired by W. Gaebel, U. Volpe and R. Ramalho, is working alongside experts in the field of digital psychiatry and WPA early career psychiatrists.

Currently, the Working Group is collaborating with WPA Member Societies, drawing a baseline on global digitalization in mental health and care by means of an international survey. The survey covers topics ranging from the grade of digitalization in general and mental health care, to the availability of national policies and regulations, barriers and facilitators for implementation, guidelines for tools and interventions, and capacity building by education and training. Building on the results, the WPA Working Group is going to transform and support the national digital infrastructures together with the Member Societies and other stakeholders, including patient and family organizations. The collaboration with WPA Member Societies will also contribute to produce evidence-based guidelines for safe and ethical use of digital mental health options at the individual, institutional and country level, including awareness building and improving digital literacy, also fostering implementation research of digital mental health and care.

The WPA Working Group is also developing and delivering scientific and training initiatives, including symposia and workshops at national and international levels. It is contributing to World Congresses of Psychiatry, e.g., the one held in Bangkok in 2022, where an in-person course on "Digitalization in Mental Health and Care" was organized from a worldwide perspective. At the same Congress, an online symposium on worldwide digitalization in mental health and care was organized by the WPA Working Group to help define methods of rapid implementation of telepsychiatry, explore the need for standardized training curricula for global digital psychiatry, and identify facilitators and barriers for cultural safety in e-mental health. The WPA Working Group will also deliver a course on digitalization in daily clinical work at the upcoming WPA Congress of Psychiatry to be held in Vienna, Austria.

Considering the fast evolving pace of digital technologies, as per WPA request, the Working Group is currently finalizing a new WPA Position Statement on Digitalization in Mental Health and Care, also to update the previous WPA Position Statement on e-Mental Health. To this aim, an exhaustive review of the current evidence on the global level of digitalization in mental health and care has been carried out. This new Position Statement will provide the WPA and its Member Societies with a roadmap on high priority and targeted interventions to support implementation and upscaling of digital mental health and care in global mental health systems.

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Education, policy and clinical care in mental health: an update on the activities of WPA Collaborating Centres

In 2016, the WPA President and Executive Committee appointed seven sites as WPA Collaborating Centres, with the aims to: a) collect and disseminate information on mental health; b) provide training and links to clinical and research centres; c) support capacity building at country or regional level; d) conduct and coordinate educational and research activities with the support of the WPA[1]. The Centres have been renewed in 2021[2], aiming to support the implementation of the WPA Action Plan 2020-2023[3-5], and to build a global alliance for better mental health.

In this period, the network of the WPA Collaborating Centres has been extended. It includes now nine sites in eight different countries: the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India; the Department of Psychiatry of the Chinese University of Hong Kong; the Africa Mental Health Research and Training Foundation in Nairobi, Kenya; the Department of Psychiatry and Mental Health, University of Cape Town, South Africa; the Okasha Institute of Psychiatry, Faculty of Medicine, Ain Shams University, Cairo, Egypt; the Department of Psychiatry and Nuffield Department of Primary Care Health Sciences, University of Oxford, UK; the Department of Psychiatry, University of Campania "L. Vanvitelli", Naples, Italy; the Department of Psychiatry at Sidra Medicine in Doha, Qatar; and the Department of Psychiatry, Postgraduate Institute of Medical Education and Research (PGIMER) in Chandigarh, India.

The Centres have been selected on the basis of the following criteria: a) high scientific reputation at national and international levels; b) eminent status in the country; c) high quality of academic and research leadership; d) stability in terms of achievements, staff and resources; e) willingness to contribute to the implementation of the WPA Action Plans; f) appropriate technical expertise. The UK site acts as the coordinating centre, organizing quarterly business meetings.

In 2021, the WPA Collaborating Centres developed a Work Plan, aiming to promote best practice in clinical work, teaching, training, research and policy development[2]. The Plan has been implemented by sharing resources, working together on educational initiatives (e.g., webinars, essay prizes for medical students and trainee psychiatrists), promoting and conducting research (e.g., on adolescents at the Collaborating Centres in Kenya, India and UK), providing opportunities to promote WPA activities, and supporting early career researchers, trainees and medical students[6]. The activities carried out by the Collaborating Centres are presented at major WPA congresses and through policy papers and educational materials, which are made available to the entire WPA community[7].

The Collaborating Centres bring considerable resources and networks to support, inform and disseminate the work of the WPA, and to lend authority to the Association's strategy and Action Plans. There is no additional budget to support the Centres. The Directors of the Collaborating Centres operate through multiple partners and global leaders to raise the profile of the WPA (for example, by publishing papers in high-impact scientific journals) and by closely collaborating with WPA Scientific Sections (e.g., those on Education in Psychiatry[8] and of Early Career Psychiatrists[9]) and Working Groups (e.g., that on Comorbidities between Physical and Mental Disorders[10]).

The Collaborating Centres have also contributed to national and international policy and guidance documents through the WPA, and have partnered with national and international organizations. In particular, the Centres are constantly in contact with institutions and research networks active in the field of mental health and psychiatry, such as the World Health Organization, the Psychiatric Genetics Consortium, the Enhancing Neuroimaging and Genetic Meta-analysis Consortium, and the World Mental Health Surveys.

All Centres have actively contributed to the promotion and dissemination of educational activities and materials focused on timely issues such as public mental health, training and implementation of ICD-11 and related clinical guidelines, management of physical comorbidities in people with severe mental disorders, benefits and innovations of digital health, and management of adolescent mental health.

Scholarship opportunities have been provided by the Centres to early career psychiatrists and researchers to attend regional and global WPA congresses through trainee and medical student prize competitions. All Centres participate in setting the competition format, selecting the winners, and providing certificates. The WPA President usually presents the awards at the relevant regional or global congresses.

The WPA Collaborating Centres have a specific commitment to improve undergraduate and postgraduate education in psychiatry. In particular, postgraduate education-

al activities provided in the different Centres include training in a range of psychiatric subspecialities (e.g., addiction psychiatry, child and adolescent psychiatry, consultation-liaison psychiatry, forensic psychiatry, intellectual disability psychiatry, neuropsychiatry) and provision of additional postgraduate diplomas, masters, and doctoral degrees in fields ranging from neuroscience to clinical psychiatry and public mental health.

The two Centres recently added to the Network (i.e., Doha and Chandigarh) have strengthened the role of the WPA in the Middle East and South Asia, respectively, and added further public health and prevention expertise. The network has also established good partnerships with national psychiatric societies, as well as with other international organizations, such as the World Association for Social Psychiatry, the World Federation for Mental Health, and the World Association of Cultural Psychiatry. Moreover, all Centres have carried out specific national and international activities on the basis of their level of expertise, focusing on such issues as health inequalities, digital health, multimorbidity, school mental health, suicide prevention, old age psychiatry, and neurodiversity. Finally, the WPA Collaborating Centres are strongly involved with social responsivity, community engagement, and advocacy for mental health.

Opportunities and links for more interdisciplinary work across Centres have been built in the last triennium, and we believe that this interdisciplinary network can further help the growth of the WPA in the near future.

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