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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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Person-centred care planning as foundational to clinical practice

The World Health Organization recently issued new guidance and technical packages for community mental health services, entitled "Promoting Person-Centred and Rights-Based Approaches"[1]. As these documents make clear, within the sphere of mental health, the provision of person-centred care is itself an issue of human rights. This is not only true in the cases of involuntary or coercive treatments – when precautions and oversight must be exercised to ensure preservation of dignity and respect under exceptional circumstances – but with regard to all forms of mental health care. All mental health care, including clinical practice, needs to be fundamentally re-oriented toward the protection and extension of each individual's right to self-determination. Re-oriented, that is, to preserving the person's integrity as an individual while facilitating and promoting the person's pursuit of his/her own unique life goals.

In terms of practice, it is important that this re-orientation takes place in the realms of both care planning and care delivery. It is not enough for care to be offered in a dignified and respectful manner if the care planning process is directed solely by the clinician, oriented toward symptom and deficit reduction, and dismissive of the person's everyday life pursuits. In the same vein, it is not enough for the care planning process to be conducted in partnership between a clinician and a patient (and possibly his/her loved ones), using a shared decision-making format, if the care that is offered is then delivered in a disrespectful manner. Person-centred care thus involves both the acknowledgement of the individual's right to self-direction with respect to the goals of care, and the protection of this right in ongoing service delivery. In these regards, mental health care does not differ substantially from person-centred care for any other medical condition, save in cases of imminent danger of death or disability.

But this does differ substantially from the ways in which mental health care has been planned and provided in the past. Compared to traditional methods of care planning, a person-centred approach: a) aims to promote the recovery of a meaningful life in the community of the person's choice rather than solely minimizing symptoms and impairments; b) is based on the pursuit of each individual's own unique life goals and aspirations; c) clearly defines the person's own role, the roles of the clinician and other staff, and the roles of various natural supports in the person's life in assisting the person in achieving these goals and aspirations; d) focuses and builds on the person's own capacities, strengths and interests; e) emphasizes to the degree possible the use of natural community settings and supports rather than segregated mental health programs and paid staff; and f) expects and allows for disagreement, uncertainty and setbacks as natural steps on the path to recovery and greater self-determination (see Roe et al[2] in this issue of the journal).

In this sense, using the metaphor of recovery as a life journey results in the care plan being used as a roadmap by which to navigate one's life and experience in care. Such a person-centred plan transforms what had been primarily viewed as a bureaucratic requirement, taking time away from the practitioner's clinical responsibilities, into what may be regarded as the essence of the work of recovery: that is, creating, implementing and modifying in an ongoing manner the person's roadmap to a fulfilling life.

Successfully forging a pathway to that life requires that an individual's rights be respected not only within the context of clinical and rehabilitative services, but in the community at large. Despite substantial progress in systems transformation around the globe, there remain limits to what formal treatment systems can do, as recovery does not happen in a vacuum but in people's day-to-day lives in their communities.

The most person-centred vocational rehabilitation program is not enough to help a person get a real job for real pay; the most person-centred residential program is not enough to help a person build a true home in his/her community; and the most person-centred supported education program is not enough to help a person feel genuinely welcome on a university campus. These programs, while valuable, are simply not enough if people continue to be discriminated against by employers, neighbours, or fellow students based on their label of a "mental illness". Realizing the true potential of person-centred care thus requires a commitment on the part of mental health systems to protect human rights not just within the context of formal services, but across boundaries to local communities and society as a whole.

It also requires acknowledging that the protection of human rights is an ethical imperative now more than ever before. At its core, person-centred care is about freedom – freedom to build a fulfilling life in the community; freedom to realize one's full potential; freedom to be free from discrimination; freedom to control choices that impact one's life and experience in care.

Both the COVID-19 pandemic and recent episodes of violence against people of color have made it painfully clear that not all people are equally free. Even in systems that strive to be person-centred, we continue to have staggering disparities in access to care, health and recovery outcomes, and the use of involuntary and restrictive treatment interventions. Truly committing to person-centred care means acknowledging the fact that we are not immune to the types of discrimination that plague our broader communities. If our goal in person-centred systems is to help *all* people live a fulfilling life in their chosen community, we cannot stay silent in the face of injustices nor perpetuate injustice in our own systems of care.

It is worthwhile noting that, although our argument above has been that person-centred care and planning are first and foremost issues of rights, there also happens to be an accumulating research evidence that transforming mental health care to be recovery-oriented and person-centred, emphasizing the role of the individual in directing one's own care, including taking on responsibility for self-care, leads to improved adherence and outcomes and decreased costs.

Recent reviews have found that person-centered and self-directed care approaches, along with the incorporation of shared decision-making and psychiatric advance directives – all of which allow individuals to exercise greater choice and control over their own care – show benefits over usual care[3,4]. These benefits are found in rates of adherence and self-management as well as in medical and mental health outcomes, yielding improved cost-effectiveness, service satisfaction, and quality of life, as well as reduced inpatient and emergency room use[5-7] and possibly involuntary care[8]. These benefits appear to be even greater when interventions are more comprehensive, intensive, and integrated into routine care[3,9].

The international recovery movement has in many ways always been rooted in a human rights mission, yet that mission has most often identified formal service systems as the primary target for change. In doing so, we have failed to realize the full potential of recovery-oriented systems transformation. The recently released guidelines of the World Health Organization reaffirm this commitment to human rights. In order to honor that commitment the field must now grapple with the many structural and social factors that often place people on the margins of society and limit their opportunities for community belonging. Person-centred care planning represents one tool that the field can use to address these challenges in supporting the whole person on his/her chosen pathway to recovery and community inclusion.

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Youth psychiatry: time for a new sub-specialty within psychiatry

In 1973, M. Rutter was appointed as the first professor of child psychiatry in the UK. He is considered the "father" of modern child psychiatry due, in large part, to his seminal epidemiological studies of psychiatric disorders in children and adolescents in the Isle of Wight and London, carried out between 1964 and 1975. On the other side of the Atlantic, L. Kanner was the first physician to practice as a child psychiatrist, but children's mental health remained within a psychoanalytic child guidance clinic model. The American Academy of Child Psychiatry (AACP) was not founded until 1953, and child psychiatry was not officially recognized as a specialty until 1959[1]. In 1972, D. Cotter was the first US-trained child psychiatrist to be appointed to a consultant post in Ireland[2].

Gradually, it was recognized that the term "child" was not adequate for the range of ages. In 1983, the title of the AACP was changed to the American Academy of Child and Adolescent Psychiatry. The age range for child and adolescent psychiatry varied internationally, but common practice in most countries was to offer a service up until a young person's 18th birthday. Young people persisting with or presenting after that age with mental health problems had to transition to, or present to the adult mental health services.

The pioneering work by P. McGorry and colleagues over several decades presents a compelling case that it is time for another paradigm shift in psychiatry similar to the emergence of the specialty of child psychiatry. In this issue of the journal, McGorry et al[3] argue that epidemiological and clinical evidence, as well as advances in developmental neuroscience, no longer support schismatic service delivery between child and adolescent and adult mental health services.

Youth is a time when the incidence of mental disorders peaks, but in which access to coherent and user-friendly secondary care services is largely absent. The transition from the family-centric child and adolescent services to adult service models is too stark, and many young people cannot engage and fall through the cracks[4]. The cut-off age between different service models could be considered structural age-based discrimination. The Transitions of Care from Child and Adolescent Mental Health Services to Adult Mental Health Services (TRACK) study demonstrates that less than 4% of youth transitioning from child to adult services experience good continuity of care[5].

The youth mental health services described by McGorry et al[3], which attempt to address this gap, are based largely within primary care, with limited access to psychiatry. In Australia, a large proportion of young people seen by these primary care services require a higher level of specialist care than can be provided there, and fall between the criteria for primary and adult secondary care. They have been called "the missing middle"[3].

There is a well-recognized relationship between continuity of care and mortality of patients with mental disorder, and this young adult age group has relatively high rates of suicide in most countries. Epidemiological studies show that mental disorders account for the greatest burden of disease in young people, yet our service delivery and training structures do not take account of this.

This period between mid-adolescence and the early twenties also coincides with many significant life changes, such as moving out of the family home, transition to third level education, starting a new career, and beginning (and ending) new romantic relationships. Furthermore, the COVID-19 pandemic has sparked growing concerns about the well-being of young people, as normative developmental milestones and protective factors have been affected[6]. The field of "student mental health" or "student psychiatry" is also emerging as a new area of interest. College life can uncover or worsen pre-existing mental health problems[7].

Youth mental health needs a specific philosophy of care in order for young people to effectively transition to independent established adulthood whilst experiencing serious mental health problems. Primary care mental health services, most often delivered by our allied health professional colleagues, have adapted much more rapidly to provide developmentally appropriate models of care for young people. The result is that a new field in mental health is developing, which targets an age group with a high incidence of serious mental disorders and suicide, largely without psychiatry input[7,8].

Psychiatry as a whole endorses a lifespan approach to mental illness. Due to high rates of comorbidity across different mental disorders, psychiatrists need training to meet the needs of those presenting with mental health problems based on an understanding of their developmental stage, culture and environmental circumstances. However, the impressive body of evidence presented by McGorry et al[3] firmly points to the need for a new sub-specialty of youth psychiatry which would be a lifespan focused sub-specialty embedded within and between child and adolescent and adult services. Such a sub-specialty would span the period between the late teens and late twenties.

There are known skillset gaps within both child and adolescent and adult psychiatry when dealing with the mental health issues of young adults, such as treatment of persistent attention-deficit/hyperactivity disorder, management of autistic spectrum disorders and other neurodevelopmental disorders, management of polysubstance use and emergent personality disorder, crisis care for suicidal behaviours, and assessment and treatment of new-onset psychoses.

Neither child and adolescent psychiatry nor adult psychiatry covers the full range of skillsets needed by a youth psychiatrist. New curricula and training are required. Formal curriculum development and training programs are being pioneered in Australia[9]. The College of Psychiatrists of Ireland has recently developed and approved a Faculty of Youth and Student Psychiatry (www.irishpsychiatry.ie). This is, to our knowledge, the first such faculty attached to a postgraduate psychiatry training body worldwide.

A new sub-specialty of youth psychiatry would particularly focus on emerging and pre-existing mental illness in the context of transitions and stresses in a young person's life, with a philosophy of care that aims to establish a young person's success and independence. Youth psychiatry should include relevant stakeholders in governance and service development, particularly young people, in order to maintain service attractiveness, quality, value and investment. Youth psychiatry services should have close links with education and training organizations as part of a whole community approach to good mental health.

In psychiatry, our service provision is not matching recent advances in developmental neuroscience or the changing place, role, challenges and expectations of young people in society. The structure of psychiatry training is stuck in a model from the last millennium. We are lagging behind the evidence and the practice of allied health professionals. Psychiatry needs to improve its offering to young people. It is time for a new approach to training and a new sub-specialty.

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Klerman's "credo" reconsidered: neo-Kraepelinianism, Spitzer's views, and what we can learn from the past

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In 1978, G. Klerman published an essay in which he named the then-nascent "neo-Kraepelinian" movement and formulated a "credo" of nine propositions expressing the movement's essential claims and aspirations. Klerman's essay appeared on the eve of the triumph of neo-Kraepelinian ideas in the DSM-III. However, this diagnostic system has subsequently come under attack, opening the way for competing proposals for the future of psychiatric nosology. To better understand what is at stake, in this paper I provide a close reading and consideration of Klerman's credo in light of the past forty years of research and reflection. The credo is placed in the context of two equally seminal publications in the same year, one by S. Guze, the leading neo-Kraepelinian theorist, and the other by R. Spitzer and J. Endicott, defining mental disorder. The divergences between Spitzer and standard neo-Kraepelinianism are highlighted and argued to be much more important than is generally realized. The analysis of Klerman's credo is also argued to have implications for how to satisfactorily resolve the current nosological ferment in psychiatry. In addition to issues such as creating descriptive syndromal diagnostic criteria, overthrowing psychoanalytic dominance of psychiatry, and making psychiatry more scientific, neo-Kraepelinians were deeply concerned with the conceptual issue of the nature of mental disorder and the defense of psychiatry's medical legitimacy in response to antipsychiatric criticisms. These issues cannot be ignored, and I argue that proposals currently on offer to replace the neo-Kraepelinian system, especially popular proposals to replace it with dimensional measures, fail to adequately address them.

Key words: Neo-Kraepelinian movement, Klerman's credo, DSM-III, mental disorder, harmful dysfunction, antipsychiatry, dimensional approaches, Research Domain Criteria, Hierarchical Taxonomy of Psychopathology, R. Spitzer

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After four decades of dominance of psychiatry by the neo-Kraepelinian symptom-based categorical vision of nosology, formally embraced in the DSM-III[1], there is a growing perception that neo-Kraepelinianism has failed and is unable to yield its expected dividends in etiological understanding and treatment progress. This perceived failure has left a vacuum that various alternative proposals and research programs are attempting to fill, ranging from the US National Institute of Mental Health (NIMH)'s Research Domain Criteria (RDoC) initiative[2-5], focused on identifying brain circuitry etiologies, to multiple research programs to dimensionalize or factor-analyze away rigid diagnostic categories such as the Hierarchical Taxonomy of Psychopathology (HiTOP) project[6-9], and many other proposals as well, such as network theory[10-13] and comprehensive risk factor analyses[14].

This nosological ferment provides an ideal time to reconsider the neo-Kraepelinian program's origins, aspirations, and its present condition as a prelude to grappling with the future of psychiatric nosology and mediating among the many competing proposals. A natural way to start such a reassessment is with G. Klerman's pivotal 1978 essay, *The Evolution of a Scientific Nosology*[15], in which he coined the term "neo-Kraepelinian". In his article, Klerman prepared his readers for the radical changes to come by elaborating a neo-Kraepelinian "credo" of nine propositions that constituted the movement's central claims and goals (Table 1). After some preliminaries, I will comment on and evaluate each of these propositions both in terms of the arguments they put forward and in light of thinking during the four decades since their formulation. I focus on conceptual issues rather than sociological or other motivational determinants.

In fact, 1978 was a remarkable year for foundations of psychiatry even beyond Klerman's essay. In considering Klerman's nine principles, I will draw on two additional seminal events of that year that must be part of a perspicuous account. First, S. Guze, a Washington University psychiatrist who was the leading neo-Kraepelinian theorist, published a defense of the movement's most basic claim, that psychiatry is a branch of medicine[16], an argument he elaborated in a later article and book[17,18]. Second, R. Spitzer and J. Endicott published the most ambitious of a series of attempts to define the concept of mental disorder as a foundation for nosology[19].

A WORD ABOUT G. KLERMAN AND HIS STANCE TOWARD THE NEO-KRAEPELINIAN MOVEMENT

In his 1978 article, Klerman spoke with considerable authority about the direction of psychiatry because he had been appointed the year before as head of the US Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) by President J. Carter. Klerman had a distinguished career as a research psychiatrist specializing in mood and anxiety disorders, and as a gifted administrator as well, holding appointments at Yale, Harvard and Cornell Universities. In the course of his research on combined medication and psychotherapy treatment of depression, he developed – with his collaborator and wife, M. Weissman – interpersonal psychotherapy[20], which remains a leading empirically supported treatment.

Klerman was very sympathetic to neo-Kraepelinian ideas, seeing them as a scientific advance that promised enormous progress in psychiatry. The wordings of his credo's propositions are often paraphrases of assertions in neo-Kraepelinian articles. However, his article's tone is more that of a summary of the movement's doctrines by an appreciative witness to history rather than an insider's fervent personal manifesto. Klerman even

Table 1 The neo-Kraepelinian credo[15]

1. Psychiatry is a branch of medicine.
2. Psychiatry should utilize modem scientific methodologies and base its practice on scientific knowledge.
3. Psychiatry treats people who are sick and who require treatment for mental illnesses.
4. There is a boundary between the normal and the sick.
5. There are discrete mental illnesses. Mental illnesses are not myths. There is not one but many mental illnesses. It is the task of scientific psychiatry, as of other medical specialties, to investigate the causes, diagnosis, and treatment of these mental illnesses.
6. The focus of psychiatric physicians should be particularly on the biological aspects of mental illness.
7. There should be an explicit and intentional concern with diagnosis and classification.
8. Diagnostic criteria should be codified, and a legitimate and valued area of research should be to validate such criteria by various techniques. Further, departments of psychiatry in medical schools should teach these criteria and not depreciate them, as has been the case for many years.
9. In research efforts directed at improving the reliability and validity of diagnosis and classification, statistical techniques should be utilized.

suggests at one point that there is bound to be a reaction against what will be perceived as the movement's excesses. Klerman identifies the leading neo-Kraepelinians as including S. Guze, E. Robins, G. Winokur, D. Klein and R. Spitzer (but see below regarding Spitzer), along with others trained during that period at the Psychiatry Department of Washington University in St. Louis. However, Klerman himself, despite giving the movement a name and a credo, did not become identified as a central figure in the movement. As we shall see, although taken with the scientific rigor of the neo-Kraepelinians, Klerman, like Spitzer, was reluctant to adopt the movement's strictly biological ideological stance to the detriment of other forms of etiological theory and research.

THE TWO PRIMARY TARGETS OF NEO-KRAEPELINIANISM

The neo-Kraepelinians' positive scientific agenda was intertwined with a negative polemical agenda of refuting two other prominent positions that they considered to be undermining the status of psychiatry. These were the antipsychiatric movement and psychoanalysis.

The antipsychiatric challenge

The philosophical motivations for neo-Kraepelinianism are often underestimated. Its central preoccupation was to justify locating psychiatry within medicine, as stated in Klerman's proposition 1. For today's younger clinicians who grew up professionally in a neo-Kraepelinian world in which the medical nature of psychiatry was obvious and respected, the neo-Kraepelinian concerns about antipsychiatry must be placed in context.

Antipsychiatrists argued that psychiatry used bogus medical categories to justify the use of medical authority and technology for the social control of disapproved behavior[21-27]. In an unlikely alliance with antipsychiatrists, behaviorists, who were a powerful constituency within psychology at the time, argued that deviant behavior is shaped by normal learning processes in deviant environments and thus that "mental disorders" are not literally medical disorders but merely socially disapproved behavioral outcomes[28]. Psychiatrists of the biopsychosocial school who were trying to integrate the multiple perspectives relevant to mental disorder added to the confusion by lacking a clear conceptual distinction between normal-range psychological distress and psychiatric disorder, leading, for example, to an argument that perhaps standard grief is a mental disorder after all[29]. This multipronged conceptual/ideological onslaught was combined with devastating empirical demonstrations of the unreliability and arbitrariness of psychiatric diagnosis[23,30,31].

The undermining of psychiatry's medical credentials took an increasing toll on the profession's credibility, morale, and public support. There was a concern that psychiatry was becoming much less appealing as a specialty as a result. For example, B. Brown, NIMH Director, observed that "the proportion of medical school graduates entering psychiatric residency dropped by approximately 15% between 1972 and 1974" [32, p.490].

The neo-Kraepelinians recognized antipsychiatry as a fundamental threat and were absorbed by the need to rebut antipsychiatric arguments and legitimize psychiatry's medical status. Guze spent considerable time rebutting the antipsychiatrists in his paper, observing that the antipsychiatrists' arguments cut to the heart of psychiatry as a medical discipline: "Attacks on the medical model for psychiatric disorders often reflect the belief that there is no such thing as psychiatric illness. According to this view, psychiatric diagnosis is merely a way that society labels its deviants… and only serves as a means of social control"[16, p.301]. Klerman, too, reviews the various antipsychiatrists' positions, commenting on Foucault, Szasz, Scheff, Laing, Rosenhan, and labeling theorists, and attempts to characterize their fundamental challenge: "common to these schools of criticism is an attack on the basic concept that mental illnesses… are appropriately treated within the medical model and that psychiatry and its treatments… are legitimate medical activities"[15, pp.108-109].

The challenge of psychoanalytic dominance

The second primary target of neo-Kraepelinianism was psychoanalysis. Neo-Kraepelinians were opposed to all approaches to etiology and diagnosis that they considered non-medical, including behaviorism, socioculturalism, and even integrative biopsychosocialism that placed the psychological and social domains on an equal footing with the biological. However, their main concern was to challenge and replace psychoanalysis as the dominant force in psychiatry.

Psychoanalytic dominance in the pre-DSM-III era was indisputable. Psychoanalysts chaired most psychiatry departments, determined the content of most graduate training, and authored the most widely used textbooks[33]. In a 1960 survey, 95% of medical schools reported teaching psychodynamic psychiatry, and "virtually every chairperson of a department of psychiatry stated unequivocally that the psychodynamic frame of reference (as contrasted with the descriptive or organic) was dominant"[34, pp.429-430].

Despite the advent of some research-oriented psychoanalytic approaches such as attachment theory[35], American psychoanalysis at the time still primarily adhered to Freud's classic Oedipal theory of neurosogenesis, according to which neurotic symptoms of varying kinds emerged due to unsuccessful defenses against anxiety produced by inner conflict generated during the Oedipal period of childhood psychosexual development. Psychoanalysts thus tended to downplay differential diagnosis based on symptom presentation as not very relevant to etiological understanding or treatment choice. In considering Klerman's credo, we shall find that the wording of his neo-Kraepelinian propositions often contains implicit barbs against psychoanalysis to hasten its decline.

R. SPITZER AND NEO-KRAEPELINIANISM: SOUL MATES OR MARRIAGE OF CONVENIENCE?

In the course of examining Klerman's neo-Kraepelinian propositions, I am going to incrementally develop what I will call a "Spitzerian" view of psychiatric nosology. Although Spitzer's views have generally been equated with neo-Kraepelinianism, in fact they are importantly different. Spitzer explicitly rejected some of Klerman's propositions and clearly framed the DSM-III as differing from standard neo-Kraepelinianism in its assumptions. I will argue that the DSM-III is a Spitzerian document that has often been misinterpreted as a straightforward neo-Kraepelinian document in ways that distort its nature.

This perspective may come as a surprise, because Spitzer is often asserted to be a prominent neo-Kraepelinian or even the leading neo-Kraepelinian, and is credited with conquering psychiatric nosology on behalf of the neo-Kraepelinian cause. Klerman refers to him as a "New York investigator identified with the neo-Kraepelinian approach" who was responsible for the DSM-III's "strong descriptive approach"[15, p.105]. Blashfield, following Klerman, labels Spitzer one of the five "most prominent members of the neo-Kraepelinian movement", despite his not being at the institutional heart of the movement at Washington University but at "an associated setting for this invisible college" at Columbia University and New York State Psychiatric Institute[36, p.3]. Such attributions continue today[e.g., 4,13].

It is easy to see why this view is appealing. Spitzer was Chairperson of the Task Force that generated the DSM-III revolution in diagnosis, which was hailed by neo-Kraepelinians as accomplishing their signature goal of reinstituting descriptive diagnosis in psychiatry. As well, in eliminating a generic category of psychoneuroses that presupposed psychoanalytic assumptions about anxiety and defense, Spitzer accomplished the neo-Kraepelinian goal of freeing psychiatry from the claimed nosological sins of the psychodynamic era. Moreover, in their nature and sometimes their literal content, Spitzer's DSM-III descriptive diagnostic criteria sets were descended, by way of the intermediate Research Diagnostic Criteria[37], from the so-called Feighner criteria formulated by members of the Washington University Department of Psychiatry in pursuit of neo-Kraepelinian research measures[38]. Spitzer also placed several leading neo-Kraepelinian adherents on his Task Force to help oversee the development of DSM-III[39].

On most substantive points, Spitzer and the neo-Kraepelinians were in agreement. Spitzer wanted to place psychiatry on a more secure scientific foundation by using the neo-Kraepelinians' Feighner-style descriptive research criteria as clinical diagnostic criteria that could serve as a starting point for bootstrapping to etiological understanding, in roughly the way neo-Kraepelinians envisioned. The overlap in scientific sensibilities and the passionate belief in shared goals meant that the neo-Kraepelinians made ideal allies in the many battles Spitzer had to fight with various entrenched powers within psychiatry to realize the shared vision of a scientific psychiatry.

However, as I will show in the course of my coverage of the nine propositions of Klerman's neo-Kraepelinian credo, Spitzer and the neo-Kraepelinians were not soul mates. Instead, they entered into a marriage of convenience. Perhaps the limits of the relationship were ambiguous at the beginning, but with time it became apparent that, on important conceptual issues about the nature of psychiatry and psychiatric diagnosis, there was considerable daylight between them.

I now turn to Klerman's propositions.

1. PSYCHIATRY IS A BRANCH OF MEDICINE

The claim that psychiatry is a branch of medicine is the most basic and momentous neo-Kraepelinian claim. I therefore examine it in some detail.

The proposition's significance may not be immediately apparent. Psychiatry is obviously a branch of medicine in a sociological or organizational sense. However, what is being raised is a conceptual question about whether psychiatry deals with medical disorders, which is the essential defining mission of medicine, whatever else it does. There can be many other reasons for being a branch of medicine in the organizational sense. Neither cosmetic surgery nor obstetrics have as their primary activity the treatment of diseases, yet those are both branches of medicine, one because the skills to be used in pursuit of aesthetic ideals are possessed uniquely by physicians, and the other for preventive reasons because pregnancy and childbirth hold many dangers to the health of mother and child.

Klerman and Schechter distinguish between the core of psychiatry as the treatment of mental disorder versus the use of psychiatric skills to help people deal with distress or realize their potential[40] (see Figure 1). Similarly, I elsewhere distinguish the es-

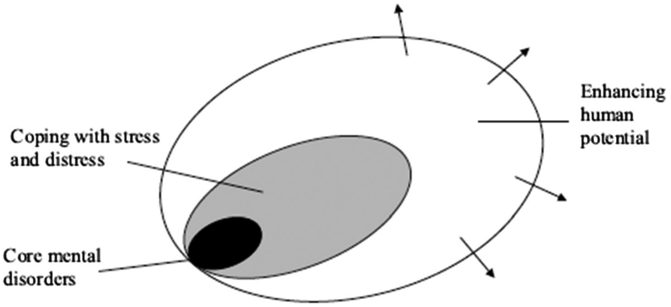

Figure 1 The core of psychiatry as the treatment of mental disorder versus the use of psychiatric skills to help people deal with distress or realize their potential (adapted from Klerman and Schechter[40])

sential tasks of a profession from a profession's derived tasks that result from the application of its skills to areas other than its essential domain[41]. The sense of "branch of medicine" in Klerman's proposition is intended to refer to being concerned with medicine's essential core task of treating medical disorders. This is evident from the title of Guze's paper published the same year, *Nature of Psychiatric Illness: Why Psychiatry is a Branch of Medicine*[16].

The "medical model" as a conceptual red herring

Given the way the debates about medicine were framed at the time, the neo-Kraepelinians decided that the way to argue that psychiatry treats medical disorders and thus is a legitimate medical discipline is to argue that it appropriately adheres to the "medical model". As Klerman explains, "The Kraepelinian revival is part of the general movement of psychiatry towards greater integration with medicine… To better understand these developments requires exploration of the 'medical model'"[15, p.105]. However, Klerman also points out that "medical model" can mean many different things and is "a code word for controversy and debate"[15, p.106].

Indeed, at the time – and, one could argue, also today[e.g.,42] – the expression "medical model" was often used pejoratively to refer to the asymmetric authority of the physician over the patient, the expansion of medical authority into areas of life such as giving birth and dying, the emphasis on biological processes rather than the patient's feelings and values, and the claimed dehumanizing effects of the technology-driven physician-patient interaction (hence, the rise of the field of "medical humanities" as an antidote).

How do Guze and Klerman think they can argue from the premise that psychiatry uses the "medical model" to the conclusion that it uses that model to treat genuine medical disorders? The argument is not crystal clear. Brilliant as they were, neither Guze nor Klerman were particularly talented conceptual analysts in the way that Spitzer proved himself to be. The usefulness of the "medical model" in treating psychiatric conditions is a pragmatic or sociological observation that cannot be equated with whether the treated conditions are genuine medical disorders, which is a conceptual-scientific question. As Spitzer came to understand, it is ultimately the conceptual question of the criterion for psychiatric conditions being genuine medical disorders, not what model one finds most useful in treating the conditions, that determines whether psychiatry is legitimately a branch of medicine in the relevant sense that would rebut the antipsychiatrists.

Klerman suggests that there are three components to the "medical model" in a modern society: a) the disease concept; b) the sick role, consisting of certain prerogatives (you are relieved of some usual obligations) and responsibilities (you try to get better); and c) the health care system, which decides who is to be considered sick and obtain the sick role. He notes that bringing the "medical model" to mental illness was an achievement of the 19th century, and that the antipsychiatric movement wants to undo this achievement. However, Klerman's second and third features – whether society decides to place someone in the sick role, and judgments that a problem should be addressed by the health care system – should follow rather than determine the judgment that a condition is a medical disorder. Only Klerman's first feature, that psychiatry's target conditions fall under the concept of disease, determines whether psychiatry is a branch of medicine in the sense relevant to antipsychiatric claims.

Guze promisingly starts his 1978 article with the questions "Are psychiatric conditions diseases?" and "How is disease defined?"[16, p.295] (Guze and the neo-Kraepelinians decidedly preferred the biologically connotative term "disease" to "disorder", a point to which I will return). But, he immediately shifts to exploring the nature of the "medical model". This path of analysis repeatedly leads him to confront the fact that the one feature of the "medical model" that is relevant to deciding whether psychiatry is a branch of medicine is whether it is used to address genuine diseases. The "medical model", he finally concludes, "is clearly related to the concept of disease" and its most basic feature is a "concern for the symptoms and signs of illness"[16, p.296].

Unfortunately, when Guze refocuses on the concept of disease, he is not able to make much headway. He notes that those who argue against psychiatric conditions being diseases often rely on a definition of disease that "requires the presence of consistent pathologic changes in one or another bodily organ or evidence of a qualitative deviation from the normal in some function or process"[16, p.297]. He argues that this anatomical/physiological definition is too narrow even as a definition of physical disease, thus should not be used to exclude psychiatric conditions from disease status. However, throughout his discussion, he seems to confuse the definition of disease – what it is for a condition to be a disease – with what we happen to know about a condition at a given time. Guze uses epilepsy and cardiac dysrhythmias as examples of conditions that were long recognized as diseases based on apparent functional impairment despite lack of understanding of their pathophysiology and etiology, concluding that "among conditions most physicians and most laymen regard as medical disorders are states for which consistent anatomical changes have not yet been recognized"[16, p.297]. He is of course quite correct: medicine generally recognizes conditions as disorders on the basis of indirect evidence long before the actual etiology is known.

However, Guze's understanding that one may not yet know the etiology of a condition and nevertheless from circumstantial evidence one may justifiably judge it a disorder does not resolve the problem of what makes it a disorder – that is, what we need to infer from the circumstantial evidence to conclude that there is a disorder.

Guze also refers to a definition of disease that he had proposed in an earlier paper: "any condition associated with discomfort, pain, disability, death, or an increased liability to these states, regarded by physicians and the public as properly the responsibility of the medical profession, may be considered a disease"'[16, p.296]. This definition is invalid, because it would encompass, for example, childbirth pain, pregnancy, and cosmetic concerns addressed by surgery. The sheer fact of discomfort or pain that physicians try to ameliorate cannot be used as a sufficient criterion for medical disorder. Even antipsychiatrists could agree that conditions targeted by psychiatric treatment often cause discomfort and are regarded as the responsibility of the medical profession. Their point is that these conditions are not genuine medical disorders.

Klerman's attempts to respond to antipsychiatry

Klerman presents various arguments to rebut the antipsychiatrists and show that psychiatric conditions can be genuine medical disorders, but these arguments tend to be weak. For example, he argues: "From research evidence and clinical experience it is concluded that certain of the experiences and behaviors of individuals labeled schizophrenic are abnormal. They are distressing to the individual and to those around him, and are profoundly maladaptive for the individual in relation to his family and his social grouping"[15, p.110]. The fact that purported disorders are "profoundly maladaptive", "distressing", or "abnormal" in a statistical sense is consistent with the antipsychiatric position. If "abnormal" is intended to mean "psychopathological", then Klerman's argument begs the question of whether the conditions are really disorders.

Klerman comments on Laing's analysis, according to which "the locus of pathology is in the family or in the society at large", by arguing that "it is a bizarre form of sophistry to deny the sick role and the opportunity of being treated to the patient by placing blame on the family or society"[15, p.110]. Again, this answer begs the question: it is sophistry only if in fact these individuals have disorders rather than unfortunate suffering due to oppressive familial or social structures.

In rejecting Szasz's view that mental disorder is a myth, Klerman argues: "If it is a myth, then… it is also a myth with a genetic transmission and a pharmacological antidote"[15, p.110]. This quip is a *non sequitur*. Antipsychiatrists such as Szasz and Laing never claimed that the *condition* that we call schizophrenia is a myth, although perhaps some labeling theorists came close to this. The "myth" is supposed to be that the condition is a mental disorder in a medical sense. Non-disordered conditions can be real, genetically transmitted, painful, and alterable by psychotropic medication.

R. Spitzer's approach to the question of psychiatry's medical status

In grappling with the rationale for eliminating the category of homosexuality as a disorder from the DSM, R. Spitzer was forced to confront the question of what it means for a condition to be a medical disorder. He continued to pursue this question after the homosexuality debate had been resolved. After some false starts in which he argued that a medical disorder was defined in terms of certain kinds of harm, such as suffering or social role impairment, his thinking changed.

His broader goal, like the neo-Kraepelinians, was to define mental disorder in a way that would convincingly locate mental disorders within medicine and counter the antipsychiatrists. In considering obvious counterexamples to his earlier definitional attempts, as well as objections from his colleagues, he concluded that the only way to accomplish this was to first clarify the meaning of medical disorder and then define mental disorder as a subdomain of medical disorder[43]. This led to his analysis of the concept of mental disorder, coauthored with J. Endicott, that was published in the same year as Klerman's article.

Spitzer and Endicott argued that the basic intuition behind the concept of a medical disorder is that "something has gone wrong with the organism" that yields harmful symptoms. They expressed the necessary condition that something has gone wrong by the phrase "organismic dysfunction". The attempt to explain why mental disorders are best understood as a subcategory of medical disorders led them to a dysfunction requirement: negative consequences alone are insufficient as a definition of disorder, due to the existence of many painful conditions that are not medical disorders. The expression "organismic dysfunction" was shortened to "dysfunction" in the definition that appeared in Spitzer's introduction to the DSM-III, which required that "there is an inference that there is a behavioral, psychological, or biological dysfunction"[44, p.6]. The dysfunction requirement has then appeared in the definition of disorder in every subsequent DSM edition, as well as in the ICD-11[45]. Whereas the symptoms are manifest, the presence of dysfunction – that something has gone wrong in the organism – is inferred from the symptoms, with the nature of the inferred dysfunction generally unknown.

Spitzer and Endicott did not yet have an evolutionary understanding of dysfunction. Indeed, Spitzer later admitted that he was quite baffled by the problem of how to explicate the idea that something has gone wrong inside the organism. However, he eventually endorsed my evolutionarily based "harmful dysfunction analysis" of medical – including mental – disorder, according to which the relevant dysfunctions are failures of internal physical or psychological mechanisms to perform natural functions for which they were biologically designed (i.e., naturally selected)[46-52]. Spitzer concluded that this is the only plausible way to scientifically ground the notion of dysfunction[53,54].

A glance at DSM confirms that the categories of disorders do seem to capture what are *prima facie* failures of biological design. That is, the categories tend to correspond to domains in which it seems highly plausible that there are biologically designed mechanisms and natural functions, and the described conditions appear to be ways in which those mechanisms can go awry. For example, human developmental processes, thought, emotions, appetite and sexuality are all areas in which one would expect that complex adaptive mechanisms have been naturally selected, so that failures of expectable functions tend to be dysfunctions.

Spitzer's analysis has to some extent reshaped the discussion on psychiatry's status. Skeptical challenges raised today, as in the neurodiversity movement's claims that autism is illegitimate pathologization of normal brain variation, in critiques of attention-deficit/hyperactivity disorder (ADHD) as pathologizing normal child rambunctious behavior, or in objections to eliminating the major depression bereavement exclusion[55-57], generally do not question psychiatry's legitimacy as a branch of medicine. Rather, they question whether the concept of mental disorder is being applied correctly to the specific category at issue and argue that psychiatric diagnostic practices are generating false positive diagnoses.

However, antipsychiatric attitudes are still powerful in some constituencies, and this struggle is hardly resolved. Even today there are sometimes reactions against the "biomedical" approach, and the argument against biomedicalization is often misdirected due to conceptual confusion. On the one hand, psychiatrists are accused of "medicalizing" various aspects of life that are not strictly disorders, and on the other they are accused of applying a narrow "biomedical" approach which neglects the broader mental health needs of the population that extend well beyond disorder.

2. PSYCHIATRY SHOULD UTILIZE MODERN SCIENTIFIC METHODOLOGIES AND BASE ITS PRACTICE ON SCIENTIFIC KNOWLEDGE

This is a proposition that anyone interested in advancing psychiatric knowledge, neo-Kraepelinian or not, could endorse. More sophisticated science is undeniably the most promising pathway to optimal diagnosis and treatment of those suffering from mental disorder. A major benefit of neo-Kraepelinianism has been the focus on generating cumulative and relevant scientific knowledge about etiology and treatment using the most advanced research methods.

Proposition 2 also appears intended as a rebuke to the American classic psychoanalytic school that was perceived as unscientific. Such criticisms seem justified. It was the sad fate of classical clinical psychoanalytic theory of that era to fail to transcend the unscientific sexual etiological theories of Freud[58].

The DSM-III's embrace of the syndromal approach to diagnosis, whatever its problems, has yielded an explosion of scientific research on mental disorders using the most advanced methodologies and data-analytic techniques. A major benefit of neo-Kraepelinianism is that the psychiatry profession's use of research-style criteria in clinical diagnosis has allowed for the generation of an increasing amount of scientific research on psychiatric conditions that is directly relevant to the clinical categories used by clinicians. Because research from varying approaches use the same criteria for sample selection, the results can be compared and accumulated into a picture of treatment effectiveness.

On the other hand, the yield in terms of major breakthroughs in etiological understanding or treatment effectiveness is much less than one might wish. Although we base practice on scientific knowledge to the degree that we can, our decision making is far from being fully scientifically based, because we know so little.

3. PSYCHIATRY TREATS PEOPLE WHO ARE SICK AND WHO REQUIRE TREATMENT FOR MENTAL ILLNESSES

Proposition 3 is a corollary of proposition 1. For psychiatry to be a branch of medicine, it must treat medical disorders as its defining core mission. However, this proposition requires interpretation because, if taken in a logically strong sense – as asserting that psychiatrists appropriately treat *only* mental disorders – it is obviously false. Psychiatrists appropriately treat many problematic psychological conditions that are not mental disorders, as the DSM-ICD systems officially recognize in their large sets of psychological "Z Codes", i.e. problematic psychosocial conditions that are not disorders but for which psychiatrists are frequently consulted.

Klerman subsequently corrected any possible misunderstanding on this score in a follow-up article with Schechter in which he explained that, in addition to its core domain of mental disorders, psychiatry is also mandated to treat "problems involving significant amounts of psychological and emotional distress associated with the stress of daily life but that do not meet the criteria for a diagnosable mental disorder" as well as "people… who seek to enhance their own potential, heighten their awareness, or improve their mental health"[40, p.122] (see Figure 1).

However, to make treatment of mental disorder the core of psychiatry's mission, one must be able to distinguish the mentally disordered from the non-disordered. This is precisely the assumption to which the antipsychiatrists objected, claiming that any such distinction consists of arbitrary labels serving social control purposes. This brings us to the neo-Kraepelinian assumption that disorder can be distinguished from non-disorder, and thus to Klerman's proposition 4.

4. THERE IS A BOUNDARY BETWEEN THE NORMAL AND THE SICK

The neo-Kraepelinians understood that a defensible disorder/non-disorder boundary, even if fuzzy, is essential for distinguishing mental disorder from normal-range socially deviant, disapproved, or problematic behavior or distress, and so is required to respond adequately to antipsychiatric critics.

Physicians clearly have the ability to at least roughly distinguish disorder from normality in most domains. Despite all the controversies and missteps in the history of medicine, if one examines the diagnostic compendiums of antiquity, one finds that, despite lack of knowledge and wildly incorrect theories of underlying dysfunctions and normal physiology, almost all the conditions classified as medical disorders still would be seen as such today. This suggests that physicians are pretty good at using circumstantial evidence to judge that something has gone wrong with how individuals are biologically designed to function. Proposition 4 thus reflects a point basic to the bootstrapping process on which neo-Kraepelinian progress in nosology rests. On the basis of syndromal symptoms, one can often (fallibly) distinguish a category of clearly disordered conditions from clear normality. This provides a starting point for research to establish one or more etiologies present in the disordered group – although carrying out this part of the program has thus far proven more difficult than envisioned.

Proposition 4 thus concerns only a disorder category's *conceptual validity*, which refers to the category's including only disordered conditions[46]. Conceptual validity is a much more limited initial goal than the more demanding ultimate goal of *construct validity*, which refers to the category's including only disorders with a homogeneous etiology based on the same type of underlying dysfunction.

DSM syndromal diagnostic criteria sets are designed to achieve conceptual validity. Every feature of the diagnostic criteria sets, including duration requirements, symptom thresholds, the specific nature of the symptoms, the frequency, intensity and persistence of the symptoms, and even contextual exclusions for scenarios in which symptoms can be better understood as normal reactions to a challenging environment, are all attempts to operationalize the notion that something has gone wrong and allow an inference to dysfunction versus a normal-range form of distress or problem in living[59-61]. There is of course also a hope, usually forlorn, that the criteria may have construct validity.

To see the two forms of validity at work, consider the first sentence of Robins and Guze's classic article on validating diagnostic categories: "Since Bleuler, psychiatrists have recognized that the diagnosis of schizophrenia includes a number of different disorders"[62, p.983]. The assumption is that one conceptually valid disorder category, schizophrenia, can be refined into multiple construct valid disorders. Klerman, too, explains that schizophrenia is a syndrome that likely encompasses multiple etiologies, so that refinement into more construct valid categories is called for. Kraepelin suggested that one way to increase construct validity from initial syndromal categories is by a gradual refinement process of addition and subtraction based on syndromal features and etiological discoveries[63]. To make the mistake of thinking that the initial syndromes are already the individuated disorders that are the end-goal of the process is to illegitimately "reify" syndromes into disorders[64].

The challenge of conceptual validity: was uniting research and clinical criteria a mistake?

Achieving conceptual validity has turned out to be surprisingly difficult, once psychiatry focused less on the asylum, with its extreme clearly disordered conditions, and more on the community, with its many varying forms of normal distress and deviance that are often difficult to distinguish from disorder strictly on symptomatic grounds. Under these circumstances, the neo-Kraepelinian vision called for an aggressive and systematic anti-false-positives stance if validity goals were to be preserved. However, such a stance was not forthcoming.

The pursuit of conceptual validity is one place that suffered possible negative side effects from Spitzer's remarkable accomplishment of uniting clinical and research criteria. The Feighner and Research Diagnostic Criteria that preceded the DSM-III were formulated with research in mind. However, Spitzer quickly recognized the potential for a revolution in psychiatric diagnosis by re-conceptualizing neo-Kraepelinian research diagnostic criteria as clinical diagnostic criteria as well. This brilliant tactic created a novel direct link between research studies and the clinician's need for guidance in treatment choice. Rather than by a gradual process of rectification of clinical and research needs, in one fell swoop clinical diagnosis was brought to the greater level of precision required in research.

The problem is that, once this link was forged, the influence went in both directions. The formulation of research criteria was now influenced by feedback from the practical concerns of the clinician. The relentless process of addition to and subtraction from diagnostic categories that might have led from initial syndromal categories to etiologically more homogeneous categories or at least more conceptually valid categories was impeded by a host of clinical utility concerns.

In clinical intervention, fear of false negatives often outweighs concerns about false positives when treatment is not risky. In the US, many clinicians need a disorder diagnosis to obtain insurance reimbursement, so there is pressure to have categories that encompass the problems for which people seek help even if they are not disorders. An admirable humanitarian impulse causes clinicians to want to help as many people as they can, and thus DSM work groups are biased toward inclusion independent of strict etiological considerations. As N. Ghaemi trenchantly put the problem: "Why should neuroanatomy correlate with wishes for insurance reimbursement?"[65]. This is precisely the opposite of what is needed for advancing the neo-Kraepelinian research agenda. The uniting of research and clinical criteria may have exacerbated the false positives problem to the point of being the death-knell for the serious pursuit of the neo-Kraepelinian program.

There are many illustrations of the approach to validity gone awry due to clinical utility considerations taking precedence, but one of the most striking concerns the category of substance abuse. Whereas addiction can be understood as a genuine mental disorder, sheer use of a substance in a way that may be excessive or harmful or causes arguments with one's family or leads to legal difficulties does not imply mental disorder. This was sufficiently apparent that the category of substance abuse, introduced in the DSM-III, was slated to be eliminated from the DSM-III-R[66]. This decision was reversed at the last minute due to the consideration that the categories and criteria should allow treatment for as many people as possible who could be helped by it.

Remarkably, during succeeding DSM revisions, this pragmatic consideration repeatedly won out over scientific validity considerations, and the substance abuse category was retained, inflating disorder estimates and confusing scientific endeavors. Finally, in the DSM-5, the category of substance abuse was eliminated. However, the work group argued that "the substance use disorders criteria represent a dimensional condition with no natural threshold". So, "to avoid a marked perturbation in prevalence without justification, the work group sought a threshold for DSM-5 substance use disorders that would yield the best agreement with the prevalence of DSM-IV substance abuse and dependence disorders combined" – that is, they attempted to match the previous dependence and abuse prevalence despite abuse's invalidity. Challenged on the grounds that such a low threshold would not represent true cases and would reduce etiological homogeneity, the committee answered: "These understandable concerns were weighed against the competing need to identify all cases meriting intervention"[67, p.841]. That is, clinical utility outweighed concerns about conceptual validity, let alone construct validity.

It is true that each DSM revision has corrected some obvious false-positive mistakes in the diagnostic criteria. For example, the DSM-5 added to insomnia disorder the requirement that "the sleep difficulty occurs despite adequate opportunity for sleep", to eliminate false positives due, for example, to a neighbor's late-night television viewing; DSM-5 oppositional defiant disorder newly excludes diagnosis if the defiant behavior is directed only toward a sibling, because sibling relations can normally include such behavior; and the DSM-5 finally introduced the requirement that a sexual dysfunction can be diagnosed only if lack of sexual response in a relationship is not better explained as a consequence of severe relationship distress such as partner abuse or violence. Such *ad-hoc* corrections are useful. However, they are no substitute for systematic category-by-category attention to the problem of false positives.

Implications of the failure to confront the false positives problem

The failure to aggressively confront the false positives problem raises a disturbing question. As unlikely as it may seem after four decades of perceived neo-Kraepelinian diagnostic hegemony, it is nonetheless possible that neo-Kraepelinianism, to borrow G.K. Chesterton's remark about Christianity, "has not been tried and found wanting; it has been found difficult and not tried"[68]. The neo-Kraepelinian program – including Klerman's pivotal proposition 1, that psychiatry is inherently medical – rests on proposition 4's claim that disorders can be separated from problematic non-disorders, so that scientific identification of homogeneous dysfunction etiologies can proceed. If psychiatry has not taken the boundary between disorder and non-disorder seriously enough to avoid having admixtures of normal distress and true disorder in many of its central categories, then that makes scientific bootstrapping to identification of distinct dysfunctions extremely difficult.

Kraepelin was well aware of the false positives problem. Although unmentioned in recent articles analyzing his approach to diagnosis, Kraepelin attended to identifying potential false positive cases and sometimes explained the basis for judging a potentially ambiguous condition to be a true case: "Morbid emotions are distinguished from healthy emotions chiefly through the lack of a sufficient cause, as well as by their intensity and persistence... Again, morbid emotions sometimes attach themselves to certain external occasions, but they do not vanish with the cause like normal feelings, and they acquire a certain independence"[69, p.68].

Sometimes, Kraepelin made a difficult judgment about a first episode that was only justified by later developments, with the benefit of time having passed. For example, he admits that some women's intense depressive episodes after the death of their husbands could be seen as a normal-range depressive reaction except for evidence that emerged later: "A woman fell ill three times of depression after the death first of her husband, next of her dog, and then of her dove. Another patient was depressed after the death of her husband, manic after a confinement and after a dental operation"[70, pp.179-180].

Kraepelin likely would have been shocked to hear the eminent psychiatric epidemiologist R. Kessler explain to an interviewer the then-controversial findings of a major psychiatric epidemiological study indicating that 50% of Americans experience mental disorders: "Well, we found that... about half the population meets criteria for at least some mental disorder at some point in their life, but I think it's important to put this in context.... There are many people who have minor phobias, who, for three or four weeks, get depressed after they move from one town to another or break up with a relationship. Perhaps they have some panic problems for a month or two after they get into a life-threatening automobile accident. But most of these things are very minor. They're self-limiting. They go away on their own. And they're the stuff of day-to-day life that we all experience at some time or another"[71].

This answer was evidently troubling enough that the then-President of the American Psychiatric Association, S. Sharfstein, felt the need to comment on the obvious doubts it raised about psychiatric diagnosis: "The study raises many questions and issues about the nature of psychiatric disorders... Does our DSM nosology have too low a threshold in selecting symptoms of mental disorders? Many of these disorders may be self-limiting and mild in response to life stresses... How much credibility does our diagnostic system lose by attaching a psychiatric diagnosis to these relatively mild and self-limiting problems?"[72].

Ultimately, however, it is not just public credibility but also scientific validity that is sacrificed if diagnostic categories are not conceptually valid. D. Regier, later the DSM-5 Task Force Vice-Chair, suggested that there was indeed a problem: "Based on the high prevalence rates... it is reasonable to hypothesize that some syndromes in the community represent transient homeostatic responses to internal or external stimuli that do not represent true psychopathologic disorders"[73, pp.112,114]. Since Kessler's and Regier's remarks, studies using superior longitudinal epidemiological methods have shown that the prevalence rates of individuals meeting DSM criteria for disorder is much higher even than Kessler's 50%[74,75].

An initial step toward taking false positives seriously was taken by P. Clayton, in her classic study of false-positive diagnoses of depression during normal grief[76]. Whereas depressive criteria had been validated previously by showing that they differentiated depression cases from cases of physical illness and from normal individuals[77,78], Clayton realized that this did not directly address the false positives problem. She adopted the strategy of studying a group of presumptively non-disordered individuals that was feared might be falsely diagnosed, namely, grief-stricken people who had recently lost a loved one. Her research established that many of these individuals did indeed satisfy standard diagnostic criteria despite presumed lack of disorder.

Clayton's work resulted in the DSM-III incorporating a bereavement exclusion to reduce false positives for major depression. Her work was not followed up with research targeting other stressful sources of transient normal-range depressive feelings, even though she herself urged such expansion[76]. Despite recent replicated epidemiological evidence that the bereavement exclusion picked out conditions that were dramatically more benign in outcome than other depressed individuals[79-85], the exclusion was eliminated in the DSM-5 as a formal part of the diagnostic criteria and replaced by an ambiguous note suggesting that clinicians identify false positives without guidance from diagnostic criteria. The resulting number of possible false positives is unknown. One hint is that a recent analysis found that about 13% of all the individuals classified as depressively disordered by DSM-5 criteria in a major epidemiological study had experienced their episodes only after the death of loved ones and lasting less than two months – and that is just for bereavement and not including the larger domain of potentially normal-range reactions to other stressors to which Clayton alluded[86].

The general lack of adequate attention to context distinguishes the DSM criteria for major depression from the way physicians from ancient times to Kraepelin thought about depressive pathology. For example, the major risk factor by far for an initial episode of major depression in an adolescent is the breakup of a romantic relationship. Classic physicians would have looked askance at any easy equation of these conditions. Galen himself provides a case in which he ponders whether a woman is suffering from melancholia or unrequited love (it turns out to be the latter). Our fascination with the symptom approach has seemingly been elevated into a fetish that has defeated the seriousness of the neo-Kraepelinian aspirations that started us down this path.

There are, of course, many ways to study false positives other than Clayton's simple and direct method (see, for instance, the later discussion on the *DRD4* gene in the section on proposition 6). Moreover, this is clearly not an issue unique to depression. The point is that the problem of false positives has simply not been pursued systematically, undercutting the possibility of giving neo-Kraepelinian aspirations a chance of being realized.

The threat to proposition 4 from dimensional approaches to diagnosis

I noted in the introduction that, in response to the perceived failure of the neo-Kraepelinian program, a variety of nosological proposals have emerged to compete as its replacement. Prominent among these options is the view that syndromes may be decomposed into a hierarchy of factor-analytically determined dimensions, yielding a fully dimensionalized classification system.

Dimensional and factor analytic explorations of the psychometric structure of the space of symptoms of mental disorders are a welcome development. However, beyond potential scientific contributions, there is a push to fully transform our nosology into a dimensional system. This movement has gathered momentum and is endorsed by many leading researchers and nosologists, as in the HiTOP version of dimensionalization[6-9]. In fact, dimensionalization was embraced as one of the prime goals of the DSM-5 Task Force: "We have decided that one, if not the major, difference between DSM-IV and DSM-V will be the more prominent use of dimensional measures in DSM-V"[87, p.649].

The most common dimensional proposals simply arrange the conditions that fall within a pre-defined DSM category according to the severity of symptoms, as was done, for example, with autism spectrum disorder and substance use disorder in the DSM-5 and personality disorder in the ICD-11. The DSM-5 Task Force intended to add such symptom-severity dimensional measures to all the major disorders, but decided against it for reasons that were scientific (the scales were not adequately validated), of clinical utility (there was inadequate understanding of how treatment choice should vary with severity rating), as well as pragmatic (reimbursers might decide to set their own severity thresholds for treatment reimbursement). Dimensionalization of this kind presupposes a symptomatically defined category of disorder on which the severity measure is imposed, and such severity scales are frequently imposed on disorders in physical medicine as well. This sort of dimensionalization involves no challenge to categorical diagnosis and is entirely consistent with neo-Kraepelinianism.

Stronger forms of dimensionalization replace and transcend the pre-existing diagnostic categories. For example, some members of the DSM-5 Task Force at one point imagined replacing the entire categorical system with a system of severity dimensions of various types of symptoms that are applied to the entire population and would yield a unique "diagnosis" for each individual consisting of a point in the multidimensional severity grid, replacing all current categorical diagnoses. A major criticism of DSM-ICD by those who want to replace the categorical nosological system with a dimensional system is that DSM-ICD categories provide "scientifically arbitrary diagnostic cut-offs"[4] or "arbitrary boundaries between psychopathology and normality"[6].

The problem with strong dimensionalism from a neo-Kraepelinian perspective is that it lacks a concept of dysfunction that locates the extreme conditions within the medical domain. Dysfunctions and normal variations alike may be on the extreme of a dimension.

So, without some additional dysfunction criterion, strong dimensionalism would dislocate psychiatry from medicine. The antipsychiatrists would be delighted with this account: what else is social deviance than being extreme on some socially defined dimensions? In fact, one typically sees dimensionalists shifting their terminology from "pathological" to "maladaptive" to reflect these presuppositions, and "maladaptive" is just one step away from "socially disapproved" and the reawakening of antipsychiatric forces. Dimensionalists criticize the DSM-ICD for having arbitrary boundaries – which, we shall see, is only partly true – and then propose a system that formally does away with non-arbitrary boundaries.

In this approach, a disorder is *nothing but* being extreme on a dimension, or perhaps being extreme on a dimension in a problematic or harmful way. An unappreciated problem with this approach is that the essence of a population-distribution dimension is different from the essence of a disorder. There are populationally distributed traits such as sadness, anxiety and weird thinking that are mostly features of non-disordered individuals. Without some additional explanation as to why those same features in their extreme versions should be considered disordered, the strong dimensionalist program yields to arbitrariness. Consider, for example, H. Eysenck, who also went down the path of dimensionalization and found that, no matter how high up he went on the psychoticism scale, it was not equivalent to psychotic disorder[88].

Nevertheless, psychologists regularly argue for strong population-based dimensional approaches based on the greater statistical analytical power they yield[4], generally ignoring the impact that such a system would have on the medical status of psychiatry, while nevertheless continuing to use medical language. Other dimensionalists, like behaviorists before them, are honest enough to confront the antipsychiatric implications of a strong dimensionalist view that offers no non-arbitrary boundary between disorder and normality. Thus, for example, the eminent geneticist and psychologist R. Plomin dramatically claims that "there are no disorders"[89, p.23], and that "the abnormal is normal, meaning that there are no qualitative disorders, only quantitative dimensions"[90, p.128].

A group of leading researchers and nosologists conclude: "all thresholds in mental illness should be regarded as arbitrary"[5, p.74]. Yet, at another point, the same authors note that "such categories as infant, toddler, child, and so on represent semiarbitrary but useful divisions along the continuum of age"[5, p.75]. Surely such divisions are not arbitrary; a normal individual at age 3 is a child and a normal individual at age 25 is an adult by the very meaning of the concepts "child" and "adult". What they presumably mean is that the distinction is fuzzy – it is non-arbitrary within extensive domains but arbitrary for a fuzzy boundary zone (and perhaps for some pathological instances or instances in which development is intentionally medically manipulated). So, if a precise line must be drawn, then there is some arbitrariness. But, the substantial non-arbitrariness due to clear cases exists for most real distinctions, including disorder versus non-disorder. The concept "extreme on a population dimension" has no such non-arbitrary domains corresponding to clear cases of disorder and non-disorder.

The dimensionalist critique of DSM-ICD includes several other standard complaints that the proposed approach is claimed to address. It is claimed that dimensionalism eliminates diagnostically messy and puzzling comorbidity because everyone falls at one multidimensional point on the system of dimensions, so everyone has just one condition. This "solution" evades all the interesting causal questions that need to be addressed about comorbidity and provides merely a technical terminological "solution" without advancing understanding. The comorbidity questions will just reappear in the statistical analyses of the co-occurrence of various factors, even if it is no longer called comorbidity. There are all sorts of reasons – e.g., common risk factors, unusually stressful environments that trigger multiple dysfunctions – why more than one disorder might occur at the same time. For comparison, about 77% of older individuals have two or more chronic physical disorders at any one time, not including additional transient disorders. Given the high level of interaction and integration among psychological modules, dysfunction in one module could tend to cause unusual behavior or even dysfunction in another linked module, even though "pure" one-module dysfunctions are also possible.

It is also claimed that dimensionalism addresses problematic heterogeneity within disorder categories. Dimensionalization provides a technical sidestepping of this issue without resolving or addressing the scientific substance. The various symptom realizations of a disorder are based on theory and clinical experience, and are supposed to reflect possible alternative ways that an inferred common type of dysfunction might manifest itself. That is correct or incorrect in each case, but is ultimately an empirical question not resolved by dimensional reorganization.

The number of different syndromal conditions satisfying some DSM-ICD diagnostic criteria sets is frequently cited to show the absurdity of the DSM-ICD system. However, this is an empirical question, and it is the criticism that is absurd. Just to take a simple example all too close at hand: upon searching, I get a list of 16 possible COVID-19 symptoms and, if any two or more of them is considered cause for inferring possible disease, that means there are 65,519 symptom profiles, many non-overlapping, that get you a likely diagnosis. It is a scientific question whether the evidence of causation from the same underlying cause is solid, not a matter of ridicule because a single dysfunction may have such a wide array of presentations. Certainly diagnostic heterogeneity will be a scientific focus as genetic studies give us the power to tease apart syndromal variations that were mistakenly lumped together under one postulated dysfunction type, and also to unite syndromal presentations that look like they are products of different dysfunctions. None of these substantive issues are addressed by sheer dimensionalization.

To become a profession concerned with dimensionally extreme maladaptive behaviors would take psychiatry into a morally controversial terrain. If it is true that "revenge is a dish best served cold", then many psychologists who objected to Spitzer's implicit medicalizing of psychiatry to end the antipsychiatric threat must be salivating now, as the totally non-medical psychological mainstay of statistical studies of populations is perhaps poised to encompass psychiatry.

5. THERE ARE DISCRETE MENTAL ILLNESSES. MENTAL ILLNESSES ARE NOT MYTHS. THERE IS NOT ONE BUT MANY MENTAL ILLNESSES. IT IS THE TASK OF SCIENTIFIC PSYCHIATRY, AS OF OTHER MEDICAL SPECIALTIES, TO INVESTIGATE THE CAUSES, DIAGNOSIS, AND TREATMENT OF THESE MENTAL ILLNESSES

Are there many mental disorders?

We already dealt with the issue of "mental illnesses are not myths" when considering the proposition 1 of Klerman's credo. Moreover, if there are mental disorders, then it surely follows that "it is the task of scientific psychiatry… to investigate the causes, diagnosis, and treatment of these mental illnesses". So, consideration of proposition 5 comes down to two further claims that can be combined into one: "there are many discrete mental disorders".

Guze elaborated the idea in his 1978 paper: "there are many psychiatric disorders, each with a different clinical picture, natural history, etiology, pathogenesis, and response to treatment"[16, p.306]. This claim was basic to the diagnostic aspirations of the neo-Kraepelinians in opposition to psychoanalytic theories postulating one Oedipal etiology, and behaviorist theories claiming that all behavior is normal learning.

How many distinct mental disorders there are is ultimately an empirical question. The neo-Kraepelinians were, of course, well aware of the many-to-many relationship of biological etiologies and symptomatic presentations in physical medicine. Even among biologically oriented psychiatrists in the 19th century, there were some who argued that all mental disorder was likely due to just one or a few fundamental pathologies. Kraepelin himself wondered toward the end of his career whether his basic division of dementia praecox and manic-depressive insanity did not hide one condition emerging in varying presentations. So, other than anti-psychoanalytic animus, what were the grounds for the neo-Kraepelinians' claim that there exist many discrete mental disorders?

One answer is that the neo-Kraepelinians were impressed by what at that time seemed to be a promising specificity of the effects of psychopharmacological medications on various psychiatric conditions, although confidence in "pharmacological dissection" has waned considerably over time. In any event, there is a more basic theoretical argument implicit in Guze's writings that suggests the plausibility of there being many discrete mental disorders. Guze argues for an evolutionary perspective on the brain as the complexly biologically designed basis for our many distinct psychological capacities and thus as a foundation for biological psychiatric theory: "I start my argument with evolution, the bedrock of modern biology. Of central interest to psychiatry is the fact that evolution has shaped the development of the brain – the organ of mental functions or what we call the mind… All brain functions, including perception, learning, thought, memory, emotions, communication, language, etc. reflect the results of such evolution. The capacity to feel, to be aware, to recognize, to remember, to learn, to talk, to think all depend upon this wonderfully evolved brain with its still mysterious complexity, made possible by what we must take to be a finite genotype… devoted to programming the brain"[17, pp.315-316].

Guze's evolutionary arguments are primarily aimed at supporting the primacy of brain functions in determining mental functions and thus a biological foundation for psychiatry. However, they also presuppose that the brain must have many distinct mechanisms to support so many distinct mental capacities. For example, thinking, perception and hunger are so different from fear, sadness and joy to lead one to suppose that the brain mechanisms which are programmed to provide these presumably evolved capacities must be distinct, whether in actual structure or in differential response capacities of the same structure. It seems plausible and indeed inevitable that dysfunctions can occur in each of these psychological domains independently of problems with the others – high rates of comorbidity notwithstanding, as that could be due to the rich interactions among the various brain features underlying the functional capacities.

In current philosophical and evolutionary-theoretical terms, the postulation of many distinct brain processes devoted to various evolved capacities is known as the "modularity of mind" hypothesis[91-96]. If one combines a recognition of the complexity of the brain's many different biologically designed processing domains with the view that disorders are individuated by underlying dysfunctions, and one adds the commonsense observation that "whatever can go wrong, will go wrong", the conclusion follows that there must be many different mental disorders. Experience seems to confirm that complexly designed entities with many designed sub-processes, whether biological or artifactual, can go wrong in many different ways.

Spitzer versus the neo-Kraepelinians on discreteness

The claim that mental disorders are discrete can have various meanings. From the time of the DSM-III through today, the generally accepted understanding of discreteness within psychiatry is in terms of the "zones of rarity" account elaborated by R. Kendell[97,98]. In early studies of depression, Kendell defined discreteness in terms of discontinuities along dimensions either of symptoms or of observable correlates of symptoms such as course, outcome, or response to treatment: "Proof that two clinical syndromes are distinct entities depends on a demonstration that patients with features of both syndromes are less common than those with features only of the one or the other… a bimodal distribution of scores must be demonstrated on some chosen dimension"[99, p.257]. Such discontinuities are evidence of natural boundaries: "Diagnostic categories defined by their syndromes should be regarded as valid only if they have been shown to be discrete entities with natural boundaries that separate them from other disorders"[100, p.4]. The wide acceptance of Kendell's zones-of-rarity test has had momentous consequences for nosology. The frequent failure to find such zones has accelerated the trend toward dimensionalization.

No doubt Spitzer had Kendell's work in mind when he renounced any commitment to the discreteness of mental disorders and thus his view became distinct from standard neo-Kraepelinianism. Soon after the appearance of the DSM-III, R. Blashfield published a paper citing the Feighner criteria and Klerman's nine propositions as the basis for an inordinately influential neo-Kraepelinian "invisible college" within psychiatry[36]. Blashfield cited Spitzer as a leading neo-Kraepelinian, so Spitzer decided to publicly clarify his position and make explicit the differences between him and the neo-Kraepelinians.

In his published commentary, Spitzer notes that Blashfield says he adheres to Klerman's "neo-Kraepelinian credo, nine articles of faith", and states unequivocally: "I take this opportunity… to offer my resignation publicly from the neo-Kraepelinian college as I do not subscribe to two of these articles of faith". The first one that Spitzer rejects is Klerman's proposition 5, that there are discrete mental illnesses. In his explanation, Spitzer quotes directly from his own introduction to the DSM-III as proof: "Article five states: 'There are discrete mental illnesses'. As stated in one of the required texts of this college, DSM-III, 'In DSM-III there is no assumption that each mental disorder is a discrete entity with sharp boundaries (discontinuity) between it and other mental disorders, as well as between it and No Mental Disorder'. This is an empirical issue and the available evidence supporting discontinuity… is far less than compelling"[101, p.592].

It may seem incomprehensible that the designer of the DSM-III categorical system denied that such a system presupposed discrete categories of disorder. Spitzer clearly intended the categories of DSM to be taken in a more flexible way than critics have construed it. For Spitzer, we have seen, the crucial test of conceptual validity – that is, that the categorized conditions fall within the medical realm, even if not yet sorted into construct-valid individual disorders – is that they are caused by something-gone-wrong dysfunctions. Dysfunctions or their symptoms might conceivably be continuous with each other, so discreteness of categories of disorder is largely independent of the deeper discreteness issue of dysfunction versus normality.

6. THE FOCUS OF PSYCHIATRIC PHYSICIANS SHOULD BE PARTICULARLY ON THE BIOLOGICAL ASPECTS OF MENTAL ILLNESS

Neo-Kraepelinianism was inspired by discoveries of brain-based etiologies for prominent mental disorders, including general paresis, pellagra and Alzheimer's disease. The neo-Kraepelinians paid lip service to various psychological, family, developmental and cultural influences on mental disorder, as well as to the fact that almost all human features result from some degree of genetic or biological interaction with environmental influences. However, when they consider the concept of mental disease, they sideline all of the non-biological factors and affirm the unique primacy of specifically biological etiologies as supporting the attribution of medical and psychiatric disorder.

"Biological" can be understood here in the sense of anatomical or physiological features. It appears that Guze, lacking Spitzer's "dysfunction" criterion, mistakenly thought that the presence of a biological substrate was needed to guarantee that a mental condition was a medical disorder. He systematically defends such a biological view, concluding: "There is no such thing as a psychiatry that is too biological… The conclusion appears inescapable to me that what is called psychopathology is the manifestation of disordered processes in various brain systems that mediate psychological functions. Psychopathology thus involves biology"[17, pp.315,317].

Guze puts forward many rather weak arguments for biological etiology. He argues that nobody has yet demonstrated a non-biological etiology for a mental disorder, but, with few exceptions, the same is true for biological etiology. He argues that the non-biological psychological and social factors often cited as causes of mental disorder are generally experiences too common in human life to be the specific cause of disorder, but does not consider the possibility of more specific factors. He argues that, even where some non-biological determinant might be shown to play a causal role, one still has to explain why some exposed to the determinant develop a disorder and most do not in terms of differential biological factors. However, he fails to mention that the same holds true for many biological determinants and that there is no reason to assume that the missing part of the explanation must be biological. Indeed, Freud used precisely the same argument to justify the Oedipal interpretation of Little Hans's development of a horse phobia after witnessing a horse accident, because, he pointed out, not all boys who witnessed such an accident would fall ill[102].

Guze exiles all non-biological factors to the scientific periphery, as influencing the disease process but not being the specific etiology: "An individual's socioeconomic circumstances, education, job, marital status, religion, and temperament may influence his risk of developing a given disorder, may play a role in determining when and whether he will seek medical care, may color the way he describes his symptoms, and may be important in determining treatment and its outcome. But the diagnosis… is not based upon this background"[16, p.299]. Guze develops an extended analogy of psychosocial factors in mental disorder to non-specific factors in heart disease: "Certain symptoms of coronary atherosclerosis, those of myocardial ischaemia, are frequently and regularly precipitated by physical activity and emotion. But no one therefore challenges the belief that coronary artery disease is a biological phenomenon and that trying to understand the genetic and epigenetic factors that lead to differential vulnerability to coronary atherosclerosis is the most promising strategy for research and hope for truly effective intervention. And no one is likely to suggest that intervening to reduce physical activity or emotion-provoking experiences is likely to be of more than marginal importance… It seems highly likely that the same overall conceptual strategies will prove to be appropriate for conditions such as schizophrenia, obsessional disorders, depression, mania, etc."[17, p.317].

Klerman does not offer much in the way of explicit argument for the neo-Kraepelinian belief in the necessary biological focus of a medical psychiatry. In fact, he seems uncomfortable with it. He makes clear that the syndromal approach to diagnosis is designed to serve the goal of creating homogeneous categories with shared biological causes. However, he observes that there is a certain arbitrariness to the seeming fixation of neo-Kraepelinians on biological explanation: "In principle, there is no reason why this approach cannot be applied to the search for psychogenic causation in early childhood experience, or to family interaction, or to communication defects, or to social deprivation. There is no reason why this approach cannot be used for the study of non-biological treatments such as individual or group psychotherapy or milieu therapy. It is an interesting observation in the history of psychiatry that those investigators who have attempted to apply these procedures most vigorously have had a biological bias… and an interest in biological treatments… Very few of the neo-Kraepelinians are willing to give other than lip service to developmental causation. They are just vitriolic about it… Very few… are personally interested in, or willing to entertain, on principle, a developmental or psychogenic causation to the major psychoses"[15, pp.115,117].

Why mental disorders need not be brain disorders

Surely, some of the more severe mental disorders are likely due to biologically describable dysfunctions. Nonetheless, Guze's biologicalism is, as Spitzer chided, an article of faith, and it remains so even today. For example, despite the fact that there is not one clearly established consensus on brain pathophysiology for a major mental disorder, N. Andreasen asserts that "people who suffer from mental illness suffer from a *sick or broken brain*"[103, p.8] and Nobel Prize winner E. Kandel argues: "All mental processes are brain processes, and therefore all disorders of mental functioning are biological diseases… The brain is the organ of the mind. Where else could [mental illness] be if not in the brain?"[104]. One finds naïve assertions such as the following one occurring in scientific journals: "We confirm, with high-powered analysis, that patients with ADHD have altered brains; therefore ADHD is a disorder of the brain"[105, p.311].

Of course, the latter inference that brain differences mean mental disorder is spurious; brain differences occur in normal conditions as well[106]. As to Kandel's "locational" argument that psychological meanings occur "in the brain", thus mental disorders must be brain diseases, the problem is that there is an equivocation in moving from the correct premise that all mental disorders are brain diseases *in the locational sense* to the conclusion that all mental disorders are brain diseases *in the narrower sense that the underlying dysfunction is describable sheerly in anatomical/physiological terms*. The invalidity of "all mental disorders are located in the brain, therefore all mental disorders are brain diseases" is suggested by the manifest invalidity of the analogous argument: all computer software runs in computer hardware, therefore all software malfunctions must be hardware malfunctions[107].

It seems entirely possible for a mental disorder to be caused by problematic meanings that cause a psychological dysfunction without causing a brain dysfunction. It might be, as in Janoff-Bulman's theory[108], that certain meanings are so central that we are not biologically designed to process them in the rare event that they are seriously challenged, so there is a breakdown in psychological processing capabilities. This notion is reflected in the characterization of post-traumatic stress disorder in the DSM-III as requiring that "the person has experienced an event that is outside the range of usual human experience"[1, p.250]. The mix of successful psychotherapeutic and psychopharmacological treatments we have today argues against a narrow biologicalist thesis and suggests that Klerman was right to be skeptical of neo-Kraepelinian biologicalist ideology.

Spitzer's rejection of neo-Kraepelinian biologicalism

The second of Klerman's propositions that Spitzer rejected in his reply to Blashfield was proposition 6. Spitzer rather bluntly rejected the claim that psychiatry, to be a part of medicine, must be distinctively and primarily about biological etiology as opposed to being about whatever is empirically established to be causing mental disorders: "Article six states: 'The focus of psychiatric physicians should be particularly on the biological aspects of mental illness.' Nonsense. Psychiatrists should concern themselves with all aspects of mental illness, including the psychological and social aspects"[101, p.592].

Spitzer completed his disengagement from neo-Kraepelinianism by tartly suggesting that, in taking an open-minded empirical approach, he had joined a different college with a credo much simpler than Klerman's: "I hope that my resignation from the neo-Kraepelinian college will be accepted, as I have already joined the faculty of a much larger institution of higher learning. The faculty of this university is multidisciplinary and its credo is simple and easy to remember: it is 'data oriented'… Faculty and students of this university are harmoniously committed to the pursuit of data that will help us understand the multiple determinants of mental illness and the relative effectiveness of various biological, psychological, and social treatments"[101, p.592].

The same year, in a paper with J. Williams, Spitzer reiterated the DSM-III's etiological neutrality and potential eclecticism: "DSM-III makes no assumption that a biological abnormality accounts for each of the mental disorders. There is only one class of mental disorders for which a specific biological etiology is established, the Organic Mental Disorders. In some of the other categories, such as the psychotic disorders and the severe forms of Affective Disorder, a biological abnormality is assumed by many, although not included in the DSM-III description. It is also widely assumed that whatever biological abnormality may eventually be discovered for these disorders, it is only one component of a multifactorial etiology that almost certainly involves environmental and psychological factors"[109, p.23].

Spitzer's understanding emerged explicitly in his DSM-III definition of mental disorder, which specifies that "there is an inference that there is a behavioral, psychological, or biological dysfunction"[44, p.6] – a direct rejection of the narrower biological-etiological vision of his neo-Kraepelinian partners. He made the point even more abundantly clear in his explanation of DSM-III's revolutionary descriptive diagnostic system. Even though the system was derived from the work of the neo-Kraepelinians, Spitzer interpreted it differently. As Klerman had observed, the logic of the system was entirely theory-neutral and therefore was not inherently biological, psychological, behavioral, and so on. It was a level playing field of operationally identified consensus disordered conditions about which the various approaches and theories – including biological theories – could now compete over etiology and treatment efficacy.

Spitzer went so far as to emphasize how competing theories were encompassed by the syndromal approach: "For most of the DSM-III disorders… the etiology is unknown. A variety of theories have been advanced, buttressed by evidence – not always convincing – to explain how these disorders come about. The approach taken in DSM-III is atheoretical with regard to etiology or pathophysiological process except for those disorders for which this is well established and therefore included in the definition of the disorder. Undoubtedly, with time, some of the disorders of unknown etiology will be found to have specific biological etiologies, others to have specific psychological causes, and still others to result mainly from a particular interplay of psychological, social and biological factors. The major justification for the generally atheoretical approach taken in DSM-III with regard to etiology is that the inclusion of etiological theories would be an obstacle to use of the manual by clinicians of varying theoretical orientations… Clinicians can agree on the identification of mental disorders on the basis of their clinical manifestations without agreeing on how the disturbances come about"[44, pp.6-7]. The DSM system can be interpreted as neo-Kraepelinian in the strict bioetiological sense if one so wishes. But, that is not inherent in the structure of the manual or in the intentions of its primary creator, R. Spitzer.

There may be a concern that allowing psychogenic dysfunctions into the medical domain creates a fuzzy line between psychiatry and clinical psychology and opens the way to jurisdictional threats from non-physicians. Fortunately, Guze and the neo-Kraepelinians recognized that this is a dispute that need not be decided for now. Despite claiming mental disorders for the medical field in a conceptual sense, the neo-Kraepelinians did not claim that their arguments delegitimized treatment of mental disorder by other mental health professions, such as psychologists and social workers, given their skills in some areas of psychotherapy.

"Disease" versus "disorder"

The difference between standard neo-Kraepelinians and Spitzer also emerges in a much-discussed matter of terminology. Neo-Kraepelinians, we have seen, preferred the term "disease" because of its manifest biological-disorder implications. Contrary to a common impression, the use instead of the generic term "disorder" for mental pathological conditions did not start with the DSM but rather has a long history. "Disease" is sometimes used for all medical problems, but its dominant use is to refer to a subcategory including infectious, genetic, and some other biologically based conditions, and so tends to exclude, for example, injuries, poisonings, and other genuine medical conditions[110]. To avoid ambiguities or premature etiological assumptions, "disorder" has long been the generic term of choice for mental and physical pathology. It was already in use in S. Johnson's *Dictionary* published in 1755, which includes entries in which, for example, "megrim" (migraine) is "a painful disorder of the head" and the "hypochondriack" is "disordered in the imagination"[111].

Psychiatry has long used "disorder" in this way. For example, in the second issue, October 1844, of the *American Journal of Insanity* (later the *American Journal of Psychiatry*), the editor, A. Brigham, published an essay on *The Definition of Insanity* that begins: "By Insanity is generally understood some disorder of the faculties of the mind"[112, p.97]. The bibliography notes that H. Johnson recently published a book titled *On the Arrangement and Nomenclature of Mental Disorders*[113]. DSM merely adopted this long-standard usage.

However, there is more to the continued use of "disorder" versus "disease" in DSM-III than mere tradition. Spitzer early expressed preference for this term specifically because it allows a slimmed-down understanding of "medical model" that rejects the ideologically loaded neo-Kraepelinian notion that requires all psychiatric conditions to be biological brain diseases. According to Spitzer and Wilson, in a 1975 handbook entry, the use of "disorder" rather than "disease" is a disavowal of the neo-Kraepelinian demand for biological etiology and treatment: "This conception of the medical model makes no a priori assumptions as to what etiological factors – physical, social, genetic, psychological, developmental – are responsible for the development of these conditions nor what kind of treatment – somatic, psychological, social, behavioral – will be most effective… However, since the word 'disease' usually does connote manifest physical dysfunction, the appropriate generic term for a psychiatric illness is 'mental disorder'"[114, p.827].

Because disorder attribution implies an inferred dysfunction, whether its nature is known or not, it is a confusion to think that disorder represents a non-theoretical "nominalist view of mental illness"[115, p.386] or that "the explicitly vague term 'disorder' reflects post-modernist cynicism about the disease concept"[65, p.36]. Disorders are not merely syndromes, they are syndromes caused by dysfunctions.

RDoC as an alternative neo-Kraepelinian strategy

With the rise of biological psychiatry as the dominant force in American psychiatry, there has been a transfer of power in departments of psychiatry from psychoanalysts to biologicalists. In reflecting further on where we stand with regard to proposition 6, I first comment briefly on RDoC and then turn to the broader picture.

RDoC is a major research initiative by the US NIMH that primarily focuses on brain circuitry activation patterns as dimensional variables linked to fundamental psychological functions[2-5]. The circuits' functions and dysfunctions need not correspond in any simple way to DSM-ICD categories, allowing for new insights unconstrained by DSM-ICD syndromal formulations. Rather than starting from syndromally defined disorders with implicit assumptions about normality in the background, RDoC starts from the identification of psychological adaptive systems that are presumably naturally selected and anchored in neural circuitry but subject to disruption, such as response to threat or loss, motivation to approach or avoid, reward responsiveness, attentional and memory systems, dominance/submission, theory of mind, appetitive systems, and other arousal, consummatory and regulating systems. After identifying brain circuitry that supports biologically designed behavior and studying the range of activation of such circuits, RDoC hopes to identify psychopathological outcomes of excessive or defective activation.

The RDoC initiative is well-timed and potentially highly fruitful due to a raft of new methods and technologies for brain research. Because of its focus on brain-level variables rather than standard DSM-ICD categories or psychological-level variables, RDoC has been controversial in the psychological and psychiatric community. However, any attempt to better understand the brain-physiological underpinnings of psychological functioning and psychopathology is desirable from both a scientific and clinical perspective, especially given recent failures to make substantial progress in etiological research.

RDoC is generally seen, and initially was presented by its creators, as a potential replacement for the DSM-ICD system, with dimensional brain-circuitry activation measures supplanting DSM-ICD syndromal categories. However, RDoC is best understood as a continuation of the neo-Kraepelinian program, with a change of tactics rather than a basic change of overall conception. The neo-Kraepelinian vision was to start with categories of disorders based on observable symptom syndromes that *prima facie* indicated failures of biologically designed functioning, then to work conceptually and empirically to eliminate false positives and create conceptually valid categories of disorder, and finally to work to refine the categories into more etiologically homogeneous construct-valid categories for which biological etiologies could be identified, and to use the discovered biological etiologies to refine the syndromal categories. The biological step of this syndrome-to-etiology process has been largely unsuccessful thus far. RDoC is a push to revive the neo-Kraepelinian vision by moving directly to the search for biological dysfunctions. Given that the relationship between symptoms and etiologies appears to be much more complicated than anticipated[116], RDoC abandons the attempt to work from syndromes to bio-etiologies and instead attempts to start directly at the brain level. The goal is not to redefine the current DSM-ICD categories according to identified alterations in the functioning of brain circuitry, but rather to reorganize classification and diagnosis around novel brain-level constructs.

RDoC thus can be understood as a realization of the neo-Kraepelinian dream of identifying brain-physiological etiologies, but approached by a different route than the syndrome refinement pathway. The neo-Kraepelinian system did not require the initial syndromal categories to remain fixed once etiologies are discovered and linked to clinical presentations; Kraepelin himself maintained flexibility about the proper syndromal organization as his etiological theories changed. Shifting to the brain level when the syndromal level presents seemingly intractable obstacles is entirely consistent with the neo-Kraepelinian vision. In the harmful dysfunction analysis's terms, RDoC investigates function and dysfunction without initial focus on harm.

However, there are several caveats to this neo-Kraepelinian perspective on RDoC[117]. First, a fundamental problem with RDoC is its commitment to biological-level etiologies and downplaying of psychological-level dysfunctions. RDoC would benefit from more Spitzerian open-mindedness; some dysfunctions at the psychological level may not be reflected in circuitry dysfunction.

Second, RDoC lacks any explicit evolutionary perspective that would provide a context for understanding which circuit activations are functional versus dysfunctional. Syndromal features often support *prima facie* judgments of failure of biological design, but brain circuit activations in themselves tell one little about which types and domains of circuit activation are normal and which disordered. For example, certain circuitry activations in the male rat brain cause aggression toward an interloping male, overlapping activations inhibit those aggressive behaviors and cause mating approaches to an interloping receptive female, and intensive activation of an overlapping region causes aggression against males and receptive females[118]. Circuitry activation in itself does not tell you that two of these are normal-range processes whereas the third is a potential disorder; for that, you need to know something about normal evolved functioning.

Third, RDoC is committed to a dimensional analysis of circuit activation across the entire normal and disordered range. The whole-population dimensional approach is valuable for the advance of knowledge of normality and disorder, and is appealing as a systematic way to approach each domain and gain a perspicuous understanding. However, this approach also presents potential obstacles to the understanding of disorder in a medical sense. Dimensions provide no non-arbitrary thresholds for disorder and thus place medical legitimacy in question. The often-stated idea that extremes on dimensions define disorder is conceptually vacuous: must it be in the top 50% or the top 1%? Adding impairment is not a solution: normal grief, normal pregnancy, and, for that matter, normal sleep are impairing. Moreover, deleterious genotypes or endophenotypes may not be at the extreme of a dimension but just a happenstance pathogenic combination. Focus on disorder as the extreme on dimensions can distract from the search for underlying discontinuities such as deleterious mutations explaining all or part of a distribution's extreme, as has been found in several mental disorder categories (see below), as well as among some physical disorder categories[119,120].

Finally and most fundamentally, RDoC appears to assume that clinically relevant brain-physiological etiological analyses can proceed without any reference to symptom syndromes. However, symptoms provide the harms that make dysfunctions into mental disorders rather than mere anomalies. It is not possible to illuminatingly explore the etiology of disorder while being blind to symptoms, because etiologies do not have their pathogenicity written on their sleeves. Even most infectious diseases, from the common cold to tuberculosis and polio, actually cause disease in only some of those who are infected. Understanding of disorder comes from studying the etiological level and symptom level simultaneously; neither alone provides the basis for judging harmful dysfunction.

The current pessimism about neo-Kraepelinian biologicalist aspirations

Despite massive amounts of biologicalist research filling our late-neo-Kraepelinian-era journals, there is not one clear discovery of a biological etiology for a major mental disorder. Modern efforts have focused on genetic determinants, but attempts to identify relatively straightforward genetic etiologies have failed, and it appears that highly polygenic solutions with many genes of small effect are generally the best we can find for disease risk. A mood of pessimism has set in, prompting philosophical rumination about whether our goals made sense to begin with[121]. Skeptics argue that we were misled by early discoveries of biological etiologies of general paresis and pellagra and that we need to find a different path. One might be tempted to respond that it has been only a few decades since the neo-Kraepelinian revolution occurred, that science rarely goes in a straight line, and that patience is a virtue in a science dealing with complexities at the level of the etiology of mental disorder. Fortunately, there is a more constructive response to biologicalist pessimism.

We stand today in an excellent position to advance our understanding of biological causes of mental disorder due to the development of novel technologies and data analytic techniques. In particular, it has only recently become possible to perform genetic analyses that allow us to infer the history of natural selection of specific genes and gene combinations without the need for a time machine, and genome-wide genetic risk analyses have become routine. Genetic analysis can provide an alternative to the current enthusiasm for dimensionalization, as the following examples illustrate.

Intellectual disability

Klerman, defending the possibility that statistical analysis of syndromes could eventually reveal etiologically homogeneous subtypes, pointed to successes in identifying genetic determinants of intellectual disability that caused individuals to fall in the extreme lower area of the IQ distribution: "The logic of the partialing out syndromes has been successful, for example, in mental retardation"[15,p.119].

Since then, genetic analysis has enormously refined our understanding of IQ and intellectual disability. There is a roughly smooth normal distribution of intelligence in the population that is polygenically determined in a way that accounts for the upper reaches, although the nature of extreme genius remains disputed[122]. The extreme low end of the distribution, on the other hand, appears to consist of two components. The larger group, accounting for most of intellectually disabled people, represents the extreme lower end of the same polygenic distribution. The remaining smaller group consists of conditions caused by many different genetic mutations that are qualitatively distinct from the genes that are responsible for the normal distribution of intelligence in the population[123].

Premenstrual dysphoric disorder

Premenstrual dysphoric disorder (PMDD) is a depressive condition occurring primarily during the days just prior to menstruation, in the late luteal phase of the cycle. In many ways, it is an extreme form of the premenstrual syndrome (PMS) that afflicts the vast majority of women in varying degrees. However, in a small percentage of women, the emotional symptoms of sadness, irritability and anxious tension, as well as physical symptoms, are so severe as to interfere with basic functioning, disrupt relationships, and block the performance of usual social roles.

Long proposed as a category of mood disorder, several concerns led to resistance to its being included among DSM categories[124]. The distribution of premenstrual symptom severity is dimensional without obvious discontinuities, so there was a validity concern that any threshold was arbitrary and would pathologize the extreme of normal variation. Skepticism about there being a dysfunction underlying PMDD was supported by studies disconfirming the standard theory that women with PMDD experienced abnormally high levels of menstruation-related hormones. Moreover, the dimensionality of PMS/PMDD meant that classification of PMDD as a disorder could easily lead to pathologization of milder PMS, perhaps reinforcing traditional stereotypes that emotional variations associated with the menstrual cycle rendered women unsuitable to certain responsibilities. Due to these controversies, PMDD was not a stand-alone category of disorder, but instead listed under DSM-IV's Appendix B of "Criteria sets provided for further study", when the revision leading to DSM-5 began.

PMDD was finally made a full criterial category of depressive disorder in DSM-5 after a panel of experts concluded that there was sufficient empirical evidence to support such a move[125,126]. The evidence that justified the DSM-5 change of PMDD to full disorder status was not evidence of severity, because that was already established by definition. Rather, evidence emerged that the severity was caused by a dysfunction, so that the extreme on the PMS dimension constituted a discontinuous and distinct condition. In ovarian steroid suppression and addback studies, women reporting PMDD and a control group were administered agonists that rid the bloodstream of circulating hormone, then gradually added back hormone into the bloodstream, simulating changing hormone levels during the menstrual cycle[127,128]. The result was that women with PMDD histories displayed pronounced behavioral and brain over-reactivity to hormone fluctuation, whereas other women did not. So, women with PMDD did not have different hormone levels, but rather different reactions to changing hormone levels. Researchers then established that the greater reactivity was due to specific genetic variations that led to overexpression of some cellular responses and underexpression of others[129]. These findings were replicated in animal models of PMDD[130]. This research revealed an underlying dysfunction of genetic response to hormone fluctuation that supports the idea that PMDD is a categorical disorder.

Autism spectrum disorder

A recent study of the genetics of autism spectrum disorder (ASD)[131] found that individual risk genes for autism are associated with cognitive advantages, and linkage studies indicate that each of these genes was individually positively selected: "Using genome-wide data, we observed that common alleles associated with increased risk for ASD present a signature of positive selection. ASD risk alleles could positively affect these [cognitive] mechanisms, causing better cognitive ability in carriers as a consequence". However, for reasons as yet unknown, certain polygenic combinations to the contrary yielded autism: "an excessive burden of these risk variants is correlated with the onset of the developmental disorders included in the autism spectrum as the evolutionary cost". Thus, "according to our interpretation of our data, such small-effect alleles were accumulated across the genome (polygenic adaptation) to the benefit of most but to the detriment of some"[131, pp.4,8,9].

This work illustrates the important point that the dimensionalist's hope that disorder can be identified as an extreme on a dimension has no basis in genetic theory. Although extremes on etiological variables may correlate with disorder, in principle seemingly arbitrary confluences of otherwise benign etiological variables can yield pathology. Dysfunction-causing combinations of what are individually positive traits may occur at non-genetic levels as well. For example, there can be several personality traits that are individually advantageous but, when they occur together and interact in a certain way, create a personality disorder.

ADHD

The Centers for Disease Control and Prevention report that about one in five high school boys in the US have been diagnosed with ADHD, with most taking stimulant medication[132]. Multiple lines of evidence suggest that such rates are inflated by substantial false-positive diagnoses. For example, of children in a given school grade, the youngest have much higher rates of ADHD diagnosis[133-135], suggesting that normal variation in developmental rate is being misdiagnosed as disorder. Consistent with this interpretation, the majority of children with ADHD exit from the diagnosis as they get older[136-140]. This has suggested a "brain maturation developmental delay" hypothesis to explain ADHD, a theory that is ambiguous between disorder and misdiagnoses due to normal variation in developmental rate occurring in a school environment which demands behavior that slower-developing children are not ready to provide.

Critics of the DSM-ICD criteria for ADHD commonly argue that normal-range children who are naturally more active than others are misdiagnosed with ADHD due to constrained school environments. The results of a multifaceted research program supports this possibility. It concerns the "seven repeat" polymorphism of the *DRD4* gene, *DRD4-7R*, which codes for aspects of the structure of the brain's dopamine receptors. This variation is considerably more common in ADHD-diagnosed children than in other children[141-144]. *DRD4-7R* slows uptake and metabolism of dopamine, thus decreasing experience of reward and heightening response to negative stimuli[145-148]. ADHD in this group can thus be seen as inattention and impulsive activity due to lessened reward and consequent boredom when sedentary, and the search for novel sources of reward. This fits with the fact that stimulants used to successfully treat ADHD enhance dopamine metabolism.

Rather than these discoveries implying that *DRD4-7R*-related ADHD is a genetic disorder, research indicates just the opposite. The occurrences of 7R variants of *DRD4* in the general population are too common to be random mutations, and there is strong evidence that 7R was naturally selected[149,150]. The 7R polymorphism is also associated with personality traits of sensation-seeking and novelty-seeking which are plausibly adaptive[151]. The gene has higher incidence in populations that resulted from geographic dispersal, is associated with risk-taking, and appears to yield a longevity benefit as well[152,153].

This polymorphism seems to adaptively increase exploration and activity, by creating the need for more intense dopamine responses that come with novel stimuli. However, in an environment such as a modern school system that demands long periods of focused and sedentary behavior, the same gene is problematic. Rather than revealing a genetic disorder, the research on *DRD4-7R* has revealed a likely naturally selected normal variation in dopamine metabolism that is being treated as a disorder due to the demands of our society. Some ADHD individuals are not disordered but have natures mismatched to the demands we make on them.

Spitzerian open-mindedness about the nature of dysfunctions and their etiologies is certainly more plausible and appealing than the fervent neo-Kraepelinian biologicalism expressed in Klerman's proposition 6. Yet, any pessimism about the power of biological discovery to help us to understand the etiological terrain, and even to help to better define the boundary between normal variation and disorder, is premature.

7. THERE SHOULD BE AN EXPLICIT AND INTENTIONAL CONCERN WITH DIAGNOSIS AND CLASSIFICATION

This proposition appears to be primarily intended as a rebuke to psychoanalysis. The oft-repeated neo-Kraepelinian narrative was that diagnosis became irrelevant in psychoanalytically-dominated American psychiatry. This issue played a role in the run-up to the DSM-III. Despite repeated overtures to the psychoanalytic community to contribute to the DSM-III, Spitzer refused to build into the nosology the unscientific assumption that a single Oedipal etiology existed for disparate conditions, and so he eliminated neuroses as a formal category[39].

Proposition 7 was particularly persuasive in the wake of progress in psychopharmacology. For example, some medications worked for panic disorder but not as well for generalized anxiety disorder. This suggested that the medications might be working to correct dysfunctional mechanisms specific to the etiology of the particular disorder. However, most of these medication results have weakened over time.

During the subsequent decades, neo-Kraepelinianism has transformed psychiatry exactly as envisioned by proposition 7. Moreover, if taken in a broad sense, even the challenges to various aspects of neo-Kraepelinianism do not necessarily alter this perception. The dimensionalist and RDoC challenges are born of a continued concern for diagnosis but dissatisfaction with the current system.

8. DIAGNOSTIC CRITERIA SHOULD BE CODIFIED, AND A LEGITIMATE AND VALUED AREA OF RESEARCH SHOULD BE TO VALIDATE SUCH CRITERIA BY VARIOUS TECHNIQUES. FURTHER, DEPARTMENTS OF PSYCHIATRY IN MEDICAL SCHOOLS SHOULD TEACH THESE CRITERIA AND NOT DEPRECIATE THEM, AS HAS BEEN THE CASE FOR MANY YEARS

Proposition 8 fires a broadside against the psychoanalytic domination of psychiatric education. As to codification, once psychiatry possessed a formal, complex diagnostic system that was the basis for everything, from insurance reimbursement to research sample selection, codification inevitably followed.

9. IN RESEARCH EFFORTS DIRECTED AT IMPROVING THE RELIABILITY AND VALIDITY OF DIAGNOSIS AND CLASSIFICATION, STATISTICAL TECHNIQUES SHOULD BE UTILIZED

The advisability of using statistical analysis to improve reliability and validity of diagnostic criteria is indisputable and has become routine. Reliability has been improved under the DSM system, although the magnitude of the improvement remains controversial[154].

The neo-Kraepelinians, including Klerman, explicitly envisioned epidemiology as providing the primary statistical basis for improving the identification and validation of true medical psychiatric conditions and separating conditions with divergent etiologies. For reasons presented earlier, it is arguable that thus far epidemiology has failed in this quest for true prevalence of disorders due to massive overinflation of prevalence rates by false positives.

CONCLUSIONS

The DSM-ICD nosological system has many problems, and I have spent a good deal of scholarly and research effort pointing some of them out. However, a close look at the neo-Kraepelinian movement and especially its Spitzerian realization, out of which the DSM-III was born, reveals the complexity of the aspirations behind the manual that must be taken into account in its assessment. The DSM-III emerged in an attempt to defeat a threat to the legitimacy of psychiatry. This discipline deals with sensitive areas of human relationships, and it will always be in danger of being seen as social control rather than medicine, as the recent neurodiversity movement reminds us. It would be easy to forget those challenges, but to do so would be a mistake. I argued that some proposed changes to our nosology, especially stronger forms of dimensionalization, do not appear to understand or address this fundamental issue. A sliding scale in clinical practice is a good thing, but an arbitrarily sliding threshold between disorder and non-disorder on an all-encompassing set of dimensions of population distributions of a variety of traits is potentially a frightening prospect sure to reawaken public worries about the legitimacy of psychiatry.

Many standard views of the DSM-ICD system are based on misimpressions that do not correspond to the system as Spitzer conceived it. For example, the diagnostic categories are not assumed to be discrete entities with zones of symptom rarity between them; etiology is not exiled forever from the manual's criteria but only excluded until the science reaches a consensus view; and the categories are not final and written in stone but instead represent provisional groups of disorders that may need to be eventually separated, and are expected to change over time to achieve greater conceptual and construct validity[155].

As a general nosological doctrine expressed in the nine propositions of Klerman's credo, neo-Kraepelinianism has three aspects. First, it makes the *conceptual* claim that psychiatry as its core mission treats genuine mental disorders in the medical sense, that are distinct from normal deviance, stress reactions and problems in living, because they are caused by dysfunctions. Second, it lays out a *theoretical* agenda that the many different biologically designed psychological capacities that humans possess imply the likelihood that there are many different ways through which psychological functioning can go wrong, even if they share upstream risk factors. Finally, it lays out a *methodological* program based on the assumption that the best way to achieve understanding of mental disorders is through scientific research starting with clinical syndromes that are conceptually face-valid as disorders. Then, through the use of epidemiology, statistical analysis, and other data-based scientific investigations, the goal is to gradually improve and revise diagnostic criteria so as to yield refined categories that are etiologically increasingly homogeneous and thus support even more productive research. In this bootstrapping process, initial syndromes transform by addition and subtraction into more construct valid etiologically understood diagnostic categories.

It is apparent that the neo-Kraepelinian methodological bootstrapping vision has not been working, or at least not working as rapidly as desired. I argued that this is partly because, in uniting research and clinical diagnostic criteria, the envisioned process was undermined. Like most well-intentioned actions, this one had unexpected side effects. The expectation, I think, was that researchers would gain their insights on the mountain of science and come down unto the clinicians and put forth the scientific law. It has not worked that way. The many truly bewildering decisions that afflicted the DSM-5 revision process, especially in failing to address false positives[57,60,156,157], have made neo-Kraepelinian bootstrapping much more difficult. The false positives problem loomed large because, once clinical intervention and research moved from the asylum to the community, aggressive steps were needed but not undertaken to control false positives, and bootstrapping to homogeneous dysfunction etiologies was undermined.

I also argued that the Spitzerian version of neo-Kraepelinianism is correct on two points of divergence. First, biological research has much to offer, but strict biologicalism about etiology cannot be taken *a priori* as the only ultimate form of etiology. Second, the degree of discreteness versus continuity of both symptom and latent factor distributions cannot be judged ahead of time, because that is an empirical issue. Until etiologies are understood, the syndrome-to-etiology bootstrapping scheme is founded on intuitions that something has gone wrong with the way people are supposed to function. This is how it was in physical medicine, but there was clearer separation of biological design versus social demands. Even so, the bootstrapping process took millennia for many disorders, and for many others we are not there yet.

Nonetheless, pessimism is not warranted. We have remarkable new technologies at our disposal that are already yielding deep insights. Although etiologies are an elusive quarry, this is what science is designed to do and what it does well – namely, it formulates competing theories about a domain and then formulates tests, the outcomes of which add evidential weight and explanatory power to one competing theory over another. True, "dysfunction" is still a broad and vague notion referring to a largely unknown domain. But, this is how science works. It starts with terms that allude to types of processes defined with minimal specified features, and then it gradually fills in the picture. For example, despite developing a radically different understanding of circulation than Galen, Harvey more or less agreed with Galen on the point that the lungs must add some "spirit" to the blood and eject some "soot". It took millennia to figure out that, roughly speaking, the added spirit is oxygen and the soot is carbon dioxide. The clever use of a variety of research strategies will hopefully allow psychiatry to go a bit faster than that.

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SPECIAL ARTICLE

Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): III. Emotional dysfunction superspectrum

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The Hierarchical Taxonomy of Psychopathology (HiTOP) is a quantitative nosological system that addresses shortcomings of traditional mental disorder diagnoses, including arbitrary boundaries between psychopathology and normality, frequent disorder co-occurrence, substantial heterogeneity within disorders, and diagnostic unreliability over time and across clinicians. This paper reviews evidence on the validity and utility of the internalizing and somatoform spectra of HiTOP, which together provide support for an emotional dysfunction superspectrum. These spectra are composed of homogeneous symptom and maladaptive trait dimensions currently subsumed within multiple diagnostic classes, including depressive, anxiety, trauma-related, eating, bipolar, and somatic symptom disorders, as well as sexual dysfunction and aspects of personality disorders. Dimensions falling within the emotional dysfunction superspectrum are broadly linked to individual differences in negative affect/neuroticism. Extensive evidence establishes that dimensions falling within the superspectrum share genetic diatheses, environmental risk factors, cognitive and affective difficulties, neural substrates and biomarkers, childhood temperamental antecedents, and treatment response. The structure of these validators mirrors the quantitative structure of the superspectrum, with some correlates more specific to internalizing or somatoform conditions, and others common to both, thereby underlining the hierarchical structure of the domain. Compared to traditional diagnoses, the internalizing and somatoform spectra demonstrated substantially improved utility: greater reliability, larger explanatory and predictive power, and greater clinical applicability. Validated measures are currently available to implement the HiTOP system in practice, which can make diagnostic classification more useful, both in research and in the clinic.

Key words: HiTOP, emotional dysfunction, internalizing, somatoform, depression, anxiety disorders, eating disorders, sexual dysfunction, negative affect, neuroticism, clinical utility

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The Hierarchical Taxonomy of Psychopathology (HiTOP) uses data from studies on the organization of psychopathology to construct a quantitative nosological system[1-4]. The HiTOP organizes psychopathology into a multilevel hierarchical structure. Hierarchical structures connect phenomena representing varying levels of specificity, i.e., a broader dimension at one level can be decomposed into more specific dimensions at lower levels. The broader dimension represents shared features that produce a correlation between the more specific dimensions; however, these specific variables still contain their own unique aspects and can be differentiated at a more fine-grained level. For example, diagnoses of major depressive disorder (MDD) and generalized anxiety disorder (GAD) tend to co-occur in individuals and, therefore, are strongly correlated with one another[2,5-7]. Consequently, they both can be subsumed within broader dimensional constructs, such as distress disorders[2,4]. However, MDD and GAD have distinctive features that need to be modeled in any comprehensive structure.

The lower levels of the HiTOP hierarchy contain specific, homogeneous symptom dimensions (e.g., insomnia) and maladaptive traits (e.g., irritability). These homogeneous elements can be combined into dimensional syndromes, some of which roughly correspond to traditional diagnoses such as MDD and GAD. Similar syndromes are combined into subfactors, such as the class of distress disorders that includes MDD and GAD. Larger constellations of syndromes form broader spectra, such as internalizing. Finally, these spectra can be aggregated into extremely broad superspectra, ultimately leading to a general factor of psychopathology[2,8-10].

The HiTOP currently includes six spectra[2]. These spectra can be conceptualized as forming three superspectra: psychosis (combining thought disorder and detachment), externalizing (subsuming disinhibited and antagonistic forms of psychopathology), and emotional dysfunction (modeling the commonality between internalizing and somatoform). Although these superspectra were not formalized in the original HiTOP system, they are supported by evidence reviewed in a series of papers published in this journal. The first paper[11] focused on the psychosis superspectrum, whereas the second[12] examined externalizing; this paper discusses the emotional dysfunction superspectrum.

The HiTOP model resolves widely recognized problems of traditional nosologies. First, traditional taxonomies consider mental disorders to be discrete categories, whereas the data show that virtually all major forms of psychopathology exist on a continuum with normality[13-19]. Consequently, systems based on dichotomous diagnoses lead to a substantial loss of clinically significant information[14,20-22]. Most notably, many patients fall short of the criteria for any disorder, despite experiencing clinically significant impairment. The HiTOP solves this problem by assessing psychopathology as a series of continuous dimensions. No patients are excluded from the system, because even those with subthreshold or atypical symptoms can be characterized on a comprehensive set of dimensions. Moreover, dimensions capture clinically important differences in symptom severity among individuals who do meet criteria for a disorder[14].

Second, dichotomous diagnoses show limited reliability, both over time and across clinicians[23-25]. For instance, the DSM-5 field trials found that many common diagnoses – including MDD (kappa = .28) and GAD (kappa = .20) – did not meet even a relaxed cutoff for acceptable interrater reliability[25]. Again, the HiTOP addresses this problem by modeling psychopathology dimensionally: extensive evidence establishes that the same clinical phenomena are much more reliable when assessed continuously[22,26-30].

Third, many diagnoses are heterogeneous and encompass diverse characteristics[6,14,31,32]. This problem is exacerbated by the fact that current nosological systems make ample use of polythetic diagnoses, such that a patient only needs to meet a specified number of criteria to have a disorder. For example, a patient needs to meet only five of nine criteria to be diagnosed with MDD in the DSM-5[33], which means that there are 227 possible ways to receive this diagnosis[32]; this number increases to 16,400 if one takes into account different symptom presentations within criteria (e.g., insomnia vs. hypersomnia)[34]. Post-traumatic stress disorder (PTSD) represents an extreme example of the combinatorial problem with polythetic diagnoses, given that there are 636,120 possible ways to receive this DSM-5 diagnosis[35]. Consequently, patients with the same diagnosis can present with very different problems and may have few – if any – overlapping symptoms[34,36]. The HiTOP addresses this problem by decomposing broader syndromes into homogeneous dimensions at lower levels of the hierarchy.

Fourth, comorbidity is a pervasive problem in traditional taxonomies[5-7,37-43]. We already have noted the strong comorbidity between MDD and GAD. High comorbidity suggests that unitary conditions have been split (perhaps arbitrarily) into multiple diagnoses, which co-occur frequently in individuals as a result. The HiTOP addresses this problem by modeling comorbidity directly. Indeed, the HiTOP structure essentially represents empirical patterns of correlations/comorbidity, i.e., strongly correlated conditions are placed near to one another (e.g., in the same spectrum), whereas less strongly related phenomena are located farther apart (e.g., in different spectra). This hierarchical system is highly flexible, such that clinicians and researchers can focus on whatever level is most informative for a given problem[2,44].

In this paper, we examine the HiTOP emotional dysfunction superspectrum. As noted, this superspectrum represents the commonality of the internalizing and somatoform spectra.

STRUCTURAL EVIDENCE

Internalizing spectrum

Internalizing is the largest and most complex of the HiTOP spectra. It consistently emerges as a distinct spectrum in structural analyses. However, the composition of this spectrum is critically dependent on the specific variables included in the analysis. Table 1 summarizes findings from the large number of studies that have modeled internalizing using diagnostic data[8,9,45-87]. Internalizing clearly subsumes a very broad range of psychopathology, including content related to depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, trauma- and stressor-related disorders, eating disorders, and personality disorders.

Several subfactors have been identified within internalizing. Table 1 presents findings related to the two broadest and best replicated subfactors[2]. First, the distress subfactor includes disorders that involve pervasive negative emotionality[6], such as MDD, dysthymic disorder, GAD and PTSD. Second, the fear subfactor is defined by disorders that involve more specific, context-delimited forms of distress and that frequently include behavioral avoidance, such as panic disorder, agoraphobia, social phobia, and specific phobia. These distress and fear subfactors are strongly correlated, and some studies have found them to be indistinguishable[47,52,67]. Relatedly, some diagnoses – such as obsessive-compulsive disorder (OCD) – do not fall clearly into either subfactor.

Growing evidence indicates that eating pathology forms a third subfactor within internalizing[2,77,78,88], although it is sometimes included in the distress subfactor (Table 1). At the syndrome level, this cluster is defined by disorders such as bulimia nervosa, anorexia nervosa, and binge eating disorder[77,78]. At the symptom level, structural/psychometric evidence has established the existence of eight specific dimensions: body dissatisfaction, binge eating, cognitive restraint, purging, excessive exercise, restricting, muscle building, and negative attitudes toward obesity. These eight dimensions have been replicated across a variety of populations[89-92].

Evidence has also emerged for a fourth subfactor of sexual problems[2,93-95]. This cluster is defined by multiple symptoms of sexual dysfunction, including low sexual desire, difficulties with arousal, low orgasmic function, and sex-related distress.

Finally, several studies have found that indicators of mania/bipolar disorder fall within the internalizing spectrum and often help to define its distress subfactor. However, other studies have linked mania to the thought disorder spectrum[8,47,49]. Accordingly, mania is currently an interstitial construct in HiTOP, with important connections to both internalizing and thought disorder. Mania subsumes several distinct symptom dimensions, including emotional lability, euphoric activation, hyperactive cognition, reckless overconfidence, and irritability[96-100]. These symptom dimensions have distinctive correlates, and more fine-grained analyses will likely reveal that they are located in different HiTOP spectra.

Table 1 Structural evidence on the internalizing spectrum

	N	Sample type	DEP	DYS	GAD	PTSD	PAN	AGO	SOC	SPE	OCD	BPD	MAN	SAD	AN	BN	BED	PSY
Internalizing																		
Dunedin Study (Caspi et al[8], Krueger et al[45])	1,037	Community/ longitudinal	+	+	+		+	+	+	+	+							
MIDAS (Forbes et al[46], Kotov et al[47])	2,900	Outpatients/adults	+		+	+	+		+	+	+	+	–		+	+	+	–
NCS (Levin-Aspenson et al[48])	8,098 & 5,877	Community/adults	+	+	+	+	+	+	+	+			+					+/–
NESARC (Keyes et al[49], Kim & Eaton[50])	43,093 & 34,653	Community/adults	+	+	+	+	+	+	+	+			+					
Norwegian Twin Panel (Kendler et al[51], Røysamb et al[52])	2,794	Community/adults	+	+/–	+	+	+	+	+/–	+		+/–			+			
WMH Surveys (Kessler et al[53])	21,229	Community/ longitudinal	+	+	+	+	+	+	+	+	+		+	+				
Conway & Brown[54]	4,928	Outpatients/adults	+	+	+	+	–		+	–	–	–	–					
Conway et al[55]	25,002	University/adults	+	+	+	+	+		+	+	+		–		+	+	+	
Conway et al[56]	815	Community/ longitudinal	+	+	+	+	+		+									
Farmer et al[57]	816	Community/ longitudinal	+	+	+	+	+		+	+			+	+		+		
Girard et al[58]	825	Mixed/adults	+	–	–	+	+					+						
King et al[59]	1,329	Community/young adults	+		+	+	+		+	–								
Kotov et al[60]	469	Inpatients/adults	+				+		+		+							
Martel et al[61]	2,512	Community/ children	+		+		+	+	+	+	+			+	+	+	+	
Martel et al[61]	8,012	Community/adults	+		+		+	+	+	+	+		+	+				+
Olino et al[62]	541	Community/ children	+		+		+	–	–	–				+				
Schaefer et al[63]	2,232	Community/ adolescents	+		+	+									+	+		
Scott et al[64]	156	Community/young women	+	+	+	+	+		+	+		+						
Verona et al[65]	4,745	Community/adults	+		+		+			+	+		+					+
Verona et al[66]	223	Mixed/youth	+		+													
Wright & Simms[67]	628	Outpatients/adults	+	+	+	+	+		+		–	+						–
Total positive			21/21	10.5/12	19/20	14/14	18/19	7/8	15.5/17	12/15	8/10	4.5/6	6/9	5/5	5/5	5/5	3/3	2.5/5

Table 1 Structural evidence on the internalizing spectrum *(continued)*

	N	Sample type	DEP	DYS	GAD	PTSD	PAN	AGO	SOC	SPE	OCD	BPD	MAN	SAD	AN	BN	BED	PSY
Distress																		
EDSP (Beesdo-Baum et al[68], Wittchen et al[69])	3,021	Community/ longitudinal	+	+	+				+		+		+		+	+	+	
NCS (Cox et al[70], Krueger[71], Levin-Aspenson et al[48])	8,098 & 5,877	Community/adults	+	+	+	+/–	+/–	+/–	–	–			+/–					+/–
NESARC (Eaton et al[72,73], Keyes et al[74], Kim & Eaton[50], Lahey et al[9])	43,093 & 34,653	Community/adults	+	+	+	+	+/–		+/–	–		+	+					
WMH Surveys (de Jonge et al[75])	21,229	Community/ longitudinal	+	+	+	+										+	+	
Blanco et al[76]	9,244	Community/ adolescents	+	+	+	+							+	+	+	+	+	
Conway et al[55]	25,002	University/adults	+	+	+	+							–					
Forbush & Watson[77]	16,423	Community/adults	+	+	+	+	–	–	–	–		–	–		–	–	–	
Forbush et al[78]	1,434	Community/ longitudinal	+	+														
James & Taylor[79]	1,197	Community/adults	+	+	+							+						
Kotov et al[80]	385 & 288	Mixed/adults	+		+	+	+	–	–	–	–		–					
Martel et al[61]	2,512	Community/ children	+		+						+				+	+	+	
Martel et al[61]	8,012	Community/adults	+		+						+		+					+
Miller et al[81]	1,325	Veterans/adults	+			+												
Miller et al[82]	214	Veterans/adults	+	+	+							+						
Mitchell et al[83]	760	Mixed/adults	+	+	+										+/–	+	+	
Slade & Watson[84]	10,641	Community/adults	+	+	+	+												
South et al[85]	1,858	Community/adults	+		+													
Vollebergh et al[86]	7,076	Community/adults	+	+	+													
Wright et al[87]	8,841	Community/adults	+		+	+	+						+					
Total positive			19/19	13/13	17/17	9.5/10	3/5	0.5/3	1.5/5	0/4	3/4	3/4	5.5/9	1/1	3.5/5	5/6	5/6	1.5/2
Fear																		
EDSP (Beesdo-Baum et al[68], Wittchen et al[69])	3,021	Community/ longitudinal					+	+	+/–	+								

Table 1 Structural evidence on the internalizing spectrum *(continued)*

	N	Sample type	DEP	DYS	GAD	PTSD	PAN	AGO	SOC	SPE	OCD	BPD	MAN	SAD	AN	BN	BED	PSY
NCS (Cox et al[70], Krueger[71], Levin-Aspenson et al[48])	8,098 & 5,877	Community/adults	+/–	–	+/–	+/–	+	+	+	+			+/–					–
NESARC (Eaton et al[72,73], Keyes et al[74], Kim & Eaton[50], Lahey et al[9])	43,093 & 34,653	Community/adults	–	–	+/–	+	+	+	+	+			–					
WMH Surveys (de Jonge et al[75])	21,229	Community/ longitudinal					+	+	+	+								
Blanco et al[76]	9,244	Community/ adolescents					+	+	+	+								
Conway et al[55]	25,002	University/adults					+		+	+	+							
Forbush & Watson[77]	16,423	Community/adults	–	–	–	–	+	+	+	+		–	–		–	–	–	
Forbush et al[78]	1,434	Community/ longitudinal							+	+								
James & Taylor[79]	1,197	Community/adults					+		+									
Kotov et al[80]	385 & 288	Mixed/adults	–		–	–	–	+	+	+	+		–					
Martel et al[61]	2,512	Community/ children					+	+	+	+				+				
Martel et al[61]	8,012	Community/adults					+	+	+	+				+				
Miller et al[81]	1,325	Veterans/adults					+	+			+							
Miller et al[82]	214	Veterans/adults					+	+		+	+							
Mitchell et al[83]	760	Mixed/adults					+	+		+	+							
Slade & Watson[84]	10,641	Community/adults					+	+	+		+							
South et al[85]	1,858	Community/adults					+		+	+								
Vollebergh et al[86]	7,076	Community/adults					+	+	+	+								
Wright et al[87]	8,841	Community/adults					+	+	+									
Total positive			0.5/4	0/3	1/4	1.5/4	17/18	15/15	15.5/16	15/15	6/6	0/1	0.5/4	2/2	0/1	0/1	0/1	0/1

+: indicator included in analysis and loaded ≥.30, –: indicator included in analysis but loaded <.30, +/–: inconsistent loadings across models or individual studies (counted as 0.5 in the total), DEP – major depression, DYS – dysthymia, GAD – generalized anxiety disorder, PTSD – post-traumatic stress disorder, PAN – panic, AGO – agoraphobia, SOC – social phobia, SPE – specific phobia, OCD – obsessive-compulsive disorder, BPD – borderline personality disorder, MAN – mania, hypomania or bipolar disorder, SAD – separation anxiety disorder, AN – anorexia nervosa, BN – bulimia nervosa, BED – binge-eating disorder, PSY – psychotic disorder, MIDAS – Methods to Improve Diagnostic Assessment and Services, NCS – National Comorbidity Survey, NESARC – National Epidemiologic Survey on Alcohol and Related Conditions, WMH – World Mental Health, EDSP – Early Developmental Stages of Psychopathology

Somatoform spectrum

Somatoform is currently the most tentative of the HiTOP spectra[2]. Early evidence suggested that somatoform psychopathology was subsumed within internalizing, based on data that somatization, hypochondriasis and neurasthenia loaded with depression and anxiety on a broader internalizing factor[101,102]. However, subsequent research has shown that, when a sufficient set of indicators is available, the somatoform spectrum is indeed separate from internalizing as well as the other HiTOP spectra[46,47,102,103,105,107-117]. These seemingly divergent sets of findings can easily be reconciled. Several studies[46,104,106] have demonstrated convincingly that internalizing and somatoform do form a single spectrum at very broad levels of the hierarchy, but, as one moves further down in levels of abstraction, somatoform separates from internalizing.

Table 2 lists 16 studies[46,47,102,103,106-117] conducted across a diverse range of countries – and using a wide range of populations and measurement modalities – that have yielded support for a higher-order somatoform factor. The indicators have mostly represented an array of bodily distress symptoms (e.g., pain, gastrointestinal, cardiopulmonary, chronic fatigue, functional neurological), akin to the bodily distress syndrome proposed by Fink and colleagues[118,119]. Although the broader categorical hypochondriasis diagnostic construct has loaded on the somatoform factor in the two studies in which it was included, this construct is multifactorial in nature[120]; it therefore would be important to determine the degree to which the components of cognitive preoccupation, bodily perceptions, reassurance seeking, and hypochondriacal worry load on this somatoform factor. Indeed, absent from all these studies are specific indicators reflecting health anxiety, which clearly includes aspects of both internalizing (i.e., anxious apprehension and fearfulness) and somatoform (i.e., somatic preoccupation and disease conviction) pathology. Future studies need to elucidate the placement of health anxiety in the hierarchy.

Role of maladaptive traits

Negative affect/neuroticism (NA/N) is a fundamental trait domain in research on personality and personality pathology. It also is a key part of the DSM-5 alternative model of personality disorders, as well as a trait qualifier in the new ICD-11 personality disorder diagnosis[121]. NA/N cuts across and ties together propensities to experience diverse negative emotional experiences – because these experiences are highly correlated – and thereby represents the central feature of internalizing. Indeed, cross-sectional data show that individual differences in broadly conceptualized internalizing psychopathology and NA/N are very highly correlated and essentially fungible[121-123].

NA/N is a higher-order dimension that subsumes many more specific facets, which are also strongly related to various forms of internalizing. Specific facets of NA/N include anxiousness, depressivity, anger/irritability, separation insecurity, and emotional lability[2,124-126], as well as social cognitive vulnerabilities such as anxiety sensitivity, self-criticism, rumination, hopelessness, and perfectionism. It is noteworthy that these social cognitive vulnerabilities show unique associations with internalizing syndromes[127-130]. For example, anxiety sensitivity is associated with panic and other syndromes, net of the general NA/N association with internalizing[128]. In addition, other major personality domains act synergistically with NA/N to affect the likelihood of experiencing specific forms of internalizing. For example, extraversion and conscientiousness mitigate the impact of NA/N on specific internalizing syndromes, such as depression[131,132].

NA/N traits also are predictive of future episodes of internalizing disorders[133-135]. Indeed, NA/N can be simultaneously conceptualized as a vulnerability for internalizing disorder, sharing causes with internalizing disorder, and lying within the same spectrum of human variation as internalizing disorder[136,137]. These connections may emerge from dynamic processes in which NA/N enhances stress, promoting internalizing symptomatology, and feeding back on general stress reactivity to further reinforce NA/N tendencies[138,139].

The strong association between NA/N and internalizing has led to a focus on articulating shared mechanisms and specific points of continuity[137]. Twin research shows that the close phenotypic overlap of NA/N and internalizing psychopathology is undergirded by shared genetic risk factors[140,141]. Distally, emerging molecular evidence also points to a genetic basis for NA/N-internalizing connections[142]. More proximally, shared neurocircuitry linking neuroticism to emotional dysregulation may constitute some of the manifest mechanisms underlying close NA/N-internalizing connections[143].

Finally, NA/N is broadly related to health complaints and somatic symptoms[144]; in fact, some models include somatic complaints as a specific facet within this domain[125,145]. NA/N has also been shown to be substantially associated with overreporting of health complaints[144], medically unexplained symptoms[146-149], health anxiety and hypochondriasis[120,150-156], and somatization/somatization disorder[157-160].

NA/N is broadly related to the symptoms, traits and disorders subsumed within the somatoform spectrum and, therefore, is partly responsible for its emergence in structural studies. Because NA/N is also broadly linked to the internalizing spectrum, it further helps to explain the existence of the emotional dysfunction superspectrum[161], which reflects important commonalities between somatoform and internalizing psychopathology.

Overall model

Figure 1 summarizes the proposed model of the emotional dysfunction superspectrum and its constituent spectra. The sections for internalizing and somatoform build upon the current HiTOP model[2] in light of the literature reviewed in this paper – in particular, highlighting those areas whose placement within this superspectrum is ambiguous or tentative. The model also includes illustrative symptom and trait dimensions that populate the lower levels of the hierarchy; these are taken from Kotov et al[2] and subsequent studies.

Internalizing consistently emerges as a distinct dimension in

Table 2 Structural evidence on the somatoform spectrum

	N	Sample type	Measure	General malaise	Pain	Neurological	Gastrointestinal	Fatigue	Cardiopulmonary	Somatic anxiety	Hypochondriasis
Cano-García et al[107]	1,255	Primary care	PHQ-15		+		+	+	+		
Budtz-Lilly et al[108]	2,480	Primary care	BDS Scale	+	+		+		+		
Deary[109]	315	Mixed	DSM-III-R questionnaire	+	+		+	+		+	
Gierk et al[110]	2,510	Community	SSS-8		+		+	+	+		
Leonhart et al[111]	2,517 456, 1,329	Routine clinical care General hospital	PHQ-15		+		+	+	+		
Marek et al[103]	810 533	Spine surgery patients Spinal cord stimulator patients	MMPI-2-RF	+	+	+	+			–	
McNulty & Overstreet[112]	925 1,199	Outpatient psychiatric Inpatient psychiatric	MMPI-2-RF	+,+	+,+	+,+	+,+			+,–	
MIDAS (Forbes et al[46], Kotov et al[47])	2,900	Outpatient psychiatric	SCID-I	+	+						+
Schmalbach et al[113]	2,386	Community	BDS Scale	+	+		+		+		
Sellbom[105]	895 42,290	Outpatient psychiatric Inmates	MMPI-2-RF	+,+	+,+	+,+	+,+			+,–	
Simms et al[102]	5,433	Primary care	CIDI	+		+					+
Thomas & Locke[114]	399	Epilepsy/NES patients	MMPI-2-RF	+	+	+	+				
Walentynowicz et al[115]	1,053	University	PHQ-15		+		+	+	+		
Witthöft et al[116]	414 308	Community Primary care	PHQ-15		+		+	+	+		
Witthöft et al[117]	1,520 3,053	University	PHQ-15		+		+	+	+		
Total positive				11/11	16/16	7/7	15/15	7/7	8/8	3/6	2/2

+: indicator included in analysis and loaded ≥.30, –: indicator included in analysis but loaded <.30, MIDAS – Methods to Improve Diagnostic Assessment and Services, PHQ-15 – Patient Health Questionnaire-15, BDS Scale – Bodily Distress Syndrome Scale, SSS-8 – Somatic Symptom Scale-8, MMPI-2-RF – Minnesota Multiphasic Personality Inventory-2 Restructured Form, SCID-I – Structured Clinical Interview for DSM-IV Axis I Disorders, CIDI – Composite International Diagnostic Interview, NES – non-epileptic seizures. General malaise includes undifferentiated somatoform symptoms, somatic depression, cognitive symptoms; pain includes fibromyalgia, musculoskeletal symptoms; neurological includes neurasthenia, conversion disorder; somatic anxiety includes physiological symptoms of anxiety (not health anxiety).

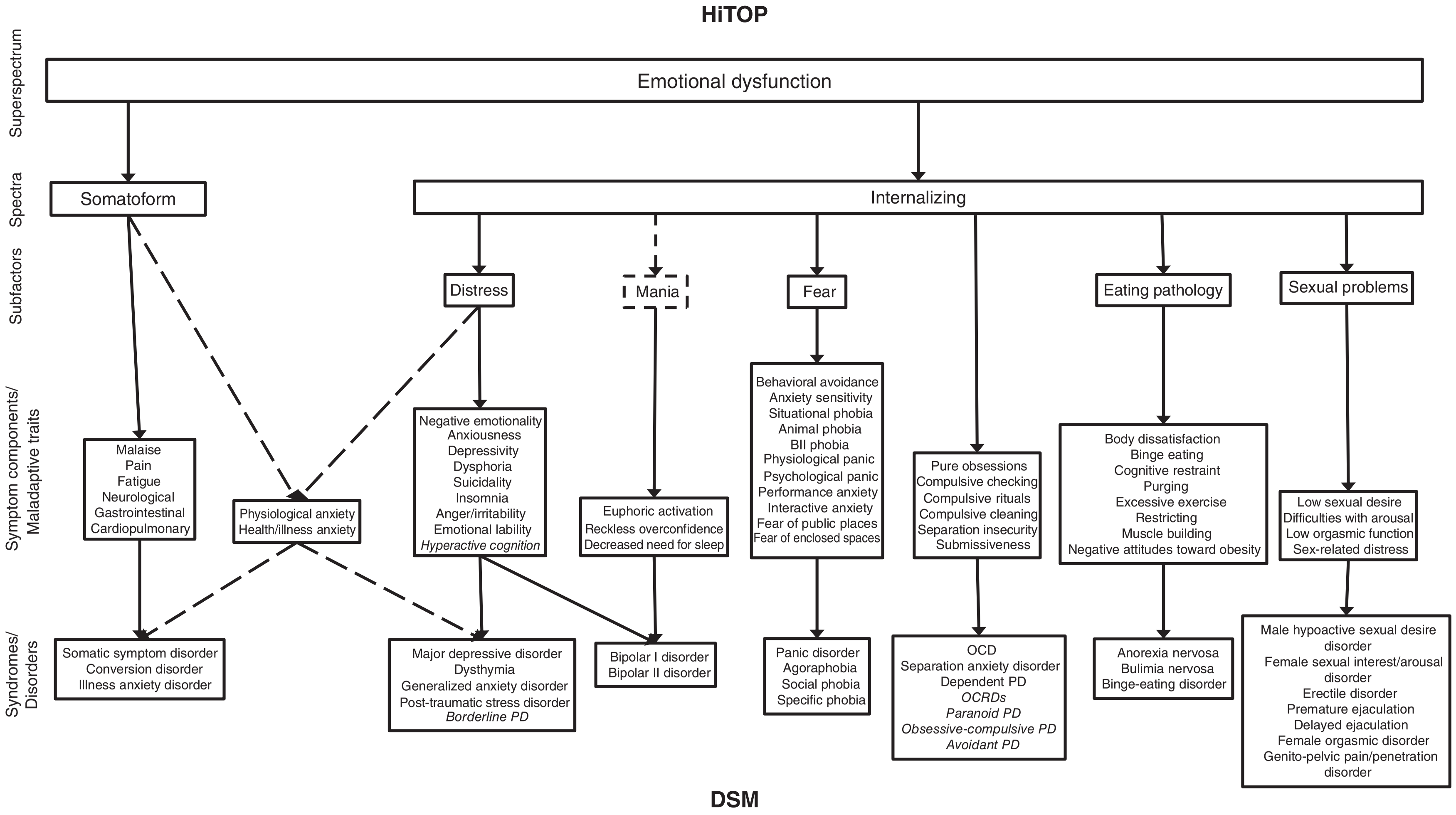

Figure 1 Conceptual model of the emotional dysfunction superspectrum. Dashed lines represent provisional inclusion. Symptom components and diagnoses with ambiguous or inconsistent structural placement are italicized. HiTOP – Hierarchical Taxonomy Of Psychopathology, PD – personality disorder, BII phobia – blood-injection-injury phobia, OCD – obsessive-compulsive disorder, OCRDs – obsessive-compulsive and related disorders

structural models, but its boundaries are unclear. For example, internalizing is strongly characterized by personality pathology related to NA/N[121-123]. However, personality disorders that load on internalizing (e.g., borderline and avoidant) often cross over into other spectra (externalizing and detachment, respectively[46,58]).

Table 1 demonstrates substantial support for subdividing internalizing into distress and fear subfactors, but evidence for the distress-fear distinction is not universal[46,52,55,56,67]. Some studies have found evidence for additional subfactors of internalizing, including sexual problems[93-95] and eating pathology[77,78], although eating pathology may form a separate structural dimension[55].

The somatoform spectrum is defined by a wide array of somatic complaints, as well as preoccupation with bodily symptoms. Somatoform problems covary substantially with internalizing psychopathology[52] and, as with internalizing, somatoform psychopathology is strongly associated with individual differences in NA/N[144]. Nevertheless, a somatoform spectrum can be distinguished from the internalizing one if a sufficient set of indicators is available[46,103,105].

VALIDITY EVIDENCE

Behavioral genetics

Twin studies suggest that the internalizing domain is moderately heritable and under shared genetic influences[51,140,141,162-167]. A substantial proportion of these genetic influences is also shared with externalizing, but the remaining vulnerability is specific to the internalizing spectrum. Importantly, these studies usually defined the internalizing spectrum as emotional problems, and the strongest genetic loadings were for MDD and GAD[163]. Within this narrower conceptualization of internalizing, there is evidence for separate genetic influences on distress and fear[168-170].

No study has examined genetic and environmental influences on all of the symptoms and traits subsumed within internalizing. However, it is possible to piece together how different HiTOP internalizing syndromes are genetically related from the research that does exist across different combinations of disorders. Multiple forms of eating pathology have common genetic vulnerability[171-173]. Moreover, twin studies indicate a shared genetic risk for eating pathology and emotional problems, including anxiety and depression symptoms[51,174-177]. There is also a substantial genetic correlation between anorexia nervosa and OCD[178]. Finally, twin and family studies indicate a partial genetic overlap between mania and unipolar depression[179-181], although the genetic association between mania and schizophrenia is substantially stronger[182-185]. Overall, there is prominent genetic overlap between different conditions within internalizing – except for mania – although there is no research on the genetic overlap with sexual problems.

In contrast, twin studies suggest that a significant proportion of genetic influences on somatoform spectrum symptoms are independent from internalizing problems[186,187]. For example, a common genetic factor contributes to four somatic symptoms: recurrent headache, irritable bowel syndrome, chronic impairing fatigue, and chronic widespread pain[188], independent of genetic influences shared with MDD and GAD. Nonetheless, the somatoform and internalizing spectra may share genetic underpinnings at a higher level of generality[51,186-191].

Overall, twin studies support shared genetic influences on the internalizing spectrum that are partially distinct from the genetic etiology of the somatoform spectrum. Future twin studies should assess a wider range of variables to test the genetic architecture comprehensively.

Molecular genetics

Genome-wide association studies (GWAS) detect genetic variants across the entire genome and allow one to compute molecular genetic correlations between traits[192]. Many genetic variants, each with a small effect size, have been found to contribute to the shared risk for internalizing. For example, depression shows high genetic correlations with generalized anxiety, NA/N, anhedonia, and PTSD (r_g>0.70)[193-196], as well as much smaller but significant genetic correlations with bipolar disorder, OCD, and anorexia nervosa (r_g=0.17-0.36)[197].

Genomic structural equation modeling (SEM) is another technique for investigating shared genetic influences across related conditions. It can extract common genetic dimensions from a set of molecular genetic correlations, and is thus useful for testing the genome-wide architecture of psychopathology. Using this approach, Waldman et al[198] identified a genetic internalizing factor, characterized by shared genetic influences on depression, anxiety and PTSD. However, bipolar disorder, OCD and anorexia nervosa were influenced by a genetic thought problems factor, rather than by internalizing. Lee et al[197] found that OCD and anorexia nervosa were influenced by a separate genetic factor from depression, whereas bipolar disorder had a uniquely strong association with schizophrenia (r_g=0.70). Finally, Levey et al[199] identified a genetic internalizing factor, which captured shared genetic influences on depression, NA/N, PTSD and anxiety.

Overall, genomic SEM supports a narrow internalizing factor that captures shared genetic influences on distress and fear disorders. Anorexia nervosa and OCD share a separate genetic factor in these studies, in line with the moderate genetic correlation between these conditions (r_g=0.45)[200]. Furthermore, the genetic vulnerability to bipolar disorder appears to align more closely with thought disorder than with internalizing. However, the high genetic overlap between schizophrenia and bipolar disorder is more specific to bipolar disorder I than bipolar disorder II (r_g=0.71 vs. 0.51), whereas depression is more closely correlated with bipolar disorder II than bipolar disorder I (r_g=0.69 vs. 0.30)[201]. Similarly, bipolar disorder cases with psychosis have higher genetic risk for schizophrenia but lower risk for anhedonia, whereas bipolar cases with a suicide attempt have elevated genetic risk for depression and anhedonia[202].

Molecular genetic studies also provide evidence for a genetic distinction between distress and fear factors. Depression and generalized anxiety show a substantial genetic overlap (r_g=0.80), but are partly genetically distinct from fear disorders, such as specific phobia and panic (r_g=0.34 and 0.63, respectively)[203]. Moreover, depression and anxiety were influenced by two distinct but genetically correlated factors (r_g=0.80), while NA/N items were partitioned between them[204]. Likewise, the molecular genetic architecture of NA/N consists of two genetically correlated factors, corresponding to distress and fear[142,205,206].

As additional GWAS summary statistics become available, more fine-grained models of internalizing can be tested. Furthermore, although there is no GWAS of somatoform spectrum disorders, moderate genetic correlations between chronic pain and depression, anxiety and NA/N (r_g=0.40-0.59) suggest that there may be considerable genetic overlap between the internalizing and somatoform spectra, that is captured by the emotional dysfunction superspectrum[207,208]. Finally, genetic correlations can be affected by the heterogeneous psychiatric diagnoses used in GWAS. Homogeneous symptom dimensions can address this heterogeneity and enhance gene discovery[209-211].

Environmental risk factors

Environmental variation shapes the development of all forms of emotional disorder[212]. A vast literature attests to this fact, but studies focus primarily on a single diagnosis or a small cluster of disorders. Only recently has research begun to investigate environmental exposures in relation to quantitative dimensions that cut across traditional diagnostic boundaries.

Few risks are as potent as childhood maltreatment. Abuse and neglect confer long-lasting vulnerability to all types of emotional and somatic complaints. Keyes et al[49] created a model to explain this non-specificity in the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). They showed that maltreatment events predicted individual differences on an internalizing spectrum that represented the commonality among interview-based anxiety and depression diagnoses. Their model also allowed for the possibility of pathways from maltreatment to the unique part of each diagnosis that was independent of all other internalizing conditions. These diagnosis-specific effects were all comparatively weak, however, leading the authors to conclude that the relationship between maltreatment and emotional complaints could be represented solely by maltreatment's link with the internalizing spectrum. Several prospective studies have corroborated this finding[8,213-216].

Adolescent stressors are often proximal triggers for first onsets of diagnosable emotional problems. Social disruption, such as peer victimization, is particularly salient during this period. Forbes et al[217] hypothesized that victimization's influence on the internalizing spectrum could explain its far-reaching effects. They found that victimization experiences, such as verbal abuse and relational aggression, were robustly linked to an array of self-rated emotional problems. They observed that these various effects were almost entirely mediated by an overarching internalizing factor. Other developmental research has documented the same pattern across a number of different challenges, including romantic problems, family discord, and financial difficulty[218]. Moreover, it appears that differences on the internalizing spectrum predict the occurrence of *future* significant stressors, setting into motion a vicious cycle of stress exposure and worsening emotional problems[1,219].

Other aspects of the social milieu have demonstrated transdiagnostic effects on emotional complaints. For instance, racial discrimination is linked with a propensity to internalizing distress, but it is not specifically related to any particular type of emotional pathology[220]. Similarly, marital dissatisfaction is closely tied to a quantitative internalizing dimension rather than to individual forms of psychopathology[85]. Other parts of the social environment also tend to have stronger effects on internalizing than on its constituent diagnostic categories[1].

It is not groundbreaking to find that environmental stressors are pathogenic. The key insight is that they seem to convey risk for such a broad range of emotional conditions because they operate primarily at the level of the higher-order internalizing spectrum, as opposed to specific manifestations thereof. This will not necessarily be the case across all environmental exposures, emotional phenotypes, or populations, but it is a robust trend thus far.

More research is needed to extend this paradigm to the full range of emotional dysfunction phenotypes. It is particularly important to investigate environmental variation relevant to the somatoform spectrum. Environmental events are implicated in the onset of somatoform disorders[221], but there is little research on this topic from a quantitative modeling perspective. Twin, adoption and quasi-experimental designs also are needed to explicate the causal nature of observed effects.

Cognitive and affective difficulties

The internalizing spectrum is associated with cognitive difficulties that can be broadly characterized as cognitive inflexibility and behavioral disinhibition. In addition, affective difficulties – such as hyposensitivity to reward and/or hypersensitivity to punishment – appear intertwined with impaired inhibition, attentional control and decision-making, and contribute to most internalizing disorders. In general, these cognitive-affective problems likely reflect a compromised ability to inhibit intrusive and perseverative thoughts and emotions governing responses such as reward seeking and/or aversion to punishment, thereby contributing to a pattern of aberrant emotional responses and maladaptive decision-making.

Cognitive and affective difficulties are common in disorders within the distress subfactor. MDD has been linked to cognitive difficulties encompassing aspects of psychomotor speed, attention, verbal fluency, visual learning and memory, and executive functioning[222-226]. These problems become more severe as the disorder progresses. Similarly, PTSD is associated with temporal changes in severity of problems in attention, memory and executive functioning[227,228]. PTSD is also linked with attentional bias towards trauma-related stimuli[229], general inhibitory control deficits[230], and attenuated reward processing[231]. These problems provide some evidence of reduced cognitive flexibility and behavioral disinhibition.

Cognitive and affective difficulties – which suggest cognitive inflexibility and behavioral disinhibition – are observed in all disorders within the fear subfactor, albeit to varying degrees of severity. There is evidence of mild executive functioning and memory problems in panic disorder, social phobia, specific phobias and GAD[232-236], whereas difficulties found in OCD tend to be more severe[236]. OCD is strongly associated with reduced cognitive flexibility, as well as difficulties in other cognitive domains[237-239]. Unsurprisingly, anxiety-related disorders are linked to difficulties in social cognition[239,240].

Disorders within the eating pathology subfactor are characterized by difficulties with attentional inhibition, biased attention to disorder-related stimuli, and attentional set-shifting; these are common indicators of reduced cognitive and behavioral flexibility[241-243] that likely underlie problems with emotional regulation and decision-making. There is additional evidence that individuals with eating disorders have compromised visuospatial ability, verbal functioning, learning and memory[244]. Other evidence suggests that eating disorders are associated with difficulties in integrative information processing, a cognitive perceptual-processing style termed weak central coherence[245].

There are limited data related to objective measures of cognitive functioning in individuals with sexual disorders. However, there is evidence of perseverative cognitive schemas[246,247], which are likely attributable to cognitive inflexibility and/or behavioral disinhibition.

Children, adolescents and college students with general internalizing symptoms show sluggish cognitive tempo[248,249], which is linked with associated decrements in processing speed[249]. Internalizing is also associated with decreased cognitive flexibility in adolescents[250], which is consistent with difficulties in executive functions across various internalizing subfactors.

Bipolar disorders I and II are associated with cognitive problems in attention, memory and executive functions[224,251-253]. Common with the other internalizing subfactors, there is evidence that bipolar disorder II is associated with reduced inhibitory control[254]. In contrast to most internalizing conditions, however, bipolar disorder is associated with *hypersensitivity* to rewards[254,255].

Finally, few studies have explored cognitive difficulties in somatoform disorders. The available evidence suggests that the somatoform spectrum is associated with difficulties in attention and memory, and reduced attentional control in relation to threatening stimuli[256,257]. The limited available data suggest that this factor is linked with behavioral disinhibition, but more research is needed.

Neural substrates: neuroimaging

Across the internalizing spectrum, the neuroimaging literature varies by subfactor and modality to include magnetic resonance imaging (MRI) sequences of functionality (i.e., blood oxygen level-dependent activation, connectivity) and structure (i.e., volumetric, diffusion tensor imaging), as well as studies using nuclear imaging to reveal regional metabolic states – i.e., positron emission tomography (PET) and single photon emission computed tomography (SPECT).

This evidence indicates a range of functional disruptions (i.e., diminished or accentuated activity and connectivity) or aberrations (i.e., decreased white matter integrity and reduced volume) in neuroanatomical regions and pathways. The severity of these disruptions and aberrations is influenced by issues involving methodology, disorder comorbidity, illness phase/severity, genetics, pharmacology, and pathophysiology. Nevertheless, most studies show mild-to-moderate differences in comparison to controls or other clinical groups. Overall, the findings highlight the shared underlying neurobiology of the internalizing spectrum, which commonly includes fronto-striatal and fronto-limbic circuitry implicated in compromised self-regulation of behavior and processing of emotions in response to salient reward or punishment.

The literature on the distress subfactor is well established. Borderline personality disorder and PTSD share common neuropathological pathways, namely those included in cognitive-limbic circuitry[258]. MDD is associated with reduced volume of both cortical and limbic regions[259]. PTSD and MDD show altered activation in regions associated with cognition and emotion[260,261]. PTSD is associated with alterations in white matter tracts involved in executive functions, context learning and memory, salience processing, and emotional control[262]. MDD and PTSD both show reduced brain volume of specific regions, with PTSD showing greater reductions overall[263]. In MDD, there are also significant reductions in white matter tracts involved in cognition, memory and emotion[264]. For GAD, there is functional and structural evidence of alterations in frontal-limbic neurocircuitry[265]. Overall, the findings suggest compromised fronto-limbic-striatal circuitry in this subfactor.

There is substantial evidence of compromised functioning and structural differences within the fear subfactor. Most data come from studies of OCD and social anxiety, followed by phobias, with less evidence for other fear disorders. Overall, there appears to be consistent hyperactivation of regions implicated in cognitive-emotional responses to threat[266-272]. Alterations in connectivity are shared between fear disorders (e.g., panic disorder and social phobia); although these might include disruptions (e.g., hypoconnectivity) within various interdependent neural networks, most often there are alterations in fronto-striatal connectivity[273,274]. Alterations within the sensorimotor network are observed primarily in panic disorder. The limited structural evidence shows compromised white matter integrity, and differences in cortical and subcortical volume[269,275].

The eating pathology subfactor is characterized by compromised self-regulation and aberrant reward processing[276-279]. Studies show compromised connectivity and abnormal regional activation in response to reward[278]. There is also evidence of underlying neuroendocrine dysfunction[280]. In terms of structural evidence, there are inconsistencies in findings from volumetric studies and a small but growing literature indicating compromised white matter tracts[281-283]. Overall, findings provide evidence to implicate disrupted functioning of fronto-striatal circuits involved in cognitive-emotional control.

There is little neuroimaging research related to sexual problems. However, the handful of papers are consistent in showing altered neural activity, namely hypoactivation of areas associated with cognition, motivation and autonomic arousal, and increased activation of the self-referential network[284,285]. Few studies have investigated structural differences or white matter integrity in this subfactor.

The mania subfactor is interstitial between internalizing and thought disorder, sharing a number of neural abnormalities with psychotic disorders[11]. However, in line with the theme observed in internalizing, bipolar disorder is associated with disrupted fronto-limbic circuitry as evidenced by altered white matter tracts and abnormal regional activation[286-289].

There is evidence of structural and functional aberrations in the somatoform spectrum. Due to methodological confounds, the literature is not as strong as in areas such as distress and fear. Nevertheless, the findings suggest disruptions or alterations in the fronto-striatal-limbic network[290].

Neural substrates: neurophysiology

Neurophysiological measures provide more direct indicators of neural activity that have greater temporal sensitivity. Internalizing conditions most frequently have been examined using electroencephalography (EEG), including both spectral power and event-related potentials (ERPs), which index a number of different cognitive, emotional and motivational processes.

Frontal EEG asymmetry is a relative difference in alpha power between the right and left frontal regions[291,292]. Alpha activity has been shown to index inhibition of cortical activity, and lower frontal EEG asymmetry scores (right alpha minus left alpha) are posited to reflect relatively less left than right cortical activity. Frontal EEG asymmetry has primarily been interpreted via an approach-withdrawal model[293], such that less relative left cortical activity is thought to reflect reduced approach motivation and increased withdrawal motivation.

The distress subfactor has demonstrated the most substantial association with frontal EEG asymmetry[294], although the evidence is inconsistent[295]. MDD and depression symptoms have been associated with a lower relative left frontal EEG asymmetry, both at rest and during emotional and motivational tasks[296-302]. Panic disorder[303] and OCD[304] have also been associated with a lower relative left frontal EEG asymmetry. In contrast, onset of bipolar disorder is predicted by *greater* relative left frontal EEG asymmetry[305].

The reward positivity (RewP), also known as the feedback negativity, is an ERP component reflecting reinforcement learning and reward system activation[306]. The RewP has demonstrated the most consistent association with the distress subfactor[307,308]. MDD and depression symptoms have been associated with a more blunted RewP in both adolescents and adults[309-316]. GAD symptoms have also been associated with a more blunted RewP [317]. The RewP has been associated with risk for, and family history of, MDD[318,319], and has been shown to predict major depressive episodes, first-onset depressive disorder, and greater depression symptoms prospectively[320,321].

The error-related negativity (ERN) is an ERP component that occurs in response to an error of commission and is posited to reflect the increased need for cognitive control and threat sensitivity[322]. An enhanced ERN has been associated with both fear and distress subfactors[323]. OCD, GAD and social anxiety all have been characterized by an enhanced ERN[324-330]. The ERN has been associated with risk for, and family history of, OCD[325,331,332], and has been shown to predict the development of first-onset anxiety disorders and GAD prospectively[333,334]. Within the somatoform spectrum, initial evidence suggests that health anxiety is associated with an enhanced ERN[335].

The P3 is a widely studied ERP component that is posited to index attentional allocation. Distress, eating and somatoform disorders all have been associated with a reduced P3[336-341]. These findings suggest that P3 alterations may be shared across the internalizing and somatoform spectra. Because P3 reductions have also been widely reported in psychosis and externalizing psychopathology[11,12], they may simply represent a marker of general psychopathology[342]. Enhanced P3, however, has also been associated with the internalizing spectrum, especially with its fear and eating pathology subfactors[343-346].

The late positive potential (LPP) is a later ERP component reflecting elaborative and sustained attention toward motivationally salient stimuli. The distress subfactor has been associated with a *reduced* LPP to emotional stimuli[347-351], whereas the fear subfactor has been associated with an *enhanced* LPP to aversive and unpleasant stimuli[349,352-355].

Other biomarkers

Disorders within the internalizing and somatoform spectra share several peripheral biomarkers related to stress reactivity. First, brain-derived neurotrophic factor (BDNF) assessed in blood serum and plasma indexes neuronal survival, synaptic signaling, and synaptic consolidation. Meta-analyses support reduced expression of BDNF in depression, bipolar disorder, suicide behavior, and eating pathology[356-361].

Second, cortisol productivity is a biomarker of hypothalamic-pituitary-adrenal axis function. Increased cortisol levels have been associated with distress[362-365], fear[233,366], and somatoform [367] conditions. Blunted cortisol, however, has also been reported[368,369], especially in PTSD[370]. Mixed findings exist for eating pathology[371,372] and may be explained by the heterogeneity in sample composition and symptom severity.

Third, elevated levels of pro-inflammatory markers in peripheral tissues are evident in emotional dysfunction disorders. Meta-analyses found elevated levels of C-reactive protein, interleukin (IL)-6, and tumor necrosis factor (TNF)-α in depression[373-376]; IL-6, IL-1β, TNF-α and interferon (IFN)-γ in PTSD[377,378]; IL-6 and TNF-α in bipolar disorder[373]; and IL-6 and TNF-α in anorexia nervosa[379]. However, there were no significant associations with bulimia nervosa[379]. Although it transcends diagnostic boundaries, inflammation might nonetheless be attributable to specific symptoms such as sleep problems, appetite changes, and fatigue[380,381].

Finally, the gut-brain-microbiota axis is closely linked to the stress response, and a differential abundance of gut bacterial groups has been identified in depressive, anxiety, PTSD, bipolar, eating and pain-related psychopathology[382,383]. Some bacteria have been implicated across multiple conditions. For example, there is a reduction in the abundance of *Faecalibacterium* in patients with MDD[384], bipolar disorder[385], GAD[386], and irritable bowel syndrome[387].

Overall, peripheral biomarker studies indicate common biological signatures for disorders within the emotional dysfunction superspectrum. However, existing research is constrained by methodological limitations, including small sample sizes and a focus on a limited number of disorders. Moreover, the implicated biomarkers are also associated with other forms of psychopathology, such as schizophrenia[388]. Studies assessing multiple forms of psychopathology are needed to clarify the specificity versus non-specificity of these biological correlates.

Childhood temperament antecedents

Models of childhood temperament consistently highlight three dimensions that capture tendencies towards negative emotionality, approach-sociability (or surgency), and effortful control (or low impulsivity and disinhibition). These dimensions have close ties with basic traits of normative personality and maladaptive personality pathology[389-392].

Given that NA/N is the core of internalizing psychopathology, it is unsurprising that negative emotionality in childhood predicts subsequent internalizing[389,393]. This prospective association has been found not only for core internalizing dimensions, such as depression and anxiety symptoms, but also for eating pathology[394-396] and somatic symptoms[397]. However, other evidence suggests that youth negative emotionality is a non-specific risk for subsequent psychopathology broadly[8], particularly externalizing psychopathology[398,399].

Individual differences and behavior genetics research both suggest that low levels of approach-sociability (fearfulness, social withdrawal, behavioral avoidance) together with high levels of negative emotionality may be a combination of traits that differentiates internalizing from externalizing psychopathology[397,400,401]. Interestingly, this combination of high negative emotionality and low approach-sociability may predict anxiety, but not depression[402]. For example, a nationally representative cohort study of 4,983 Australian children followed from age 5 to 13 found that high negative emotionality in early childhood represented a broad risk for subsequent psychopathology, but low approach-sociability only uniquely predicted higher levels of anxiety[403]. This is consistent with the research finding that behavioral inhibition – a combination of negative emotionality and low approach – is a robust predictor of anxiety[404,405]. By contrast, high negative emotionality and *high* approach-sociability (and extraversion) were found to predict subsequent purging behaviors in adolescence[394], which is more consistent with patterns seen with externalizing disorders[403,406].

The third temperamental domain, (low) effortful control, appears to have an inconsistent association that is not specific to internalizing after controlling for concurrent levels of externalizing psychopathology[404]. Similarly, both high and low effortful control (persistence) in early childhood have been found to predict eating pathology in adolescence[407,408]. This domain seems to be a more specific and robust predictor of subsequent externalizing[12].

Illness course

Data from the US National Comorbidity Study Replication suggest that anxiety disorders generally have an earlier age of onset (50% by age 11) than depressive disorders (50% by age 32). However, this distinction is largely driven by disorders within the fear subfactor[409-411]. Age of onset for somatoform disorders appears to fall in between (50% by age 19[412]). Rates for both anxiety and depressive diagnoses decline in midlife (e.g., >55 years[413]).

Although traditionally discouraged as a diagnosis before adulthood, borderline personality disorder frequently emerges in late childhood or early adolescence[414]. Within eating disorders, anorexia nervosa appears to have a mean age of onset between 16 and 19 years, with bulimia nervosa slightly later between 17 and 25 years[415].

Internalizing and somatoform diagnoses follow an episodic, oftentimes chronic, course. Within a hierarchical framework, there are three primary ways of conceptualizing course: homotypic (i.e., course within a single condition), heterotypic (i.e., relations between different conditions over time), and latent liability (i.e., the course exhibited by a shared underlying factor). Psychiatric research traditionally has emphasized homotypic course. For example, using the NESARC dataset, which has two waves separated by approximately three years, Lahey et al[416] found moderate to strong homotypic continuity of six internalizing diagnoses (tetrachoric r = .41-.56). Bruce et al[410] showed that the probability of recovery was only moderate for GAD, social phobia, and panic disorder with agoraphobia, but high for MDD and panic disorder without agoraphobia; however, risk for recurrence was high for all disorders over a 12-year span. Shea and Yen[417] found that MDD showed high rates of both remission and recurrence over a two-year follow-up; in contrast, anxiety disorders had very low recovery rates, even after five years. Similar findings emerge in epidemiological samples, although more individuals appear to recover without recurrence[418].

Two studies of large clinical samples found high rates of remission (85-99%) for borderline personality disorder over the course of 10-16 years, with moderate rates of relapse (10-36%)[419,420]. A review suggested that anorexia and bulimia nervosa both show high remission (70-84%) over 10-16 years, with those who have not remitted often transitioning to an eating disorder not otherwise specified[421].

High rates of comorbidity raise questions of how this covariation manifests across time. Heterotypic continuity frames the question of course in terms of whether a given form of psychopathology (e.g., MDD) at one point in time conduces to another (e.g., GAD) at a later point[422]. Lahey et al[416] found that heterotypic continuity was widespread within and across internalizing and externalizing diagnoses, although somewhat stronger within spectra. In fact, heterotypic continuity was comparable in magnitude to homotypic continuity, with significant heterotypic effects persisting after adjusting for all other diagnoses. Likewise, heterotypic developmental trajectories are the rule rather than the exception across childhood and adolescence, with childhood symptoms such as emotion dysregulation and irritability considered markers of a broad vulnerability for subsequent mental illness[423,424]. Relatedly, Moffitt et al[425] found that neither GAD nor MDD preferentially preceded the other, and ordering effects were symmetrical. Few studies have examined the stability of somatoform disorders, but four-year stability in early adulthood was high when considering heterotypic continuity[426].

Given this widespread heterotypic continuity, it becomes important to chart the course of the shared liability attributable to the higher-order spectra. In early adulthood (ages 18-25), longitudinal continuity among diagnoses was best accounted for by the stability of a general internalizing factor[427]. The same appears true in later adulthood, as latent internalizing factors were significantly correlated between age 41 and ages 56 (r=.51) and 61 (r=.43); these associations could largely be explained by genetic factors[428]. Relatedly, the substantial heterotypic continuity of depression and anxiety symptoms, and of different eating pathology symptoms, was largely attributable to stable, common genetic influences[173,429,430]. Finally, Wright et al[431] found that an interview-assessed, disorder-based internalizing factor strongly predicted a symptom-based internalizing factor (beta=.60) assessed via daily diary 1.4 years later. Overall, the evidence suggests that spectra represent the primary pathways of illness course, and constitute liabilities for the development of multiple conditions across the lifespan.

Treatment response

Given the high rates of comorbidity and the ubiquitously positive treatment response to cognitive behavior therapy (CBT) across various internalizing disorders[432-434], there has been a focus on testing treatments that were designed to be transdiagnostic (i.e., target multiple disorders). Meta-analyses of transdiagnostic theory-based CBT protocols for internalizing have demonstrated medium to large effect sizes for anxiety and depression, that were maintained at post-treatment follow-up[432-435]. There are particularly large effects for CBT in youth when parents are more involved in treatment[436].

Findings indicate no significant differences between transdiagnostic CBT and disorder-specific CBT protocols, which supports the efficacy of transdiagnostic CBT for internalizing[434,435]. Moreover, although there has been concern about including certain diagnoses (e.g., OCD and PTSD) in transdiagnostic CBT treatments, Norton et al[437] showed that transdiagnostic treatments for DSM-IV anxiety disorders were not associated with differential outcome by diagnosis.

Similar to transdiagnostic CBT, the unified protocol (UP) for the transdiagnostic treatment of emotional disorders was specifically designed to target co-occurring internalizing disorders[438,439]. Studies show that the UP is equivalent in effectiveness to gold-standard treatments designed to target single disorders[438,440]. The UP is much more efficient than single-disorder treatments, because clinicians only need to learn one protocol to treat internalizing disorders. Preliminary efficacy data show that, across diagnostic categories, the UP results in significant improvements in daily functioning, mood, depression, anxiety, and sexual functioning[441-444]. Treatment benefits from the UP were maintained at 6- to 12-month follow-up[443-445]. Transdiagnostic interventions are now being extended to flexible modular protocols in adults[446], mirroring efficacious modular transdiagnostic treatments across the internalizing spectrum in youth[447].

Interpersonal psychotherapy (IPT) is efficacious for treating certain internalizing disorders, such as depression and bulimia nervosa[448,449], although results were less pronounced and slower to emerge for the latter condition[449]. One review indicated that IPT was superior to CBT in treating depression[448]. Variants of IPT, including interpersonal social rhythm therapies (IPSRT), are beneficial as acute and maintenance treatments for both unipolar and bipolar depression[450-452], but have not been studied extensively in other forms of internalizing. Thus, there is support of IPT as a treatment for some, but not all, forms of internalizing, with the majority of research showing that it may be a useful treatment for distress and eating disorders, with limited efficacy for fear-based disorders, such as social phobia[453].

The limited available evidence indicates that treatments used for internalizing disorders (i.e., CBT and antidepressants) also are efficacious for somatic symptom disorders[221,454]. Although findings are mixed, CBT has been found to have lasting benefits for up to 12 months post-treatment[455-458].

Turning to pharmacological treatments, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are efficacious for the treatment of several internalizing disorders compared to placebo[459,460]; however, SSRIs are associated with an increased risk for sexual dysfunction[93]. Meta-analyses showed that atypical antipsychotics were significantly more efficacious for treating unipolar and bipolar depression and PTSD compared to placebo[461-464]. Another meta-analysis of off-label uses of antipsychotics found that quetiapine resulted in significant improvements in GAD symptoms, whereas risperidone significantly reduced OCD symptoms[465]. A large clinical trial found that olanzapine significantly increased weight gain in the treatment of anorexia nervosa compared to placebo[466]. However, atypical antipsychotics had limited benefits for improving quality of life in people with depression[467] and did not impact psychological symptoms in individuals with anorexia nervosa[466]. Overall, substantial data indicate that SSRIs and SNRIs are beneficial for treating most internalizing conditions, with accumulating evidence that atypical antipsychotics may be useful adjunctive medications. The available evidence for the efficacy of pharmacological treatments for somatoform disorders appears mixed and of low quality[468].

Summary of validity evidence

Table 3 summarizes the validity evidence reviewed in previous sections. It is noteworthy that virtually all associations are transdiagnostic in nature. That is, the studied variables are not simply related to a single form of psychopathology, but rather are associated with multiple conditions within the emotional dysfunction superspectrum (and, in many cases, to other forms of psychopathology as well). Studies have shown that multiple dimensions falling within the superspectrum share genetic diatheses, environmental risk factors (e.g., childhood maltreatment, financial difficulty, racial discrimination), cognitive and affective deficits (e.g., cognitive inflexibility, behavioral disinhibition), neural substrates (e.g., impaired fronto-striatal and fronto-limbic circuitry, blunted RewP, enhanced ERN) and other biomarkers (e.g., pro-inflammatory markers), as well as childhood temperamental antecedents (e.g., high negative emotionality, low surgency). Not surprisingly, therefore, dimensions within this spectrum respond to the same transdiagnostic treatments (including CBT and SSRIs) and are substantially related to one another both concurrently and prospectively.

These validity data are quite congruent with the structural evidence reviewed earlier. That is, many variables are related to both internalizing and somatoform conditions, and these shared factors can be captured by the emotional dysfunction superspectrum; other variables are more clearly linked to one spectrum than the other, thereby accounting for their emergence as distinct spectra at a lower level of the hierarchy. Similarly, some variables show relatively non-specific associations with all major forms of internalizing, which helps to account for its coherence as a structural dimension; in contrast, other variables show stronger links to some types of internalizing than to others, consistent with the emergence of distinct subfactors within internalizing.

Two caveats are important to mention. First, several validators were also linked to other spectra (e.g., the psychosis superspectrum also responds to antipsychotics, the externalizing superspectrum also shows high childhood maltreatment, and all three superspectra are positively associated with pro-inflammatory markers)[11,12], such that the specificity of these associations is uncertain. Second, some internalizing conditions show a distinct profile on certain validators, which underscores the value of the lower levels of the HiTOP hierarchy. Mania, in particular, is distinct with regard to genetic liability, affective deficits, and episodic course.

UTILITY EVIDENCE

The internalizing and somatoform spectra show greater utility than traditional diagnoses with respect to reliability, explanatory power, and clinical utility.

As discussed earlier, the reliability of emotional dysfunction diagnoses tends to be unimpressive. The DSM-5 field trials found that interrater reliability (kappa coefficient) ranged from .20 (GAD) and .28 (MDD) to .61 (complex somatic symptom disorder) and .67 (PTSD)[25]. In these field trials, patients used a 5-point scale to report key symptoms of depression, anxiety, sleep, suicide, and somatic distress. Dimensional assessment substantially improved reliability for individual symptoms, with retest correlations ranging from .64 to .78 (mean=.70); symptom composites were even more reliable[27]. This underscores a consistent pattern that dimensional descriptions of psychopathology are more reliable than categories. Of note, some studies – such as a field study of ICD-11 diagnoses[469] – reported higher interrater reliabilities for diagnoses, but they used less stringent designs that may inflate reliability estimates[23].

In longitudinal studies, latent internalizing spectra have shown high long-term stability in childhood (test-retest r=.85 over 3 years)[62], young adulthood (r=.69 over 3 years)[45], and middle adulthood (r=.74 over 9 years)[470]. Likewise, the distress and fear subfactors showed impressive stability over two months (r = .81 and .87, respectively)[80], one year (r = .85 and .89)[86], and three years (r = .60 and .64)[73]. Comparable data are not available for other conditions within the superspectrum. Overall, a meta-analysis estimated the reliability of internalizing dimensions to be .82, a substantial improvement over categorical diagnoses[22].

The ability to explain functional impairments, risk factors, outcomes and treatment response is an essential feature of diagnostic utility. A meta-analysis found substantially higher explanatory power for internalizing dimensions (mean correlation r=.51) than categories (mean r=.32) across multiple validators[22]. Several studies directly compared HiTOP-consistent and DSM descriptions of internalizing psychopathology, finding that HiTOP dimensions explained twice as much variance in functional impairment[471] and the probability of antidepressant prescription[472]. Also, compared to DSM diagnoses, HiTOP dimensions explained six times more variance in impairment related to eating pathology[88], and predicted two times more variance in clinical outcomes 6-12 months later[473]. Thus, the HiTOP characterization of internalizing problems can substantially increase clinical utility.

The clinical utility of a nosology encompasses additional considerations, such as facilitating case conceptualization, communication with professionals and consumers, treatment selection, and improvement of treatment outcomes[474,475]. Existing research is limited by reliance on practitioner ratings, global evaluation of a system rather than individual spectra or disorder classes, and primary focus on personality disorders. Nevertheless, recent research consistently indicated that practitioners give higher ratings to dimensional descriptions than categorical diagnoses on most utility indicators[476-479]. In the DSM-5 field trials, dimensional measures were rated positively by 80% of clinicians[480]. Nevertheless, it is important to investigate the clinical utility of the internalizing and somatoform spectra specifically, and to study objective criteria of clinical utility, such as measured improvement in treatment outcomes.

The clinical acceptability of HiTOP is unsurprising, as it is

Table 3 Validators of the internalizing and somatoform spectra

		Internalizing					
	Somatoform	**Overall**	**Distress**	**Fear**	**Sexual problems**	**Eating pathology**	***Mania***
Genetics							
Family/twin heritability	+++	+++	+++	+++		+++	++
Molecular genetics	+	++	++	++		+	+
Environment							
Childhood maltreatment		+++					
Adolescent stressors	+	+++					
Racial discrimination		+++					
Relationship satisfaction		+++					
Cognition							
Cognitive deficits	+	+++	+++	+++	++	+++	+++
Affective deficits	++	+++	+++	+++	++	+++	+
Neurobiology							
Structural	+	++	+++	+++		++	++
Functional							
Neuroimaging	+	+++	+++	+++	+	+++	++
Electrophysiology	+	++	+++	+++		+	+
Biomarkers							
Reduced BDNF expression	+	+++	++	+		++	++
Cortisol alterations	++	+++	++	++	+	++	++
Pro-inflammatory markers	++	+++	++	++	+	++	++
Gut-brain microbiota	++	+++	++	++		++	++
Antecedents/Course							
High negative affectivity	+	+++	+++	+++	+	+++	
Low approach-sociability		+++		++		–	
Low effortful control		+					
Age of onset	+		+++	+++		+++	+++
Chronicity/stability	+		+++	+++		+++	+++
Treatment							
Response to CBT	++	+++	+++	+++	+		
Response to UP		+++	++	++	+		
Response to IPT		++	++	+		+++	+
Response to SSRIs	+	+++	+++	+++	–	+++	
Response to SNRIs	+	++	++	++		++	
Response to atypical antipsychotics		++	++	++		+	+

+: some evidence for effect, ++: some replications, +++: repeatedly replicated finding, –: effect in the opposite direction, BDNF – brain-derived neurotrophic factor, CBT – cognitive behavior therapy, UP – unified protocol, IPT – interpersonal psychotherapy, SSRIs – selective serotonin reuptake inhibitors, SNRIs – serotonin-norepinephrine reuptake inhibitors. Subfactors with ambiguous or inconsistent structural placement (in this case, mania) are italicized.

grounded in an established practice of conceptualizing patients according to symptom and trait dimensions. The HiTOP advances this practice by providing a rigorous system of dimensions and validated tools to assess them. It also recognizes the need for categorical decisions (e.g., to treat or wait) in clinical practice[481]. Multiple ranges of scores (e.g., none, mild, moderate and severe psychopathology) have been identified to support clinical decisions. The HiTOP consortium is developing additional ranges for specific clinical questions (e.g., indication for suicide prevention) using strategies that were established in other fields of medicine for optimal categorization of dimensional measures[482,483].

In this, the HiTOP builds on a strong foundation of research and practice. Dimensional measures of emotional dysfunction are among the most widely used instruments in psychiatry, including the Hamilton Rating Scale for Depression[484], the Beck Depression Inventory[485], the Beck Anxiety Inventory[486], the Patient Health Questionnaire[487], and the Columbia-Suicide Severity Rating Scale[488]. However, such measures were developed to assess specific clinical conditions and none covers the internalizing or somatoform spectra comprehensively.

MEASUREMENT

Several broad symptom measures have been created to assess multiple higher- and lower-order internalizing dimensions. The original and expanded forms of the Inventory of Depression and Anxiety Symptoms (IDAS and IDAS-II, respectively) contain self-report scales assessing symptoms of depression, anxiety, PTSD, OCD and mania[100,489]. The IDAS-II scales index the HiTOP-consistent factors of distress, obsessions/fear, and positive mood/mania, with high internal consistency and stability over short intervals[100]. The Interview for Mood and Anxiety Symptoms targets dimensions similar to the IDAS-II, but with an interview format to capture the strengths of clinician-based assessment[80,471,490]. These instruments can be supplemented with the self-rated[90] and clinician-rated[491] versions of the Eating Pathology Symptoms Inventory, which provide comprehensive assessment of eating disorder symptoms. Widely used measures of sexual functioning are problematic[492], indicating a need for better assessment.

Omnibus personality inventories have demonstrated strong overlap with symptom measures of internalizing[105,493]. The Personality Inventory for DSM-5 (PID-5)[494], the Schedule for Nonadaptive and Adaptive Personality[495], and the Dimensional Assessment of Personality Pathology - Basic Questionnaire[496] all contain personality trait facets (e.g., depressivity, emotional lability) that index the higher-order NA/N domain. The PID-5 specifically matches the DSM-5 alternative model of personality disorders as well as the proposed five ICD-11 trait domains[494,497,498]. The Minnesota Multiphasic Personality Inventory-2-Restructured form (MMPI-2-RF)[499] and the Personality Assessment Inventory (PAI)[500] both provide clinical measurement (with population representative norms) of the internalizing and somatoform spectra, with well-validated scales that capture the higher-order level (e.g., MMPI-2-RF emotional/internalizing dysfunction and somatic complaints) and much of the lower-order level (e.g., MMPI-2-RF: low positive emotions, stress/worry, anxiety, malaise, neurological complains; PAI: depression-cognitive, anxiety-physiological, somatic conversion)[2,501,502].

Evidence for a distinct somatoform spectrum[47,103,105] indicates the need to measure somatization symptoms in detail. A systematic review of self-report questionnaires for common somatic symptoms has identified a total of 40 measures, with the majority deemed unsuitable for future use[503]. The authors concluded, however, that the Patient Health Questionnaire-15[504] and the Symptom Checklist-90 Somatization Scale[505] were the most suitable scales, given their validity, internal consistency, content coverage, replicable structure, and short-term stability[503]. The Bodily Distress Scale (BDS)[108] is a more recent measure of the bodily distress syndrome[118,119], which encompasses a large range of somatoform facets. None of these measures cover health anxiety, however, which can be assessed using the Whiteley Index[506] or the more comprehensive Multidimensional Inventory of Hypochondriacal Traits[120].

RESEARCH IMPLICATIONS

The HiTOP model highlights the limitations of traditional case-control studies in which patients with a given disorder are compared to individuals without that disorder[11]. The key problem with this design is that cases will differ from controls on many variables other than the assessed disorder. In particular, these studies ignore the pervasive problem of diagnostic comorbidity[2]. In light of this comorbidity, it is unclear whether a reported finding actually is due to the target disorder *per se*, or instead is attributable to another comorbid condition or even non-specific features that are shared between them (e.g., the higher-order internalizing spectrum).

The HiTOP emphasizes the importance of assessing highly correlated “near neighbor” conditions that show particularly strong comorbidity. For example, Kessler et al[507] examined 12-month DSM-III-R diagnoses in two large national samples: the National Comorbidity Survey (NCS)[508] and the Midlife Development in the United States Survey (MIDUS)[509]. Of those diagnosed with GAD, 58.1% (NCS sample) and 69.7% (MIDUS sample) also had MDD. Thus, in a typical case-control study, many – perhaps most – patients with GAD also will meet criteria for MDD. Without also assessing MDD, it is impossible to know whether any observed findings are actually attributable to GAD.

However, the identification of broad spectra and superspectra in the HiTOP model indicates that the problem is much more pervasive than this, such that most forms of psychopathology co-occur beyond chance and are positively correlated with one another. For example, an analysis of NCS diagnoses indicated that 87.6% of those with agoraphobia, 83.4% of those with simple phobia, and 81.0% of those with social phobia met criteria for at least one other lifetime disorder; moreover, roughly half of these individuals (54.0%, 52.5%, and 48.0, respectively) met criteria for three or more additional disorders[510]. Of those who met criteria for agoraphobia, 46.5% also were diagnosed with social phobia, 45.9% had MDD, 45.6% had simple phobia, and 36.3% met criteria for substance abuse. As a general rule, those who are diagnosed with a given disorder are also likely to show elevated rates of many other forms of psychopathology[422,511].

Consequently, studies need to assess psychopathology broadly in order to produce interpretable results. For example, if one only assesses agoraphobia, it is unclear whether any observed findings are attributable to this disorder, another internalizing condition, or the broad internalizing factor that represents shared features of these disorders. Furthermore, without assessing conditions that fall outside of internalizing, it is unclear whether findings are actually specific to this spectrum or are even more broadly associated with psychopathology.

Fortunately, the HiTOP provides a highly efficient framework for designing maximally informative studies. As a general principle, it is important to concentrate assessment on those regions of the hierarchy that are nearest to the condition of interest; other portions of the structure can be sampled more sparingly. To facilitate the development of a more comprehensive design, we recommend population-based sampling (perhaps oversampling those who are likely to report elevated levels of psychopathology) with very broad inclusion criteria. With regard to measurement, we encourage the use of the types of HiTOP-conformant instruments that were described earlier; homogeneous dimensional scales are more efficient, reliable, valid and informative than traditional categorical diagnoses.

CLINICAL IMPLICATIONS

The HiTOP facilitates a flexible approach to treatment. Its hierarchical structure models psychopathology dimensions at increasing levels of generality, ranging from narrow, homogeneous symptoms and traits to broad spectra and superspectra. Clinicians are free to focus on whatever level is most informative for case conceptualization and treatment. In this regard, it is noteworthy that the broader dimensions occupying the upper levels of the hierarchy are congruent with the increasing focus on transdiagnostic approaches to treatment, which were reviewed earlier[432-446]. Among these transdiagnostic treatments, the UP [438-445] is particularly relevant to the forms of psychopathology discussed in this paper. The UP was developed to be "applicable across anxiety and mood disorders, as well as other disorders in which anxiety and emotional dysregulation play a significant role, such as many somatoform and dissociative disorders"[512, p.89]; it is therefore designed to treat the full range of psychopathology subsumed within the emotional dysfunction superspectrum. The UP focuses particularly on helping patients to regulate negative emotions more effectively; in recent years, it has shifted to concentrate directly on reducing levels of NA/N[513,514].

Thus, the HiTOP provides some particularly efficient targets for transdiagnostic treatment. Nevertheless, some clinicians may be wary about working with dimensions. We therefore address two common concerns that have been raised with regard to dimensional measures in treatment. The first is that cutoffs are essential in practical clinical decision-making. It is true that scores often need to be dichotomized at some point to inform clinical decisions. It should be noted, however, that traditional diagnoses are not optimized for any particular clinical action[4,11]. Consequently, dimensional scores offer the distinct advantage that they can be cut in multiple ways to optimize different types of clinical decisions. For instance, Stasik-O'Brien et al[515] created three different cutoff scores for the IDAS scales: a screening cutoff (which is more lenient and maximizes sensitivity), a diagnostic cutoff (which is more conservative and maximizes specificity), and a balanced cutoff (which optimizes differentiation between those with and without a disorder).

A second argument is that dimensional models hinder the communication of clinically important information. However, quantitatively based dimensional schemes have been found to improve clinical communication, rather than hindering it[36,516]. This is because – all other things being equal – homogeneous dimensions are more easily interpretable than heterogeneous categories, and thus provide clearer, more trustworthy sources of information. If one is told that a patient has a high score on a narrow, specific symptom such as anhedonia, it is reasonably clear what that means. In contrast, if one is informed that a patient has been diagnosed with PTSD, it is much less clear what this means, given the marked heterogeneity of this disorder.

FUTURE DIRECTIONS

The HiTOP requires further development in several ways. First, the structure is currently incomplete. Some important forms of psychopathology (e.g., autism, neurocognitive disorders) are currently not included in the model due to insufficient evidence. More generally, the DSM-5 includes 19 diagnostic classes. At present, the HiTOP incorporates eight of them fully, six only in part (i.e., modeling some, but not all, conditions within the class), and five not at all[517].

Second, the placement of certain conditions needs to be clarified. For example, mania is interstitial and shows important connections to both internalizing and thought disorder. As noted earlier, it seems likely that specific symptom dimensions within mania (e.g., emotional lability, euphoric activation) fall in different parts of the HiTOP hierarchy. Consequently, these specific dimensions should be modeled in future structural work.

Third, future research should examine the emotional dysfunction superspectrum itself. The existence of this superspectrum remains provisional and is based on limited evidence. Furthermore, as discussed previously, some studies have found that somatoform symptomatology can be subsumed within internalizing[2]. It will be, therefore, important for future research to explicate the nature of the links between internalizing and somatoform pathology.

In addition, the HiTOP largely reflects associations between different forms of psychopathology that were assessed at the same point in time. As such, it essentially represents a static model of concurrent associations. Additional longitudinal research is needed to determine how different forms of psychopathology relate to each other dynamically over time. These dynamic relations are likely complex. For instance, early work suggested that anxiety symptoms and disorders were much more likely to precede depressive symptoms and disorders than vice versa[5,518]. However, a more recent meta-analysis found that "depressive disorders may be prodromes for social and specific phobia, whereas other anxiety and depressive disorders are bidirectional risk factors for one another"[519, p.1155].

Finally, as shown in Tables 1 and 2, the HiTOP model was created using data collected from different age groups and from a large number of countries. Nevertheless, the generalizability of this structure is limited. It will be important to test the generalizability of the hierarchical structure across a broader range of countries and age groups.

CONCLUSIONS

The HiTOP offers a dimensional, hierarchical conceptualization of psychopathology. It addresses problems of heterogeneity, comorbidity, poor coverage, and unreliability, thereby providing more valid and informative clinical descriptions than traditional nosological systems. It has been extensively validated and already demonstrates considerable utility.

Validated measures are currently available to assess the dimensions falling within the internalizing and somatoform spectra. Although further research is needed, the model is ready for use by scientists and clinicians.

APPENDIX

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Living through interminable adversity: the mental health of the Afghan people

The return of the Taliban regime to power after twenty years of war represents yet another crisis in the long history of armed conflict and invasions in Afghanistan. Successive generations of Afghans have been exposed to systemic violence resulting in widespread human rights violations and mass displacement. Adding to these stressors are country-wide conditions of adversity related to poverty, drought, food shortages and the COVID-19 pandemic. There are compelling reasons for concern, therefore, that these cumulative experiences of threat and stress will have lasting impacts on the mental health of the population.

Five million Afghans are currently displaced from their homes, three million within their own country and over two million to neighbouring Pakistan and Iran. There is a long history of Afghans seeking asylum in Western countries, the largest group of some 170,000 having settled in Germany. During the turmoil of 2021, 120,000 Afghans were airlifted from Kabul, and more than 60,000 fled to neighbouring countries. According to the United Nations High Commissioner for Refugees, up to half a million additional Afghans could flee the country in the near future[1].

Mental health services in resettlement countries should expect an increased demand for assistance from both long settled and newly arrived Afghan refugees, presenting with a range of common mental disorders related to traumatic stress, loss and grief. Services in many countries have built important expertise in engaging with Afghan persons, and in some countries there is a substantial cadre of trained and experienced Afghan professionals and community workers who can ensure that services are sensitive to the culture and history of persons from their homeland[2]. Host governments should be proactive in supplying enhanced funding and training to service providers to meet the inevitable increase in mental health needs of Afghan refugee communities. Strategic support should also be given to community agencies led by Afghans who can assist newly arrived refugees in adapting and resettling in their new environments.

Based on international data, it can be expected that approximately 10% of populations exposed to mass violence and/or forced displacement need immediate mental health treatment, and an additional 20% require psychosocial support[3]. These figures represent only averages, however, and studies conducted in Afghanistan prior to the current crisis revealed remarkably high rates of common mental health symptoms amongst adults and children across the country. It seems probable that this pattern of elevated symptoms was related to the cumulative effects of stress associated with repeated periods of conflict and social disruptions experienced by the population over several decades[4,5]. High levels of pre-existing distress within the population in turn increases the risk that many Afghans will manifest frank symptoms of mental disorders such as post-traumatic stress disorder (PTSD), anxiety and depression after being confronted with the challenges of the contemporary crisis. At a population level, repeated social disruptions, losses and dislocations undermine cohesion at the community, kinship group and family levels, potentially exacerbating psychosocial problems such as intimate partner violence and childhood abuse and neglect.

Women are at high risk of psychosocial distress in Afghanistan, as indicated by the findings of successive mental health surveys. Over many decades, women have been excluded from higher education, professional training, employment opportunities, and participation in the social and political life of the country. The previous government made some progress in addressing gender inequalities, but early signs, such as restricting girls from attending high school, suggest that these advances may be reversed by the new regime. This major setback will greatly undermine the morale of women, increasing their risk of developing mental disorders such as depression. International advocacy is urgently needed to defend and promote the human rights of women in Afghanistan, an initiative that should be strongly supported by international psychiatric and mental health organizations.

There has been a long history of discrimination and victimization of ethnic and religious minority groups in Afghanistan. The previous government has had some success in curtailing prejudice against minorities by promoting their access to education, employment and roles in government. Reports of atrocities and acts of reprisal against minorities in past months raise concerns that harsh forms of discrimination will be imposed on these groups. If this trend continues, it is likely that there will be an escalation in the number of minority group members fleeing the country to join compatriots in neighbouring and Western nations. Mental health interventions provided to these minorities must be sensitive to the culture and religion of these groups, and to dealing with the legacy of mistrust and avoidance that they have developed in interacting with government services. Involving leaders and representatives of each community in the planning and delivery of services is essential in overcoming understandable initial hesitancies in accessing and utilizing mental health services.

Conditions of armed conflict and social upheaval have greatly limited efforts to establish durable mental health services in Afghanistan. In addition, stigma, lack of awareness, and geographical constraints on access continue to present difficulties to ensuring the equitable utilization of services. Nevertheless, important progress has been made in recent times. A milestone was the inclusion of mental health in the Basic Package of Health Services and the Essential Package of Hospital Services[6] in Afghanistan in recent years. Hundreds of psychosocial counsellors were deployed in governmental health facilities throughout the country[7]. In addition, training was provided to primary health community professionals to enable them to provide basic mental health assessments and treatment[8].

A recent survey suggested that modest but meaningful gains were made during the early phase of this program in providing care for persons with severe mental illnesses, and to a limited extent to those with common mental disorders[9]. It would be a major setback if this momentum was lost now that the new regime has assumed power. There are compelling reasons, therefore, for the international community to continue supporting local and international agencies already operating mental health and psychosocial support services in the country.

Afghanistan has often been referred to as the "graveyard" of empires, a label likely to be reinforced by the recent crisis, and one that generates an attitude of pessimism about the value of supporting service development in the country. At the same time, international agencies in mental health have a long history of working under adverse conditions in politically challenging environments. An important principle to uphold is that sound mental health is fundamental to building a strong and resilient society whatever the conditions of adversity that may exist in the country at the time.

In relation to policies of resettlement of Afghan refugees, some simple lessons from the past should be kept in mind. Confining displaced peoples in refugee camps or under conditions of protracted insecurity only serves to prolong their mental health and psychosocial problems. Rapid resettlement and early support by providing culturally-relevant mental health services offer the best insurance of integration of displaced persons into host countries.

Afghan refugees have already demonstrated the positive contributions they can make to strengthening their own communities and those in which they have sought asylum. The indomitable spirit of the Afghan people continues to inspire those who work with them in the mental health field by demonstrating in practice the power of mutual support and community-mindedness that refugees can exhibit even after experiencing long periods of adversity.

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The utility of patient-reported outcome measures in mental health

For decades, clinician-rated outcome measures have been the central source of data informing clinical practice and policy. Patient reported outcome measures (PROMs) more directly assess the lived experiences of service users, capturing their perspectives on their health status and essential subjective constructs such as goal attainment, quality of life and social inclusion. Patient reported experience measures (PREMs) assess their experiences of using health services, including communication, responsiveness and recovery orientation.

Here we argue for the systematic implementation of co-developed, user-selected PROMs and PREMs; identify implementation challenges; and propose future priorities. By "co-developed" we mean that people with lived experience, including but not limited to peer researchers, should be meaningfully involved in each stage of measure development and evaluation. Involvement may range from providing advice to help reduce bias favoring clinician priorities, through to peer researchers fully leading the process of developing patient-generated PROMs (PG-PROMs). We also emphasize the distinction between PROMs/PREMs in which service users have played a primary role in the selection of specific measures to be used versus those in which measure selection has been clinician-driven.

We identify three rationales supporting widespread routine use of PROMs/PREMs: ethical, clinical and institutional.

The ethical rationale is that lived experience is necessarily central in and aligns with both the vision of recovery and the rights-based global movement towards increased participation and leadership by users of mental health services[1]. Patient-rated data should be the main source of information informing clinical decision-making, with clinician-rated data re-positioned as secondary or adjunctive.

Clinically, empirical studies reveal significant discordance between assessments by clinicians and service users on a broad range of issues, such as health and social needs. The use of PROMs/PREMs helps identify these discrepancies and acknowledges multiple perspectives. Measurement-based care, which includes systematic integration of PROMs/PREMs during service encounters to inform treatment, enhances structural accountability by supporting regular consultation with service users regarding their progress towards self-defined rather than clinician-identified goals. This ongoing dialogue, in turn, leads to improved communication and therapeutic alliance, key components of personalized psychiatry[2].

At the institutional level, PROMs/PREMs render sociopolitical processes more visible. Service user movements have criticized the primacy given to clinician perspectives, which results in the epistemic injustice of service user perspectives being de-prioritized or de-legitimized[3]. Co-developed PROMs/PREMs have the potential to collect different and more ecologically valid, and hence more relevant, information than clinician-rated measures

– thereby contributing to the goal of measuring what matters instead of what is easiest to measure. Aggregated patient-reported data capturing information beyond the traditional clinical domains also make institutional processes visible and can inform system transformation. If the goal of mental health services is to support people in living lives of their own choosing, then improvements in patient-reported outcome and experience assessments is the best measure of service success.

International reviews find that PROMs/PREMs are underutilized[4]. Implementation barriers include attitudinal, availability, usage and feasibility challenges. Clinical ambivalence can reflect unstated paternalistic beliefs that service users cannot accurately prioritize and report their own experiences. Service user involvement in the development and selection of patient-rated measures is limited[5] and replicates traditional disempowering processes. Despite recent global harmonization initiatives[6], there remains a lack of consensus on which measures to use. Finally, experiences from countries early to develop routine outcome monitoring infrastructure – such as Australia (https://www.amhocn.org), Canada (https://www.ccim.on.ca), Israel (https://www.health.gov.il) and the Netherlands (https://www.phamous.nl) – identify significant feasibility barriers to routine collection and use, including limited access to complete PROMs/PREMs and difficulties in segmenting of data for constructive use by all stakeholders.

We propose four future priorities for supporting PROM/PREM implementation. First, a much greater focus on co-developed PROMs/PREMs is essential. Involvement of service users and peer researchers helps ensure that the highest-valued domains of outcome and experience are assessed, and that language used is sensitive and person-centered. Assessment domains may include areas traditionally neglected in clinician-driven measures, such as support for medication discontinuation. Measures which are not co-developed may simply provide a patient-rated version of a measure that nevertheless reflects clinician, not patient, priorities. The lack of meaningful service user involvement and leadership in PROM/PREM development risks undermining the claims we make here about the value and importance of PROM/PREM integration.

Second, it is equally fundamental that individual service users play a primary role in the selection and prioritization of measures to assess their clinical progress, to avoid the use of measures that they might find disempowering. The latter may include being asked to rate progress in a domain of low personal value or, worse, being required to self-rate on a construct perceived as strengthening rather than challenging traditional epistemic and power hierarchies within psychiatric services. In addition to service user involvement in selecting measures, novel approaches are emerging to capture individual differences in value that service users attribute to a variety of domains of experience and outcome. An example is the INSPIRE assessment of clinician support for recovery (https://www.researchintorecovery.com/inspire), in which service users rate recovery support only in domains which matter to them, producing a score reflecting personal values and priorities. Other approaches include goal attainment scaling and individualized outcome measurement[7].

Third, the widespread use of mental health apps provides new opportunities for easily collecting, analyzing and presenting ecologically valid PROMs/PREMs which can support self-management, shared decision-making and recovery processes[8]. Similarly, machine learning approaches to aggregating big data could revolutionize the understanding of various trajectories of recovery and complex patterns of multiple influences, leading to treatment optimization and better prediction of outcomes[9]. This can help fulfil the potential of continuously learning mental health systems which adapt, innovate and improve services through continual harnessing of data and analyses informing constant discussion between key stakeholders.

Finally, there is a need to develop international consensus on the choice of PROMs/PREMs, which involves addressing challenging questions: How to capture and use aggregable data whilst supporting individualized assessment? How to assure meaningful involvement and relevant accessible PROMs/PREMs for a heterogenous group that can vary considerably in a range of ways? How to balance the traditional priority given to psychometric robustness, which results in more subjective domains being less assessed, with the reality that many aspects of the human condition are difficult to measure yet are intrinsic to mental health services? Given that PROMs/PREMs are primarily developed in higher-resource countries and then translated, how can the ethnocentric dominance of Global North values be adjusted to address cultural and geopolitical differences?

These future priorities for supporting PROM/PREM implementation can help make a reality the vision of routine outcome collection, management and sharing to facilitate more equitable and higher quality of care. The long-term promise of PROMs and PREMs is to locate service users exactly where they should be in the mental health system: at its centre.

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The role of self-compassion in psychotherapy

All psychotherapists should be aware of self-compassion as a powerful resource for enhancing well-being. When we give ourselves compassion, this allows us to cope with the pain of life without becoming derailed by it. Here we offer a panoramic view of the benefits of self-compassion and consider how psychotherapists can integrate it into treatment.

We can define self-compassion as being comprised of three core components: kindness, common humanity and mindfulness[1].

Most people try to be compassionate toward their friends and loved ones when they make a mistake, feel inadequate, or suffer misfortune. We tend to be much harsher with ourselves, however, saying cruel things that would never be said to a friend. Self-compassion turns this around, allowing us to acknowledge shortcomings while accepting ourselves as flawed, imperfect human beings. The kindness that characterizes self-compassion means that we are emotionally moved by our own pain, stopping to say: "This is really hard right now. How can I care for myself in this moment?". When we respond to ourselves with goodwill, we generate positive emotions that help us cope.

The sense of common humanity inherent to self-compassion helps us to feel connected to rather than separate from others. When we fail or feel inadequate in some way, we tend to irrationally feel like everyone else is just fine and it is only *me* who is struggling. This feeling of isolation creates a sense of disconnection that greatly exacerbates our suffering. Self-compassion recognizes that struggle is part of being human, an experience we all share. Unlike self-pity, compassion is, by definition, relational. It implies a basic mutuality in the experience of suffering, and springs from the acknowledgement that the shared human experience is imperfect.

In order to have compassion for ourselves, we need to be mindful of our pain. We cannot show ourselves compassion if we do not acknowledge that we are suffering. At the same time, if we fight and resist the fact that we are suffering, our attention becomes completely absorbed by our pain and we cannot step outside ourselves and adopt the perspective needed to give ourselves compassion. Mindfulness allows us to recognize that our thoughts and feelings are just that – thoughts and feelings – so that we can have compassion for our struggles.

There is a growing body of research demonstrating the potential of self-compassion in psychotherapy to relieve suffering across a range of clinical disorders, including depression, social anxiety disorder, eating disorders, dementia, and personality disorders[2]. In correlational studies, the trait of self-compassion is consistently associated with decreased psychopathology[3]. A meta-analysis of research on interventions such as compassion-focused therapy[4] found that treatment significantly relieved psychological distress among clients with a variety of diagnoses, even compared to active control groups[5]. A meta-analysis of self-compassion interventions in non-clinical populations found strong effect sizes in terms of reducing maladaptive eating behavior and rumination, and moderate effect sizes for reducing stress, anxiety, depression and self-criticism[6].

Bringing self-compassion into the therapy room can help clinicians be more effective. Psychotherapy is a challenging profession because therapists listen to the painful experiences of others all day long. Since human beings are hardwired to feel the emotions of others as their own, therapists inevitably experience empathic distress, which can lead to stress and burnout. Research indicates that self-compassion reduces burnout among therapists[7]. If therapists are compassionate toward their own empathic pain, not only will they be less distressed, but their compassion will be felt by clients through emotional attunement[8]. Over time, exposure to a therapist with a self-compassionate presence is likely to change how clients think and feel about themselves. Therefore, if therapists want their clients to become more self-compassionate, the first step is for them to cultivate self-compassion.

Psychotherapists can also directly teach clients how to respond to their difficulties in a more compassionate manner. For example, after a client reveals that he was sad after fighting with his son, the therapist might follow up by asking "Right now, what do you think you need?" or "If you had a friend in the same situation as you, what might you say to your friend, heart-to-heart?". These questions direct the client to explore how he could respond compassionately to his emotional pain, thereby building the resource of self-compassion.

The conversation also opens the door to practicing at home what was discovered in session. Fortunately, there are several practices available to clinicians that can be customized for individual clients to practice self-compassion. For example, the Mindful Self-Compassion training program contains seven formal meditations and twenty informal practices that can be used in daily life, and is available in workbook format[9]. Compassion-focused therapy[4] also provides a range of techniques that help clients both give and receive compassion.

Psychotherapists should be aware, however, that some clients may have negative reactions to self-compassion at first. The distress that arises when people give compassion to themselves or receive compassion from others is known as "backdraft"[1]. Backdraft can take the form of *thoughts*, such as "I'm unlovable"; *emotions,* such as grief or shame; *body* aches and pains; and *behaviors,* such as withdrawal or aggression.

Backdraft is an intrinsic part of the transformation process of self-compassion. Compassion activates old memories and makes them available for reprocessing – it provides an opportunity to receive the kindness and understanding that was lacking when the painful experiences originally occurred. This is a delicate process, and therapists need to go slowly and make sure that their clients are not overwhelmed, especially when backdraft consists of traumatic memories. As the resource of self-compassion develops, however, clients can develop the sense of safety needed to explore their inner and outer world.

In summary, self-compassion is a highly effective tool to help alleviate suffering in psychotherapy, changing the lives of both patients and therapists for the better.

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In support of supportive psychotherapy

People get carried away by bells and whistles, but sometimes it is the basics that matter. Psychotherapists, like their patients, face discomfort with and may shy away in the face of strong emotions[1]. Yet focusing on strong emotions lies at the heart of psychotherapy. That is what good therapy, and particularly good supportive psychotherapy, should do.

At least before cognitive behavioral therapy took the world by storm, supportive psychotherapy was cited as the most widely practiced form of psychotherapy[2]. But what is supportive psychotherapy? It has meant too many things. The term initially denoted the lesser alternative to psychoanalysis in the last century, the treatment offered to patients who could not tolerate the interpretations or lack of structure of free association on the couch. In other words, anything other than psychoanalysis was supportive psychotherapy. Supportive psychotherapy has been variously described as an attempt to shore up rather than alter psychic defences and as gentle hand-holding. It has probably encompassed various forms of muddled eclectic psychotherapy[2].

Thirty years ago, we developed a time-limited, manualized form of affect-focused supportive psychotherapy in response to the longstanding research conundrum of what constitutes a psychotherapy control condition. Over the years we and others have tested this brief supportive psychotherapy (BSP) in nine randomized controlled trials to treat mood and to a lesser degree anxiety disorders, with a tenth study currently underway. In all of these instances, BSP has been the underdog comparison condition.

We recently amassed the results of those trials and found that BSP worked as well as the favored treatments in seven of the nine trials, and finished a credible, near-miss second in the other two[3]. This is actually big news: BSP performed very well, considering that researcher allegiance often affects trial outcomes[4]. On balance, the data indicate that BSP may have failed to resolve the dilemma of the less-active psychotherapy control condition. Whereas waiting lists and “treatment as usual” (at least in the fractured US health care system) are often unfairly weak comparisons, BSP may be too potent an intervention to serve as a less-active control[3]. On the contrary, it deserves listing in depression treatment practice guidelines. Other studies have used unmanualized, generic treatment titled “supportive therapy” (not BSP) with less positive results.

What is BSP? It is an elemental treatment: it distills psychotherapy to its emotional essence. Based on the work of psychotherapy giants such as C. Rogers[5] and J. Frank[6], BSP comprises the “common factors” building blocks that are part of all effective treatments and that account for the majority of all psychotherapies’ outcomes[7] – the common factors, and not much more. Those common factors are: affective arousal, feeling understood by the therapist and developing a therapeutic alliance, providing a framework for understanding and a therapeutic ritual, evincing optimism for improvement, and encouraging success experiences[6]. Above all, BSP focuses on the patient’s emotions and on emotional tolerance. Emotional tolerance may indeed constitute many patients’ principal success experience in treatment. If psychotherapies are broadly divisible into exposure-focused and affect-based therapies, BSP surely falls in the latter camp: the only exposure here is to one’s own emotional state.

BSP therapists are active listeners, often silent but encouraging, letting patients lead sessions, intervening only to steer patients towards recognition and tolerance of affect. The stance incorporates curiosity, sympathy, a search for mutual understanding of the patient’s emotional state. Maintaining eye contact, the therapist mirrors the patient with nonverbal synchrony. Recognizing that patients are beset not only by outside stressors but by the stress of uncomfortable internal emotions, therapists help patients recognize and name their feelings (“What kind of upset? Which emotion is that?”). The therapist does not avoid powerful affects but seeks and tolerates them, demonstrating by example the mantra of treatment that *emotions are powerful but not dangerous*. Affect regulation, with the appreciation that one’s uncomfortable feelings are meaningful reactions to life circumstances, is clinically helpful. This therapy is simple in its approach, yet not simple to deliver well.

While the patient is doing most of the talking, the therapist mentally sketches an emotional portrait of the individual. Who is this person? How does he/she react to particular situations, and with which emotions? Depressed and anxious patients frequently avoid interpersonal confrontations, having trouble asserting their wishes and struggling to say no. Helping to elicit emotionally-laden desires and particularly negative affects such as anger and sadness, the therapist normalizes them: “Is it reasonable to feel angry if you don't like what he's doing?". This gives the patient implicit permission to understand, tolerate, accept, and perhaps express such impulses.

A danger with fancier, technique-heavy psychotherapies is that they can become mechanical, intellectualized, affect-drained exercises. One reason for the rise in so-called "third wave" cognitive behavioral therapies has been recognition of the sapping of affect from exposure-based treatments. In contrast, BSP focuses almost exclusively on the pursuit of affect: eliciting emotion, letting the patient sit with it (catharsis), eventually validating it where appropriate. Normalizing strong and subjectively "bad" negative affects such as anger and anxiety comes as therapeutic relief for patients ("Oh, I'm angry for a reason!"). Emotion makes sessions memorable. Emotion integrates insights as felt understandings rather than intellectualizations. Less can be more.

At a time when psychiatry faces training and reimbursement challenges, when the flash of novelty may obscure deeper meaning, too many psychotherapists collude with uncomfortable patients in pulling away from exploration of affect[8]. It may be time for a supportive psychotherapy comeback. A new BSP manual[9] provides a framework for this back-to-the-basics approach.

Moreover, even therapists who may not want to conduct BSP as such might benefit from a return to understanding the fundamentals of psychotherapy: learning how to dig for, sit with, and validate emotion, and how to use the "common factors" in appropriate balance. Again, these common factors are integral to every effective psychotherapy, important as well to pharmacotherapy in promoting the treatment alliance necessary to having patients accept taking medication[2,9]. Psychotherapists coming to BSP from exposure-based training backgrounds have remarked on how an understanding of these supportive techniques broadens their psychotherapeutic outlook and approach[3,9]. Thus, a supportive approach can hone and highlight understanding of the basic skills at the foundation of other therapies.

There are other affect-focused treatments, including interpersonal psychotherapy, well-conducted psychodynamic psychotherapies, and mentalization-based therapies. BSP is the pared down core of these approaches. It lacks and needs no bells and whistles. It just sticks with feelings. By letting the patient lead and focusing on his/her emotions, it maximizes patient autonomy. The therapist assigns no homework and applies no structure beyond the affect focus. A transportable, disseminable, inexpensive intervention, affect-focused BSP deserves a second look.

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Designing and scaling up integrated youth mental health care

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Mental ill-health represents the main threat to the health, survival and future potential of young people around the world. There are indications that this is a rising tide of vulnerability and need for care, a trend that has been augmented by the COVID-19 pandemic. It represents a global public health crisis, which not only demands a deep and sophisticated understanding of possible targets for prevention, but also urgent reform and investment in the provision of developmentally appropriate clinical care. Despite having the greatest level of need, and potential to benefit, adolescents and emerging adults have the worst access to timely and quality mental health care. How is this global crisis to be addressed? Since the start of the century, a range of co-designed youth mental health strategies and innovations have emerged. These range from digital platforms, through to new models of primary care to new services for potentially severe mental illness, which must be locally adapted according to the availability of resources, workforce, cultural factors and health financing patterns. The fulcrum of this progress is the advent of broad-spectrum, integrated primary youth mental health care services. They represent a blueprint and beach-head for an overdue global system reform. While resources will vary across settings, the mental health needs of young people are largely universal, and underpin a set of fundamental principles and design features. These include establishing an accessible, "soft entry" youth primary care platform with digital support, where young people are valued and essential partners in the design, operation, management and evaluation of the service. Global progress achieved to date in implementing integrated youth mental health care has highlighted that these services are being accessed by young people with genuine and substantial mental health needs, that they are benefiting from them, and that both these young people and their families are highly satisfied with the services they receive. However, we are still at base camp and these primary care platforms need to be scaled up across the globe, complemented by prevention, digital platforms and, crucially, more specialized care for complex and persistent conditions, aligned to this transitional age range (from approximately 12 to 25 years). The rising tide of mental ill-health in young people globally demands that this focus be elevated to a top priority in global health.

Key words: Youth mental health, integrated mental health care, primary care platforms, global mental health, early intervention, prevention, digital platforms

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People aged 10-24 years make up a quarter of the world's population[1]. Mental ill-health represents the number one threat to the health, well-being and productivity of these people, with 50% of mental disorders first emerging before 15 years of age and 75% by 25[2]. Mental disorders are extremely common in young people, with more than 50% impacted by the age of 25[3-5].

This landscape appears to be changing for the worse. Young people have experienced disproportionately worse mental health outcomes since the start of the COVID-19 pandemic[6], with 74% reporting that their mental health has worsened during this period[7]. Well before the pandemic, substantial evidence indicated that young people were facing a rising tide of mental ill-health, including anxiety, depressive symptoms, psychological distress and suicide[8-12].

Mental ill-health accounts for a staggering 45% of the overall burden of disease in those aged 10-24 years[13] and, through suicide, is the second most common cause of death[14]. The consequences of this are enormous, affecting young people, their families and community, as well as the economy at a local, national and global level.

Adolescence and the transition to adulthood is a dynamic and developmentally sensitive period. Mental ill-health during this life stage disrupts a range of milestones, including identity and relationship formation, educational and vocational attainment, financial independence, and achieving autonomy.

Key demographic changes have transformed this threat into what has been termed a "perfect storm"[15]. Although childhood mortality has fallen dramatically over the past century, the birth rate is dropping and the human lifespan is lengthening. This increases greatly the dependence of society on the health and productivity of young people. We simply cannot afford the loss of productivity wrought by preventable, untreated or poorly treated mental ill-health in young people. More than ever, we need to prevent or reduce premature death and disability in young people to enable them to shoulder the burden of the dependent older population.

Furthermore, because mental ill-health in young people is a potent yet largely ignored risk factor for age-related physical illnesses later in life[16], effective treatment of mental ill-health in youth will help to reduce the total burden of disease in older people. Responding effectively to this "perfect storm" will deliver enormous benefits not only to young people but to people across the lifespan and the whole of society.

THE DEVELOPMENTAL CHALLENGE

The journey from childhood to mature adulthood is now more complex and protracted than ever before, as a result of the changing social construction of the transition, the extension of the lifespan, the later age of marriage and childbirth, and a raft of other destabilizing social, technological and economic changes in society, including globalization, rising inequality and climate change[17,18]. All this has introduced new features into the landscape of the developmental process, which have been captured under the rubric "emerging adulthood"[19].

The voices of young people confirm how different it is to be a young person navigating the transition to mature adulthood now than it was even 20 years ago, and provide deep insights into how society and health care systems should respond[20]. Young people's journey to maturity is accompanied by increased levels of instability and risk[20], which helps to explain why we are facing this public health crisis.

The journey involves several key phases, beginning even prior to birth, with early childhood a particularly crucial stage during which key risk and protective factors influence life chances and trajectories of opportunity. However, the period from puberty to mature adulthood is also of enormous importance, with dramatic external changes in biological maturity, mirrored by less visible changes in brain structure and function, in psychological development and in social and vocational progress[17].

The challenge of evolving a sense of self, of individuating from one's family of origin and establishing a life and family of one's own is daunting, and stress, frustration, risk and loss are ambient within the ecosystem of growth. The philosopher J. Campbell characterized the "Hero's Journey" as a monomyth with deep relevance to the human condition[21], and this is a metaphor which is useful in normalizing the level of challenge and threat that we all face during the struggle for maturity. It creates the space for a "positive psychology" perspective, that is a strength-based stance to distress and struggle during the transition to adulthood. It also allows us to accept and see value in a soft border, a flexible boundary between mental health and mental ill-health during the struggle, and to validate a role not only for the "scaffolding" of the family and the social network surrounding the young person, but also for mental health professionals and treatment of mental "injury" and illness.

This concept navigates the space between the concern about labelling common experiences as abnormal and recognizing the crucial need for help and support, including expert medical and professional help under certain conditions. Finally, while it confronts and accepts the extent of the threats and challenges and the possibility of defeat, it holds out the hope of ultimate success even in the darkest times. These are all valuable elements for a positive, modern day approach to the mental health care of young people.

THE ECONOMIC IMPERATIVE

From a socioeconomic perspective, emerging adulthood is a crucial period for "mental wealth". Mental wealth is defined as an individual's cognitive and emotional resources that provide the foundation for educational and vocational success, high quality of life and significant contribution to society[22,23]. The development of mental wealth during emerging adulthood has impacts across the life course and, if disrupted, may perpetuate a cycle of poverty, homelessness or crime[24,25]. Mental ill-health in youth, therefore, influences the social cohesion and productivity of the whole community.

Society invests heavily in nurturing young people from birth to the threshold of productive life. If they become disabled or die during this transition, or even if they fail to reach their potential and underachieve, there is a serious and widespread erosion of productivity. The World Economic Forum first recognized this in 2011, when it discovered that mental illness makes the largest contribution to loss of gross domestic product among all non-communicable diseases, accounting for 35% of the global economic burden, followed by cardiovascular disease (33%), cancer (18%) and diabetes (4%)[26].

The World Economic Forum estimated that by 2030 mental ill-health alone would account for a loss of US$16 trillion in global economic output. This impact is specifically because of its timing of onset in young people and consequently its extended impact across the decades of productive adult life. Most young people do not receive evidence-based care in a timely or quality way, hence much of the burden of mental illness, while avertable, is *not* averted, resulting in chronic, persistent and disabling illness across the productive decades of adult life, causing enormous suffering and weakening economies and societies.

In terms of economic participation, the employment landscape is rapidly evolving and young people are facing one of the most disruptive workforce changes, due to economic developments in automation, globalization and collaboration[27]. Seventy percent of young people are currently entering the labour market in roles that will likely be obsolete or radically transformed over the next decade[27]. The young workforce has been casualized, and is highly insecure. Inequality is rising steadily across the world and even increased during the COVID-19 pandemic[28].

The future job market will place a high premium on skilled labor[27], meaning that educational participation and success will be critical. Forty-eight percent of people who develop a severe form of mental illness fail to complete high school[29] and the erosion of educational attainment surges further within higher education. Compared to their peers, young people with mental illness are nearly twice as likely not to be in education, employment or training (NEET)[30], reducing both the workforce and tax base. Together with an ageing population, a declining youth workforce and tax base will likely increase the burden on the working population, raise expenditure on long-term health care[31], and reduce economic growth.

While the economic impacts of mental ill-health are clear and overwhelming, adequate investment in mental health, including for young people, has been grossly neglected worldwide, especially in non-WEIRD (Western, Educated, Industrialized, Rich and Democratic) countries[32,33]. This state of affairs reflects a combination of factors, including morbidity and mortality from communicable diseases, widespread poverty as well as lack of political will and stability, and limited infrastructure. The influence of the COVID-19 pandemic on this mindset will be interesting to analyze.

The economics of mental health extend beyond the need for funding. Inaction or insufficient investment comes with a range of avertable and long-lasting costs, including lost productivity, loss of earnings and welfare dependency, that impact all of society[34-36]. Early diagnosis and treatment is one proven strategy to mitigate the social and economic impact of mental disorders which can be scaled up[37]. The costs of inaction fall heavily on governments and economies, highlighting that policy-makers cannot afford to underfund youth mental health. Return on investment analysis enables decision-makers to compare investments in the youth mental health system[37] with those in other areas of the health system and the economy.

CURRENT STATUS OF MENTAL HEALTH CARE FOR YOUNG PEOPLE

To understand why such an obvious public health opportunity has been overlooked until recently, we need to examine the history and evolution of mental health care. It is only relatively recently that adult mental health care evolved from the alienist era of stand-alone psychiatric institutions to join the mainstream of general health care. This is a process by no means complete across the globe. Even where this has occurred, it has often been poorly designed and funded, and has continued to focus almost exclusively on the extremely acute or the prevalent cases, that is middle-aged people with chronic, persistent and disabling illnesses.

Young adults, where the bulk of incident cases emerge, were not placed at a premium, as are incident cases in cancer and other major non-communicable disease fields. Rather, they and their families found that they had to "prove chronicity" to "deserve" and justify access to a model of care characterized by a blend of the "soft bigotry of low expectations", the "clinicians' illusion"[38] and a culture of neglect and low morale. Early intervention has been a very hard sell in psychiatry[39-41].

If we now turn to child psychiatry, its origins are quite different. The sub-specialty originally arose from the child guidance movement, and initially focused on younger children. While in recent decades its focus has reached up to include adolescents and it is now labelled "child and adolescent psychiatry", it has adhered to a paediatric model in which the boundary with adult health care is set at 18 years on legal, rather than health and developmental grounds.

The epidemiology of mental illness and the developmental needs of young people demand a radically different approach in psychiatry[42,43]. Mental illness is the mirror image of physical illness, with the greatest need for care located during the period of maximum physical health, at least in modern globalized societies. Furthermore, while adult psychiatry has struggled for parity within health systems, child and adolescent psychiatry has faced an even greater challenge to establish itself, and remains seriously underdeveloped and underfunded. Even in the prosperous European Union, child and adolescent mental health services are sparse or invisible, except in a very small number of countries[44].

The result of the weak and divergent evolution of these two traditions within psychiatry is that adolescents and young adults, despite having the greatest level of need, have the worst access to timely, quality specialized mental health care. The same applies to primary mental health care which, just like specialized care, is poorly designed and culturally ill-equipped to engage and respond to mental ill-health in young people, who typically do not seek or access help from traditional primary care providers[45]. Young people are well able to explain why current health and mental health services simply do not appeal to or work for them[20].

In summary, the health system has been designed to meet the needs of people with physical illness, which means a dominant focus on young children and older adults. Mental health care has been "shoehorned" into this system with little foresight, logic or equity. The paediatric model of care simply does not work for mental health, as recent research has shown[46,47]. Not only the majority of young people fail to gain access at all or do so only after long delays but, even for those who do, an appropriate transition from child and adolescent mental health services to adult care is rarely achieved[48]. Access and quality for the 19-25 age group is also very poor.

The different origins and cultures of these care systems, funding neglect and the fact that the transition is demanded at the worst possible point in time are jointly responsible for young people's low rates of service access and engagement. Young people and their families are forced to navigate a new and often quite different system before they are ready and when they are least able to do so. Barriers to accessing appropriate care, or reluctance to engage with developmentally inappropriate services, are strong contributors to a majority of young people not accessing or receiving mental health care when needed.

The success of the early psychosis model and its "proof of concept" for early intervention[49] has encouraged the wider application of early diagnosis and specialized treatment for the full range of emerging disorders in young people[50-52]. The early psychosis model delivers timely, comprehensive evidence-based intervention from the earliest stages of psychotic illnesses with the necessary "scaffolding" assembled and supported so that young people maximize their chances of recovery. Consistent evidence supports its cost-effectiveness[53,54], and the embedding of specialist education and employment services, such as Individual Placement and Support[55], offers long-term economic benefits[37].

The early psychosis model has demonstrated, as with other non-communicable diseases, that early detection and pre-emptive stage-linked treatment will improve prognosis and reduce disability and disengagement. From initial service development in the early 1990s, there are now early psychosis intervention services established in many countries across the world[52,56-61].

While the principles of early intervention, co-design, and holistic biopsychosocial care could be translated from early psychosis to the full spectrum of mental ill-health in young people, it was clear to us, as we began this task in 2001, that the scale of unmet need and the epidemiology of mental illness demanded a more complex and tiered or staged approach. In any given region or catchment area, the incidence of psychosis is dwarfed by the total incidence of mental disorders in young people. This includes anxiety, mood disorders, eating disorders, personality disorders, and substance use disorders, and blends of these dimensions. Specialist services alone would inevitably fail to address the scale of the problem.

Early intervention demands rapid and smooth access to care and this all pointed to the essential value of a high volume primary care model[43]. It has been recognized for some time by the World Health Organization that the fulcrum of mental health care across the globe needed to shift to and focus on primary care[62]. There are so many advantages in pursuing this as the entry portal: reduced stigma, greater bandwidth and capacity, and genuine feasibility across most health care contexts, including low- and middle-resource settings, in terms of cost and workforce. However, the problem we immediately faced in high-resource settings, such as Australia, was that general practice and standard primary care was not seen by young people as a setting to seek help for mental ill-health and related distress. Nor was this setting youth friendly or sufficiently skilled or resourced to respond[20].

BUILDING A SYSTEM OF YOUTH MENTAL HEALTH CARE FOR THE 21ST CENTURY

In response to the limitations and failures of the traditional mental health system[20], a broad-spectrum youth mental health approach has emerged since the turn of the century and is gaining traction in many high-resource settings[63-65]. New models of integrated youth primary mental health care have spread across the globe[65]. The focus is now the age group 12-25 years, ending the harmful transition point at 18 years.

This focus requires developmentally and culturally appropriate design features that acknowledge the complex and evolving biopsychosocial issues, recognizing the developmental crises, fluid symptom patterns and comorbidity seen in this age group[42,43]. This means that services must be co-designed, accessible, with "soft entry" (i.e., no or very low barriers to entry), community-based, non-judgmental and non-stigmatizing, where young people feel comfortable and have a sense of trust, and their families and friends are included[66].

It also means that the center of gravity must be located in the community, with an enhanced primary care model, that a clinical staging approach[67] should be adopted, and that secondary or more specialized mental health care will have to restructure and align to enable more intensive and sustained, longer-term care.

An international network of academics, health professionals, educators, young people, families and other leadership – the International Association for Youth Mental Health (www.iaymh.org) – was established in 2010 to support this process of global reform. In 2019, the World Economic Forum started a formal partnership with Orygen to work with stakeholders worldwide to develop a Global Framework for Youth Mental Health[68]. This process involved literature reviews of the scientific evidence, global surveys, face-to-face workshops and extensive online and face-to-face consultations with young people and other key stakeholders from many different countries and settings. A number of principles were agreed upon and a framework for different levels of health resources was proposed.

The key principles underpinning the implementation of youth mental health care include: a) prevention and early intervention; b) youth participation, respect, empowerment and co-design; c) community engagement, education and consultation; d) "soft entry" without stigma or financial barriers; e) choice regarding options for access and for treatment and care; f) family engagement and support; g) scientific evidence as a key guide. The way models of care can be deployed in different resource setting is captured in Table 1.

It has proven relatively easy to get a global consensus around the principles to guide youth mental health reform. Translating these principles into practice is a more challenging step, but there has been encouraging progress in recent years in many parts of the world. These advances can be described within a comprehensive framework including the following key elements: a) community awareness; b) prevention programs; c) volunteers, youth and peer workers; d) digital mental health platforms; e) educational settings and workplaces; f) integrated primary youth mental health care; g) specialist youth community mental health care; h) residential care.

COMMUNITY AWARENESS

The first step in reducing the burden of mental ill-health in young people is to educate the public in every society about the nature and pattern of mental ill-health and how it can be prevented, recognized, and responded to safely and effectively as soon as it emerges. Community awareness, anti-stigma and mental health promotion programs have been successfully delivered in many countries in recent years, though most have been generic or adult focused[69,70].

There are many worldwide examples of youth focused awareness campaigns, which have been a mix of mental health promotion and education on the warning signs of emerging mental ill-health. Mental Health First Aid[71] has produced a version for adolescents[72] and this has recently been evaluated[73,74]. There are sustained benefits for participants, but benefits for young people have been difficult to demonstrate and the focus on under 18s is a significant limitation. "headspace Day" in Australia is another example (https://headspace.org.au/about-us/our-campaigns/). ReachOut, which was one of the first to use the power of the Internet to reach young people, is one of the best examples. More recently, Batyr has complemented an online approach with face-to-face strategies in educational settings. Jack.org in Canada is youth-led and delivers nationwide programs and campaigns in youth mental health awareness and promotion. In the UK, YoungMinds is creating a youth-led movement to improve mental health awareness and the support available to children and young people. These programs are described with some more details in the following sections.

ReachOut

Established in Australia in 1998, ReachOut is a web-based mental health promotion, early intervention and prevention service for young people aged 12-25[75]. Co-design and youth participation have been central to its development and delivery[76].

ReachOut aims to improve young people's mental health literacy, resilience,

Table 1 Delivering youth-specific mental health care across resource settings

	COMMUNITY	PRIMARY CARE	SECONDARY CARE	TERTIARY CARE
HIGH-RESOURCE SETTINGS	Community education, screening and early detection programs Prevention programs (e.g., anti-suicide, anti-bullying) School, university and workplace awareness and early detection programs Digital mental health platforms	Integrated youth (12-25 years) health and social care platforms as "one-stop shops" School and university mental health services Digital interventions and telehealth integrated with primary care	Multidisciplinary youth mental health systems providing face-to-face and online care closely linked to primary care and community platforms Complementary integrated digital platforms	A suite of specialized, co-designed youth inpatient and residential services linked to acuity and stage of illness Home-based acute care and assertive community treatment
MEDIUM-RESOURCE SETTINGS	Community education, prevention, and school-based programs Digital mental health platforms	Integrated youth health and social care platforms as "one-stop shops" School and university mental health services Digital interventions and telehealth integrated with primary care	Multidisciplinary community mental health teams (face-to-face or online) Complementary integrated digital platforms	Inpatient services distinct from adult facilities and home-based acute care if this is not feasible
LOW-RESOURCE SETTINGS	Community education, prevention, and school-based programs Digital mental health platforms	Volunteer, peer or lay worker programs (Friendship Bench concept) Digital interventions and telehealth platforms	Primary care health professionals, including general practitioners and volunteers, trained in youth-friendly practice and mental health skills, providing care within community primary care settings with face-to-face, telehealth and digital options	Home-based acute care

social connectedness, and help-seeking behaviors through self-help information, peer support forums and referral tools[75,77]. It also offers support and resources to parents and schools. The service is accessed by more than 2 million people in Australia annually[78].

Nearly three-quarters of young people accessing ReachOut are experiencing high or very high levels of psychological distress[75]. A recent evaluation found that the service is accessible and relevant to young people, increases help-seeking behaviors, and significantly reduces depression, anxiety, stress and risk of suicide[78,79].

batyr

Launched in 2011, batyr is a preventive mental health organization in Australia that aims to reduce stigma and promote help-seeking. The batyr model draws upon a body of evidence highlighting the association between disclosure, stigma and well-being[80].

batyr delivers educational workshops on mental health in schools (batyr@school), universities (batyr@uni) and workplaces (batyr@work). Presenters are trained through the Being Herd program, a free two-day workshop that aims to empower young people (18-30 years) to share their lived experience of mental ill-health.

The Being Herd program has trained over 700 young people to date and has been associated with improved well-being in trainees as well as reduced self-stigma and stigma towards others[80]. The batyr@school program has reached over 200,000 young people across 352 secondary schools in Australia.

An unpublished randomized controlled trial found that batyr@school reduced stigma and increased attitudes and intentions to seek professional mental health care[81]. These findings were maintained three months after the program[81]. Both secondary and university students report that the batyr programs are highly engaging (82% and 85%, respectively) and increase the likelihood of seeking mental health support (70% and 78%, respectively).

Jack.org

Recognizing an absence of programs to train youth mental health advocates in Canada, Jack.org was established in 2010 as a youth-led mental health promotion and prevention initiative targeting young people aged 15-24.

The organization aims to increase mental health literacy, reduce stigma, and improve help-seeking behaviors through three core programs: Jack Talks (peer-to-peer mental health presentations), Chapters (community-based, youth-led working groups), and Summits (youth-led conferences). Online resources are also available to educate young people on how to support their peers.

In 2019, Jack.org reached over 170,000 young people, and 446 Jack Talks were presented by trained and certified speakers. Eighty-seven percent of Jack Talks attendees report that the presentation helped them think more positively about mental health.

YoungMinds

YoungMinds is a UK charity focused on ensuring that all young people receive the mental health support that they need when they need it. It offers online support, workshops and face-to-face training to young people, parents, schools and professionals.

In 2019/2020, nearly 2.5 million UK users visited the YoungMinds website and 11,959 parents and carers contacted its helpline, with 77% of parents reporting that they modified their approach to support their child following advice from the helpline[82]. An evaluation found that the helpline is beneficial to 88% of those who use it[83]. In 2019/2020, YoungMinds provided in-house training to 70 schools and organizations, with 97% of trainees rating the course highly[82]. Training is delivered to over 10,000 professionals each year.

YoungMinds also offers a flagship three-year activist program for young people aged 14 to 25 with a lived experience of mental ill-health, who campaign to raise awareness of youth mental health. Ninety-seven percent of activists reported better knowledge of their mental health and 83% felt more confident to speak about mental health issues[82].

PREVENTION PROGRAMS

Prevention is better than cure, and many of the risk and protective factors for mental ill-health are well characterized[84]. However, there is evidence for a rise in incidence and prevalence of mental ill-health in young people and of suicide rates, especially in young women[12,85]. A role is suggested of social media and new technologies, climate change and a range of socio-economic forces in undermining the mental health and well-being of young people[18,86].

Specific programs targeting some of these risk factors, for example, anti-bullying programs[87], chatsafe to reduce risks of suicide via an online strategy[88], and resilience programs in schools[89,90], have some value[91]. However, other risk factors are not especially malleable and are more widely social and economic in nature and scope (e.g., climate change and social media).

Prevention is a concept that extends across a spectrum and includes all stages of care. Fusar-Poli et al[92] recently reprised in this journal the US Institute of Medicine model of the spectrum of prevention in mental health[93], highlighting the distinction between universal, selective and indicated prevention and confirming that indicated prevention has been the most promising avenue for progress in recent years and has further potential[94].

As with other major non-communicable disease areas such as cancer, all aspects of prevention and preventively oriented treatment are valuable. However, what can be delivered in the foreseeable future in terms of universal prevention[95,96] remains uncertain. Preventive health care can operate across the full spectrum, and unnecessary false dichotomies between classic primary prevention and treatment merely undermine consensus and momentum[92].

"SOFT ENTRY": INNOVATIONS WITH VOLUNTEERS, YOUTH AND PEER WORKERS

The extreme shortage of mental health professionals in low-resource settings, and the relative shortage due to high need and inadequate funding in middle- and high-resource settings, has driven valuable innovation.

The most famous example of this is the Friendship Bench[97], devised and implemented in Zimbabwe. This concept has been enhanced as a "Friendship Bridge", a flexible way of engaging marginalized young people from a variety of cultural backgrounds. Similarly, in some high-resource settings, youth mental health models have drawn upon students and other young volunteers to facilitate engagement and make it more informal and less of a barrier (e.g., https://www.ease.nl and https://headspace.dk).

The advent of paid peer workers in youth mental health has similar goals and benefits[98,99]. With appropriate training, volunteers and peer workers can not only help to absorb substantial need for care at the front end of services, but also make the experience of entering care less challenging and more welcoming, especially for first time users, offer compassionate support, and deliver simple therapeutic interventions.

This is a component of youth mental health care which can be developed in all communities, and is in fact not a substitute for scarce workforces, but adds substantial value irrespective of the level of health financing and resources.

DIGITAL MENTAL HEALTH PLATFORMS

Young people are digital natives and the digital world is a fundamental element in their lives. While the establishment of integrated youth mental health services has improved young people's access to mental health care (see below), the volume of demand and workforce challenges have highlighted the need to develop further platforms that can adequately address the scale and diversity of need. The delivery of high quality mental health care through digital technology is considered key to this endeavour, emphasized by the COVID-19 pandemic[100].

The integration of digital technologies within youth models of care has several advantages, including improved service efficiency and access to care[100,101], potentially reducing the treatment gap in all resource settings. While the use of digital technologies in low- and medium-resource settings is acceptable, feasible and potentially effective[102], particular considerations are needed regarding factors such as language, culture, level of education, access to technology, digital literacy, and infrastructure[103].

There has been a rapid growth in digital mental health research[104] and, while there have been challenges in the implementation and uptake of new digital technologies[105,106], their integration within clinical services has the potential to enhance engagement[107].

For anxiety and depression in young people, a range of digital mental health interventions are available[108]. These involve text-messages (e.g., ReachOut, Rise Up), computer games (e.g., SPARX), online programs (e.g., MOST, MoodGYM), video games (e.g., Maya), online courses and chat groups (e.g., Master Your Mood), and mobile apps (e.g., Mayo Clinic Anxiety Coach). Interventions that involve supervision or regular contact with a therapist are more likely to be effective than unsupervised educational programs. Engagement and retention are issues requiring attention[108].

Promising platforms that combine face-to-face mental health care with digital interventions are described in the following sections.

Moderated Online Social Therapy (MOST)

Developed in Australia by a multidisciplinary team of clinical psychologists, designers, young adult novelists, comic artists and software engineers, Moderated Online Social Therapy (MOST) is a seamless digital solution adopting a user-centred design model. It is safe, effective and valued by clinicians, young people and families.

The intervention offers young people continuous access to evidence-based therapy and peer and clinical support from any Internet-enabled device. All included therapy has been adapted and enhanced based on a decade of youth feedback and usage data, to ensure that the young person's perspective is captured and the range of interventions feels uniquely relevant to their daily life. This therapy is embedded within a supportive online community of other young people working on their mental health, aiming to shift the treatment experience from one of isolation to one of shared mission.

MOST combines guided therapy journeys, targeted coping strategies, and mental health tracking with a social network of peers, providing an enriching therapeutic environment where young people can safely work towards their goals, take positive interpersonal risks, and broaden and rehearse coping skills for long-term well-being. Therapists work alongside face-to-face clinicians to offer wrap-around support to young people and provide advanced intervention tailoring. Specialist vocational consultants further support young people with work and study.

MOST seamlessly blends human and digital support to facilitate rapid detection and response to any indicators of risk or relapse between scheduled clinician contacts. It is an evolving model, and through successive iterations it has been adapted for a range of populations: first episode psychosis[109-111], ultra-high risk for psychosis[112], depression[113], social anxiety[114], mental ill-health[115], suicidal risk[116], and relatives[117,118].

A recent randomized controlled trial[110] in young people with psychosis demonstrated that Horyzons (MOST version for youth psychosis) was associated with a 5.5 times increase in the likelihood to find employment or enrol in education, as well as half the rates of visits to emergency services and hospital admissions due to psychosis, compared with treatment as usual, over 18 months following discharge from specialized youth psychosis services.

Synergy

Also in Australia, Synergy is a digital platform that aims to enhance the health, social and physical outcomes of young people through the delivery of personalized and measurement-based care[119]. The platform is embedded within youth mental health services and can be configured to meet local needs.

Co-designed with end-users[120,121], the platform facilitates a number of key processes, including multidimensional assessment, allocation of clinical stage, feedback of assessment results, shared decision-making, and monitoring of change over time[119]. A clinical trial of Synergy is currently underway[122].

The "digital clinic"

In the US, the "digital clinic" offers a hybrid model of mental health care, augmenting and extending services at the Beth Israel Deaconess Medical Center in Boston with a smartphone app[107]. The clinic has a core focus on therapeutic alliance, measurement-based care and shared decision-making[107].

Components of the clinic have been specifically designed to address key barriers among patients and clinicians that reduce uptake and engagement with digital mental health care[107]. These components include the Digital Opportunities for Outcomes in Recovery Services (DOORS)[123] and the Digital Navigator[124,125] programs, which provide digital literacy training to patients with serious mental illness and clinicians, respectively.

The mindLAMP (Learn, Assess, Manage, Prevent) app, a digital health platform used by the clinic and designed in consultation with end-users, is customized to each patient and has the potential to advance youth mental health care[126]. Core functions of the app include education, assessment via surveys and sensors, digital phenotyping, self-management tools, data sharing with patients, and clinician support.

The mindLAMP app can be adapted for implementation in all resource settings[126] and is currently being used by researchers and clinicians in over 20 sites globally. Preliminary findings of mindLAMP have highlighted the feasibility and potential utility of digital phenotyping to augment clinical care, although individuals under 25 years were found to complete fewer activities on the app than older individuals[127].

SCHOOLS AND EDUCATIONAL SETTINGS AND WORKPLACES

Educational settings offer the opportunity to promote mental health and well-being, to educate students and teachers about mental ill-health and how to recognize and respond to it, and to offer a primary care level of initial response[128-130]. This logic extends beyond school settings to university and other tertiary educational settings, where greater recognition of the opportunities for proactive youth mental health care is emerging in many countries[131-133].

These settings are best regarded as community-based populations of most, but not all, young people in which a bespoke primary care level system of care can be formulated and linked to other resources, including specialist care and digital mental health platforms.

INTEGRATED PRIMARY YOUTH MENTAL HEALTH CARE

Integrated health care[134] is a widely endorsed approach to optimizing health care, in view of its capacity to meet multiple health and social needs from a single platform of care. Its adaptation to young people has been at the vanguard of reform in youth mental health care over the past two decades in high-resource settings. As a version of primary mental health care[62], it should be at the heart of global reform, as a gateway to and component of staged care[65], and ultimately in all resource settings[62,68].

Although there were earlier examples of this approach[135], the trigger for global spread can be traced back to 2004, when the Australian government agreed to fund a new program of enhanced primary care, named headspace. This program was designed by Orygen and partners, including national professional organizations representing general practice and psychology[136]. Other countries soon followed, notably Ireland and Canada[50,137-139].

This wave of innovation in youth mental health care is now spreading globally, with at least 12 other countries adopting an integrated youth primary care model that is adapted to, and often limited by, the local cultural, health finance patterns and workforce context. The success of the headspace model, in particular, has seen its expansion into Denmark, Israel, the Netherlands, and Iceland. Similar programs under different branding have also been established in Ireland, Canada, Singapore, and the US. New Zealand and France had independently developed a similar model of care a little earlier.

Common features of these models include the following. First, there is a physical, developmental and cultural separation of youth mental health platforms from those for both younger pre-pubertal children and those for older adults, with an overdue shifting of the upper boundary of youth mental health care from 18 to 25 years.

Second, the value of youth participation and co-design is a universal success factor and has not only changed the culture, but also increased trust, and greatly minimized the stigma associated with help-seeking. This has been enhanced by the creation of trusted, stigma-free brands, something which has not been previously achieved in mental health care.

Third, the "one-stop shop" aspect of integrated care, from a single location with high visibility in the heart of the local community, enables better multidisciplinary care to occur, and helps to future-proof the service against the risk of defunding, to which more diffuse wrap-around models, based on fragmented funding streams, are more vulnerable. This approach also mobilizes local community support, including from local political representatives, and draws in collaborative support from other services and agencies.

Fourth, a flexible or "light touch" approach to diagnosis, especially in the early fluid stages of mental ill-health, and a needs- and strengths-based stance, which suits primary care, has been a common feature across many settings and is congruent with the staging model. Finally, a critical success factor, which improves outcomes, is ensuring model fidelity through accreditation, continuous monitoring and quality improvement, and trademark licensing strategies. This limits erosion of the evidence-based aspects of care, often justified under the guise of local adaptation.

Common challenges that have emerged are related to patterns of commissioning, workforce, professional work practices, and the lack of secure financial channels to support the model of care. A devolved pattern of commissioning undermines the capacity to safeguard model fidelity. Many of the examples so far struggle to attract and retain the full range of professionals and rely more heavily than is ideal on youth volunteers and peer workers, invaluable as these are in any youth mental health approach.

Even when the model has a good balance between youth volunteers/peer workers and mental health professionals at the primary care level, the success of the "soft entry" approach in enabling young people with all levels of need to gain access means that a cohort of young people with more complex and enduring mental health conditions are welcomed to enter the service. However, the model currently lacks the capacity, the skillsets and the tenure to fully meet the needs of this subset of young people and improve their outcomes. We have used the term "missing middle" to denote this cohort, since, due to the underfunding and neglect within specialist mental health care, even in high-resource settings, they fail to gain access to the next tier of care unless they reach a threshold of acute and severe illness or chronicity[140].

Nevertheless, affording primary care access at an early stage does at least highlight the existence of this crucial group of young people from whom spring the ranks of the future severely mentally ill, and creates the potential for earlier preventive treatment. A hidden waiting list of people with a need for care is brought out of the shadows and ultimately must be responded to.

Examples of programs of integrated primary youth mental health care are described in more detail in the following sections.

New Zealand: Youth One Stop Shops and Piki

New Zealand pioneered the establishment of "Youth One Stop Shops" in 1994. These provide young people (aged 10-25) with a range of accessible, youth-friendly health, social and other services in a "wrap-around" manner.

An evaluation of 14 services in 2009 revealed that occasions of service ranged from 2,000 to 15,000 per area, with a mean of 11,430[141]. While objective data regarding improvements in access and health were unavailable, young people (94%) and stakeholders (89%) reported that the service was effective in improving health and well-being[141].

Following successful pilot of Piki, a youth mental health service for young people aged 18 to 25, the New Zealand government recently committed to a rollout of youth-specific primary mental health and addiction services for young people aged 12 to 24 years. Services in 13 locations have been announced to date. These services will be offered in a range of places, including in Youth One Stop Shops and community centres.

France: Maisons des Adolescents

The "Maisons des Adolescents" (MDAs), which began in 1999 in Le Havre, France, are integrated health care services for young people with physical, psychological or social problems. While the target age range is 11 to 21 years, sites can extend this to 25 years[135]. Operating under a common brand across 104 locations and with a national office in Rennes, each centre provides care to between 700 and 1,000 young people each year, and the average number of visits is between two and three.

Young people report that the service contributes to their well-being, while professionals are satisfied that the service responds to individual needs[142]. Services are varied in the content they offer, which includes a "health and prevention space" for listening and assessment, mobile teams for hospital in-reach and also home and community outreach visits, arts and cultural programs, vocational support, specialist consultations and network meetings.

Steps have been taken recently to improve regulation and standardization of the model to optimize the care provided, prioritize needs and adapt the approach to new societal issues. As with other models, there is evidence of tension between a light touch "listening" stance and more therapeutic interventions.

Australia: headspace

headspace was funded and designed in 2005 by the Australian government in response to an extensive advocacy campaign for reform and investment in a national youth mental health program, which was motivated by low levels of awareness, access and quality of mental health services for young Australians. The campaign gained bipartisan political support, and government funding was secured to support the design and implementation of the program initially within only ten Australian communities from 2006[66]. This has progressively been scaled up to 136 centres, through a series of government funding rounds, and aims to reach 164 communities by the end of 2023[143].

Over 130,000 young Australians access a range of services via headspace every year, and over half of young people attending headspace present with high or very high levels of psychological distress[144]. By late 2020, headspace had supported 626,000 young people with over 3.6 million occasions of service[145].

The headspace model provides a youth-friendly "one-stop shop" service for young people to access a range of health and social programs, including mental health, physical and sexual health, vocational and educational support, and drug and alcohol education and interventions[43,66]. A national online support service (eheadspace) is also available over extended hours, where young people can chat with a mental health professional online or by phone.

headspace also delivers mental health programs in schools nationally, in partnership with beyondblue (www.beyondblue.org.au), which enhance mental health literacy and skills among teachers and offer suicide postvention support[145]. Online work and study support is available to complement face-to-face vocational (Individual Placement Support) interventions.

headspace operates on an enhanced primary care model, providing a multidisciplinary team structure with close links to local community supports (e.g., schools and specialist mental health care). It is a form of franchise with a national brand which requires adherence to a measurable template of care. Until 2016, the headspace national office commissioned a single lead agency within a wider local consortium at each site to deliver the service. Now 31 devolved regional primary health care networks perform this function on behalf of the Australian government, while the national office assesses adherence to the model and controls the license and trademark.

headspace has undergone two separate independent evaluations[146,147], which showed major improvements in access for young people, including for marginalized groups, notably Indigenous and lesbian, gay, bisexual, trans and intersex (LGBTI) young people. More than 60% of young people experience short-term improvements[148], and a follow-up study of those who engage has shown sustained benefits with high levels of satisfaction among young people and families[149]. A third evaluation is in progress.

The current headspace funding model is modest and supports only brief episodes of care, yet open access is provided to *all* young people, including the "missing middle", the large cohort of young people who need more intensive, sustained and complex interventions but fail to access them. In Victoria, specialist services are now being aligned with the 12-25 headspace age range and will be substantially boosted[150]. Early psychosis programs linked with headspace exist in a number of regions of Australia, also span the adolescent-young adult age range, and can be expanded transdiagnostically to fill this gap.

The rising level of unmet need and the widely known and trusted brand and entry portal are now resulting in increasing waitlists[151]. Workforce shortage, and the relative financial weakness of the model and of the specialist back-up system of care, are issues that must now be addressed. Fortunately, political and community support for headspace has led to a boost in investment in the 2021 federal budget.

headspace, as a disruptive and popular reform, and still a work in progress, has had its critics, which to a degree have been helpful in eliminating flaws and improving the model of care[39,152-154]. Finally, the COVID-19 pandemic created obvious challenges, generating an increased need for care with reduced accessibility[7]. The latter was buffered by the federal government's support for telehealth and mobile outreach.

Ireland: Jigsaw

In 2006, in the context of a national reform, concern about youth suicide, and influence by headspace in Australia, the

One Foundation created headstrong as the national youth mental health foundation of Ireland. Jigsaw became the publicly facing brand for the service and later the single brand for the whole organization[139,155].

Prior to its development, there was very limited mental health access available to young people in Ireland, particularly for those with mild to moderate mental health needs, with state funded child and adolescent mental health services seriously under-resourced and only able to provide care to a small minority of young people with more severe mental illness, and not even up to the age of 18.

Jigsaw's approach incorporates free one-to-one clinical supports and brief clinical interventions that are accessible to young people when and where required. Community and school based programs are additional features.

The program has grown from five pilot sites in 2010[155] to 14 services in 2020 (including one digital service), with an additional service opening in 2021. Services have provided access and care to over 44,000 young people since 2007. The program is highly accessible and significantly reduces psychological distress (62% aged 17-25 show a reliable and clinically significant improvement), with high levels of satisfaction among young people and their parents[156-158].

For a number of years, Jigsaw was only funded by philanthropic sources, but eventually the national government came on board, and in 2015 the program was included in the national Health Service Executive annual service plan and received significant mainstream funding. This funding has grown year-on-year to support the expansion of services, and the Health Service Executive now funds the majority of costs associated with service delivery.

The challenge, as in Australia, now involves filling the gap between Jigsaw, as the entry point to youth mental health care with only brief and limited capacity, and the specialist mental health services for young people, which needs major reform and investment to engage with the primary care reform. A stronger role for general practitioners is hampered by the lack of universal health care and government funding for primary care in Ireland.

Canada: ACCESS Open Minds, Foundry, Youth Wellness Hubs Ontario, Aire ouverte

Youth mental health reform in Canada followed a common pattern, with catalytic leadership from philanthropy. The Graham Boeckh Foundation allocated substantial funding, in partnership with the Canadian Institutes for Health Research, to create ACCESS Open Minds, a pan-Canadian network transforming mental health care for young people in 16 diverse communities (seven provinces and one territory), with an emphasis on high-risk populations (e.g., Indigenous communities)[137,159].

The ACCESS Open Minds model is adapted to local circumstances, reflecting the geographic, political and cultural diversity in Canada. Key elements of service transformation within each site include: systematic service planning; early case identification; rapid access; integrated youth space; appropriate care; active youth and family engagement; training of clinical staff; and building research and evaluation capacity[137].

A total of 7,539 young people between May 2016 and August 2020 have received services with rapid access, high levels of satisfaction and small to medium effect size improvements in distress, symptoms, and social and vocational functioning[160].

A wide range of clinical and social services are offered. In contrast to other models, the majority of young people are experiencing moderate to severe conditions[160], and it is this subgroup that improves more with the interventions that are provided. A key feature has been the success achieved with Indigenous communities, LGBTI and ethnic minorities, in which trust and ease of access has been demonstrated[160]. Evaluation of ACCESS Open Minds is underway[161].

The widespread advocacy and support from the Graham Boeckh Foundation has led to several provincial integrated youth services initiatives in Canada. These include Foundry in British Columbia, Youth Wellness Hubs in Ontario, and Aire ouverte in Quebec.

Established in 2015, Foundry is a network of service centers across British Columbia, offering low-barrier (i.e., self-referral, walk-in and free) access to mental health, substance use, general and sexual health care, and social services. A team of care and service providers work with each young person, and services are appropriately targeted to the young person's level of need using a stepped care approach.

Each Foundry centre is operated by a lead agency that brings together local partners, service providers, young people and caregivers. During the first two and a half years, 4,783 young people accessed care through six service locations. Eighty-one percent of young people who accessed the service had high or very high levels of distress[162]. The model has improved outcomes and ensured greatly improved access to marginalized subgroups, including Indigenous, LGBTI and others, and is continuing to expand across the province.

Youth Wellness Hubs Ontario was initiated following the development of three integrated youth mental health services launched in Toronto as part of YouthCan IMPACT, a federally-funded randomized controlled trial of the integrated youth mental health service model compared to treatment as usual in hospital-based outpatient adolescent psychiatry services[163].

In 2017, the Government of Ontario expanded the integrated youth services model to six additional communities. Initial service delivery emphasized integration of existing mental health, substance use, general health and social services, provided in-kind, with modest funding enhancement from government and philanthropy. These services unified under the Youth Wellness Hubs Ontario umbrella to form a network of ten integrated youth services which was included in the Ontario government's strategic mental health plan and secured permanent funding[164]. Work is ongoing to expand the model and demonstrate its feasibility, appropriateness and outcomes in Ontario's diverse communities.

In the province of Quebec, a network of integrated youth services ("Aire ouverte") has also been established for young people aged 12-25. Similar to the above, these services aim to provide low-barrier and easy access to a range of health and social services. There are currently three centres, with others due to open throughout the province.

Denmark: headspace

headspace Denmark was established in 2013 as an initiative of Det Sociale Netværk, a non-governmental organization. While based on and branded similarly to the Australian model, the Denmark model has been adapted to meet local needs.

headspace Denmark is a free support and counselling service predominately delivered by trained volunteers, including young people, who work in pairs. The service does not yet offer clinical treatment to young people. Instead, it provides a young person with "someone to talk to". Approximately one in five young people accessing headspace Denmark are referred to other services for treatment or specialized care.

At present, there are 28 centers in Denmark in 26 municipalities (in addition to a nationwide anonymous video and text-based chat service). The government is now engaged and contributing funds. Through continued state co-financing, it is anticipated that headspace Denmark will expand to 32 centers in 2022, which will establish it as a nationwide face-to-face service with 50% coverage, and expand its position as the largest preventive and mental health-promoting civil society project for vulnerable young people in Denmark. Formal evaluation of headspace Denmark is currently underway.

Introducing clinical expertise and, as elsewhere, building a bridge with specialist clinical services for young people, will be crucial challenges.

Iceland: Bergid headspace

Bergid headspace was established in Iceland through the advocacy of S. Bergsdottir. Since 2019, this low-threshold support and counselling service operates in Reykjavík, with outreach counselling available in other regions of Iceland in addition to online. By the end of 2020, a total of 390 young adults had accessed its services.

A range of data, including self-report questionaires, are collected. The average number of sessions attended is four, but young adults often return for subsequent episodes of care. The average age of those who sought services is 19 years, and 90% of the individuals are from the capital area around Reykjavik.

Israel: headspace

headspace Israel was established in 2014 in response to low help-seeking rates and a lack of public health services for young people with emerging mental ill-health. Once again philanthropy, this time from Australian sources, was instrumental in the service being established. Commencing in Bat Yam, a second site in Jerusalem has been added.

headspace Israel is a youth-friendly, multidisciplinary enhanced primary care model ("one-stop shop"), with close links to locally available specialist services, schools and other community organizations.

In its first year of operation, headspace Israel successfully increased the level of accessibility and familiarity of mental health services available to young people, with 652 youth accessing the service in Bat Yam.

Netherlands: @ease

@ease, which began in January 2018 in Maastricht and Amsterdam, is a walk-in support and counselling service for young people delivered mainly by trained volunteers (including psychology students and young people).

Since @ease was established, it has expanded to Rotterdam, Gröningen and Heerlen. It has been complemented by an online chat service and by psychiatric and other professional support, and over 1,000 young people have accessed care to date.

United States: allcove

In the US, the allcove program, developed through the Stanford Psychiatry Center for Youth Mental Health and Wellbeing, has opened its first two centers in 2021. Created through a collaboration with Santa Clara County, the first two allcove sites are in San José and Palo Alto.

Inspired and supported by headspace Australia and Foundry, this US integrated youth mental health model for young people aged 12-25 years will include early mental health care, primary medical care, substance use services, peer and family support, and supported education and employment services.

The State of California has committed seed funding for a further five centers in San Mateo, Sacramento, Los Angeles (two centres) and Orange counties. Potential expansion across five other states is also in progress.

Singapore: Community Health Assessment Team (CHAT)

Established in 2009, and building on the Singapore Early Psychosis Intervention Programme, CHAT is a national youth mental health check and outreach program under the Institute of Mental Health[165].

CHAT focuses on young people aged 16-30, and provides free, personalized care in a non-stigmatizing environment. The service comprises allied health professionals, doctors, administrative support, youth mental health advocates, CHAT ambassadors (a volunteer-based youth peer group), an outreach function, webCHAT (an online screening service), and on-site brief support to young people with poor access to specialist services[166].

Over its first decade of operation, 3,343 young people (54% of all referrals) received a complete mental health assessment at CHAT. Forty-seven percent experienced a 25% or higher reduction in distress, while 20% showed a 6-25% reduction[166].

United Kingdom

While no systematic health care youth mental health reforms have emerged so far across the UK, the same issues have influenced service provision through a system of variable Youth Access centres at local levels.

In several parts of the UK, notably Norfolk and Birmingham, specialist mental health services have restructured to accommodate a youth mental health perspective with some success[167-169]. Further reform is under consideration by the national government.

Hong Kong

The success of early psychosis reforms in Hong Kong[170-172] has prompted the academic and clinical leadership to explore youth mental health reform more broadly, and a series of surveys have been conducted to prepare for this.

The recent social unrest and the extreme pressures mounting upon the young people have underlined the crucial need for better mental health support and access.

SPECIALIST COMMUNITY MENTAL HEALTH CARE

In high-resource settings, youth-specific specialized community mental health care is an essential back-up system for the integrated primary care platforms for young people. A key barrier that has to be overcome is the paediatric model of child and adolescent mental health services, with its low level of resourcing and a transition point to adult mental health services anchored at age 18, as discussed above.

A recent breakthrough in Victoria, Australia[150] will align the specialist mental health services with the headspace network's age range (12-25 years) and enable a common clinical governance system to operate both tiers of care in a seamless manner. This alignment and vertical integration will facilitate the operation of a clinical staging approach to treatment, and should enhance the effectiveness of care and outcomes.

RESIDENTIAL CARE

In high-resource settings, a suite of residential options for young people is needed and possible, ranging from acute inpatient care, with the alternative of intensive home-based care or "hospital in the home", through subacute or recovery oriented therapeutic programs and longer-term residential care in the community.

It remains a work in progress to fund and design these facilities in partnership with young people and families. Such settings need to be streamed separately from young children and older adults, and must be designed and operated with gender, cultural and developmental maturity issues at the forefront.

PARADIGM TENSIONS

Any change which seeks a paradigm shift will encounter major challenges and resistances, and these have indeed emerged as the youth mental health reform has unfolded. Some of these challenges are conceptual and political; others are practical. Psychiatry has struggled to overcome an intrinsic pessimism and lack of self-belief, which has been perpetuated by stigma, discrimination and low status within health care and medical research.

Underfunding and the sense that mental health care is at best a zero-sum game or, at worst, a shrinking pie, leads different areas of psychiatry to compete with one another and undermines progress in any one field[39,41,173]. It is difficult to secure unity of purpose and mobilize a team effort within mental health to achieve beachheads and objectives of any kind. Doubt is introduced even when solid or highly promising scientific evidence has been assembled, for reasons and in ways that we do not see happening in other areas of health care[40]. Scepticism is a vital force in an empirical and pragmatic field like medicine, but it can be counter-productive and harmful if excessive or motivated by insecurity, vested interest or a self-defeating mindset.

A new paradigm of youth mental health care can be seen as a threat to the *status quo*, or alternatively as a way of strengthening both child and adult psychiatry. There are indications that child and adolescent psychiatry at least is starting to embrace the opportunity. Yet the recent reforms in this area have not flourished through logic and scientific evidence alone, essential as these safeguards and guides assuredly are. Nor have they been hampered by doubt disguised as genuine critique.

A key success factor to date has been consumer demand and support. Determined global leadership from a range of clinical and academic pioneers has also been a key feature. Economic arguments are now adding strongly to the momentum, since mental health care, largely due to its timing in the life cycle, is the one remaining area of health care where major return on investment is achievable.

CONCLUSIONS

Youth mental health care has the potential to be a transformational new paradigm, one which could inspire societies to value and develop much greater faith in mental health care. The energy and optimism that can be generated, if combined with a positive experience of care, better outcomes and return on investment, are powerful forces for change. We have argued here for youth mental health care to assume its place as a critical transitional zone within a lifespan approach to mental health care. This ultimately involves the creation of a new professional field, not merely new models of care.

The main feature of the emerging models of youth mental health care is shifting and embedding the focus upon the transitional developmental stage from puberty to independent adulthood, which extends approximately from 12 to 25 years, though the boundaries are flexible and variable. The engagement of young people and families in the conception, design and operation of the models, and the strong community and political support they have mobilized, are essential components of their success. The reform has typically been led by clinicians, academics and philanthropists. Politicians, however, waiting for solutions to the pessimism and stagnation in mental health care, have often been eager to support these optimistic approaches to early intervention and youth mental health.

Features that reduce barriers to entry and promote a normalizing and welcoming entry portal, such as the use of volunteers and peer workers, a de-emphasis on formal diagnosis and a focus on encouraging help-seeking for mild and potentially transient problems, can create tensions with professionals from more specialized settings. The under-resourcing of youth mental health care and the understandably defensive mindsets contribute to this tension. In fact, if we can assemble the necessary resources to build a flexible and proactive system of staged youth mental health care powered by new workforces, including a new sub-specialty of "youth psychiatry"[174], then this tension can be dispersed and seen for what it is – a false dichotomy, one of many in the mental health field.

These new infrastructures of youth mental health care are enabling the early stages and boundaries of potentially serious mental illness in young people to be understood and mapped across the transdiagnostic landscape for the first time. They allow novel therapies to be explored and trialled, and their safety, acceptability and effectiveness to be explored and examined in a transdiagnostic setting[175].

Critics have alleged that this strategy produces harm through labelling and overmedicalization of teenage angst and overtreatment. In fact, with a needs-based approach, in which diagnosis is de-emphasized and treatment sequenced according to clinical staging, with its intensity guided by risk-benefit balance considerations, the opposite is true, and the hard data from all these programs strongly support the need for care that the help-seeking young people manifest.

The high degree of unmet mental health needs in young people worldwide demands that youth mental health care be elevated to an absolutely top priority in health care. Global reform and adequate investment in youth mental health will not only substantially improve the health and lives of young people, but will pay for itself and promote mental wealth for all of society.

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The challenges of youth mental health: showing the hero out of the panopticon

One of the challenges we all face – as researchers, clinicians, leaders and parents – in youth mental health is the dynamism and complexity of adolescence and early adulthood.

As McGorry et al[1] allude to, one of greatest dangers is that this complexity and dynamism can itself become a reason for lack of self-confidence in professionals and an excuse for passivity and quietism. Young people can present for clinical support and yet professionals look to time and development ("he will grow out of it"; "it is just a phase") as a response to help-seeking or look at the wider context of the young person's life, undercutting the distress he/she is reporting. We clinicians have to sail between Scylla and Charybdis: to remain optimistic, flexible, problem-focused and non-stigmatizing, yet realize the real clinical difficulties young people may be suffering, and the level of professional help and expertise that may be required[2].

McGorry et al refer to "soft entries" to services, which are essential to limiting hurdles and thresholds for support. In the UK, many child and adolescent mental health services have operated from a distinct clinical base, with a system of referral and appointments and long waiting lists, which can make access for young people in education, or whose families have wider difficulties, problematic. Flexible, non-stigmatizing, blended models of access are crucially important. Alongside smoother access, we need to consider methods of "soft exit and re-entry", so that services can respond and map onto the changing needs of young people and their families.

However, this optimistic and flexible approach to services should not be conflated with staff being less clinically skilled in the management of complex mental health problems. Many young people and families report that they have been seeing a certain service for a period of a few years but feel that they have not been helped, and that evidence-based interventions have not been offered.

Young people often see access to services and professionals as the end-point of their journey to seek care, and we need to make sure that, when they do access services, they find staff that are adequately skilled to assess and deliver the interventions which are required, and, as teams, have the clinical wisdom to pivot between different models of distress, and to move between the various levels of provision of care and support that a clinical staging approach requires, acknowledging the multimorbidity that young people often experience.

In the work of the University of Birmingham Policy Commission *Investing in a Resilient Generation*, the problem of a skilled workforce in youth mental health care became very clear[3]. The Commission calculated that scaling up mental health services so that every young person receives the help needed would require an investment in the UK of £1.77 billion. To meet this need would require an additional 23,800 clinical staff.

The report was published as Brexit was still progressing through government. With the UK having left the European Union, and considering the impact of the COVID-19 pandemic, these workforce challenges have now become even more pressing.

We are trying to increase capacity in the youth mental health workforce through implementing our own training programmes and supporting allied professional groups to develop expertise in mental health. These include primary care physicians[4], members of the emergency services, and school staff, with evaluation of the government's Trailblazer programme underway[5]. We are also supporting peer-led initiatives and the use of digital health innovations.

Given this workforce issue, we are stressing the importance of implementing preventive strategies alongside improvement in services. Despite all innovations, we are unlikely to fully meet the mental health needs of young people, and hence it is important to try and address the increase in incidence of youth mental problems. The above-mentioned Commission identified several possible preventive strategies, including enhanced perinatal support, parenting programmes, reducing adverse childhood experiences (such as violence, bullying, victimization), mental health friendly education and employment, and supporting transitions between educational stages and employment. We have begun implementing some of these strategies in the University and City of Birmingham.

McGorry et al's use of Campbell's idea of the "Hero's Journey" myth seems an apt lens for thinking around youth mental health. Many of the young people we work with do themselves turn to a life-course perspective in their understanding of mental ill-health, looking to their past and to their future. One relevant theme is their often-mentioned claim that they feel they have experienced an "absence of adolescence", i.e., a movement from childhood to adulthood, with no intervening period of safe experimentation. Our youth advisory group members mentioned having an awareness of almost being a "brand" defined by social media. A fear was that what had been captured online could not be erased or forgotten and hence there were less opportunities to make mistakes safely. The internalized panopticon of Foucault (i.e., a consciousness of constant surveillance) seems to be experienced.

The second theme of the Hero's Journey that seems relevant is the destination. McGorry et al mention the concern that young people have over climate change, and this can be linked to the feeling that prior generations have failed them, and the sense of responsibility they feel for the future. Relatedly, and echoing the point around increasing economic inequality and casualization of labour[1], the neo-liberal social contract is one that often seems either unattractive or unattainable or both. Many of the young people we work with were children during the recession and periods of austerity in the UK: they talk about their parents' struggles with employment, with debt, and the use of food banks. The idea of working hard, and getting one's own place and secure employment seems an unrealizable goal. Given this, a sense of meaning and purpose is important for us to engender in our politics and society, to offer a new Hero's Journey to young people. If one wanted to take a Keynesian approach to mental health, investing economically in young people to carry out volunteering and altruistic acts may have a benefit on their mental health, while at the same time contributing to create more equal and inclusive societies[6].

A final point I want to make is the importance of co-production and having young people at the centre of mental health service developments. Many of us are aiming to move from participation and involvement to full equal co-production with those with lived experience of mental ill-health. Epistemic injustice is a term developed from feminist philosophy to describe someone's capacity as a knower being devalued or ignored due to factors such as gender, class or ethnicity. Young people with mental ill-health may be treated unjustly for multiple reasons[7] (age, health, gender, ethnicity, social class) and, given the benefits they can bring to us in their knowledge of services and their personal experience, it is crucial for us all to do what we can to minimize injustice and scaffold and support full democratic and equal production. A first step towards this can be charting such injustices in real clinical and research contexts and developing steps to mitigate them.

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Meeting the challenges of the new frontier of youth mental health care

Youth mental health (YMH) services are mental health's new frontier, buoyed by the widespread implementation of early intervention in psychosis services[1]. McGorry et al[2] provide an excellent account of YMH services across many high-income countries. Here we focus on the key challenges that need to be addressed for the future success of these services.

While the key principles of prevention/early intervention, youth and family participation, community engagement, stigma-free open access, choice and empowerment, and research and evaluation should guide future YMH services, it is unlikely that any one service model will meet these objectives across variations of local social, political, economic and cultural circumstances.

An enhanced primary YMH service is a most welcome innovation. However, an entirely new system parallel to any existing services may neither be feasible nor advisable in many jurisdictions. It will be prudent to incorporate existing resources in each community into the new system. Given the large variation in the way different communities transform their YMH services, testing adherence to the key principles will be necessary in evaluating their effectiveness. Producing evidence for the effectiveness of new YMH services, designed to address different levels of severity of all mental disorders, is more complex than was the case for early intervention in psychosis services, but nonetheless essential.

The primary objective of providing unencumbered stigma-free access to youth experiencing all levels of mental health distress needs to be balanced by the ability of the service to address priority needs of those with existing or emerging mental disorders. Assumed that the practice of a diagnosis-based entry for mental health services is undesirable, the question of what is a "case" in the proposed open access service has to be answered. Determining "caseness" may involve a combination of measures of youth-reported subjective distress and perception of mental health problems with clinical and functional impairments observed by the clinician[3] .

To achieve a valid and reliable definition of a YMH "case" will require carefully designed prospective studies comparing different thresholds for dimensions of distress, symptoms and functioning with currently used diagnostic categories. This becomes particularly relevant considering reports of a recent explosion of YMH problems during the COVID-19 pandemic[4]. This increase in youth distress is not necessarily indicative of a sustained increase in the incidence and prevalence of mental disorders[5]. Much of this distress is likely related to specific problems of economy (jobs, training) and a forced breakdown in social relationships.

Such widespread increase in youth distress may not be best served exclusively within the structure of even newly designed mental health services. The resulting increased workload may produce a negative impact on the already well-known delay in treatment of highly prevalent mental disorders. The front-line open door of the new YMH services providing rapid access to initial assessment must be backed by timely access to specialized mental health services and specific interventions (e.g., psychotherapies) for a range of mental disorders.

To make this core mission clear, we will need to confront the epistemic issues related to mental health/disorders/wellness or other new terms that continue to come into use. For example, some YMH services are set up as wellness centres, although they provide services for those with mental disorders. Such terminology is likely to be confusing to the potential consumer, given the varied meanings attached to the expression "mental wellness"[6].

The considerable overlap in the age at onset of substance abuse and mental disorders in youth, and the resulting long-term association between the two[7], creates one more challenge. The new YMH services must be equipped to both assess and treat emerging as well as established substance abuse problems. While heavy use of alcohol and cannabis is transient among many young people, it may also be harbinger of later abuse and dependence. There is indeed an opportunity for effective prevention of substance abuse problems among heavy users through relatively brief, non-invasive, and effective interventions, some of which can be provided online[8]. Including substance use services on an equal footing with those for mental disorders will require a more complex infrastructure, staffing, training and evaluation than what seems to be the case currently. Last, but not least, the epidemic of opioid abuse and the tragically high mortality associated with it remain largely absent from YMH service narratives, with some exceptions[9]. Mental health services for these highly vulnerable youth will need to be connected to other interventions and systems of care currently in place for opioid abuse, so that youth can navigate between different aspects of care for these deadly problems.

There is an implicit agreement that the new YMH services are designed for the age group of 12-25, based on the high incidence of mental health and addiction disorders during this period and the assumption that child psychiatric services are more adequately provided for the 0-12 year period. However, there is little empirical evidence to support the specific age range for which an entirely new system of care is being built, and issues of continuity with the age groups before and after should be addressed. Among those under 12 years of age, a substantial proportion present with developmental disorders, making them particularly vulnerable to future mental disorders. The new YMH services must be deeply connected with the system of care for developmental disorders and ensure the same unencumbered access for these youth as for those without prior developmental problems. At the other end of the age spectrum, most major disorders are likely to persist beyond 25 years of age and, therefore, need both episodic as well as continuous care of the highest quality. Shifting transition from 18 to 25 may postpone the problem, but not solve it[3].

In summary, in setting up the new YMH system in multiple jurisdictions, some key issues need to be addressed, including connections with existing services, extending the transformation of service to the age period before and beyond 12-25 years, and providing equally weighted services to those with substance use disorders and pre-existing developmental disorders. The key principles underlying these services must guide an evaluation of a variety of methods of service delivery, as one model is unlikely to fit all circumstances and jurisdictions. Such evaluation will require innovative designs, as traditional randomized controlled studies will be difficult to conduct and we cannot hold back the progress that is already taking place.

It would be prudent, even if not popular, to clearly define the boundaries of mental health and disorders to be able to serve those with the greatest needs. This will require research into different definitions of "caseness", matched by provision of care appropriate to the stage and level of an existing or an emerging disorder. It is unlikely that YMH services can address all forms of distress in youth, the origin of and solution to some of which may be outside the field of health. This is likely to be particularly the case for the greatest proportion of youth on the planet who live in low- or middle-income countries, where poverty, political oppression, gross human rights violations, gender discrimination and violence, often resulting from post-colonial legacies, are major sources of distress.

In the context of these environments, the current models of YMH services are not only unlikely to be workable but may be grossly inappropriate. Much of the globe will need to find its own solution to problems of youth, including mental and addiction disorders, using its own unique assets, but still able to incorporate the key principles generated from the current wave of YMH services discussed in this Forum.

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Implementing 21st century "end-to-end" and technology-enhanced care for young people

The advent of health services specifically designed for young people with emerging anxiety, mood or psychotic disorders is the most appropriate response to the peak age of onset of these disorders, the evidence favouring early intervention, and the problems with access to clinical care[1]. The primary goal of these services is to provide an attractive "front door" that engages youth at risk of progression to major disorders. The available data suggest that they are largely fulfilling this basic purpose[1].

While health service innovations alone are unlikely to reduce population-level disease burden, it remains the principal goal of clinical care to provide high-quality and more personalized interventions. If the more substantive aim is to halt or even reverse illness course and, thereby, prevent premature death or long-term functional impairment, then it is timely to ask: are the new youth services optimally designed to deliver these outcomes?

To date, national health systems have never seriously moved to implement an integrated "supply-chain" of clinical services, operating across the spectrum from indicated prevention to continuing specialist care. By contrast, the traditional response to the ever-increasing demand is to add new stand-alone service "blocks" to the existing disconnected structures.

New service "blocks" are often based on historic concepts of primary, secondary and specialist care. Typically, access to specialist services remains severely restricted, being reserved largely for those who have already progressed to later stages of illness. This traditional hierarchy of care has been viewed as the most equitable way to ensure basic population coverage for very common, persisting or chronic conditions.

However, these pyramidal structures often ignore the reality that early intervention only works when delivered early in the course of illness. While most new services focus on increasing access to primary care, the reality is that enhanced access alone does not deliver improved outcomes. Analyses of longitudinal data from primary-care based youth services indicate both the continued progression of those with early to later stages of mood and psychotic disorders[2], and that the majority of those who enter with impaired social, educational or occupational function do not make substantive long-term gains[3].

So, is it time to rethink our assumptions and seriously consider alternative options? Digital health services are rapidly developing in new directions, with a variety of stand-alone or integrated models of clinical care[4,5]. Importantly, as private investments in these more personalized alternatives are also growing substantially, we are likely to see considerable competition and disruption (i.e., "uberization") of mental health care in both developed and developing economies[5]. Much of this will be dictated by financial considerations rather than evidence of superior effectiveness.

So, are we really closing in on our main target, namely, "Right Care, First Time, Where You Live"[4]? In reality, this would require the combination of much more innovative clinical models with new technology-enhanced modes of practice[4]. Beyond the concept of supporting an integrated "supply-chain", a fundamental consideration is the extent to which new digital technologies can support effective implementation of each element of this enhanced care model[4].

"Right care" means skilled assessment and choice of interventions that are highly personalized. It does require multidimensional assessment, including elements such as lifetime trajectories, clinical stage of illness, pathophysiological mechanisms, comorbidity, recognition of social and cultural setting, and personal choice[4]. Much of this material can be collected efficiently through data entered directly by service users and their families[4]. It is greatly assisted by using new (passive and active) personalized devices that monitor *in vivo* motor activity, sleep, social connections, mood, physiological arousal, cognitive performance, metabolic health, and engagement with education or employment[5].

"First time" rejects the typical health services mantra of "stepped care" in favour of "staged care"[6]. That is, it promotes immediate specialized care for those presenting with first episodes of major disorders. Technology-enhanced triage systems that bring timely specialized clinical assessment to the start of the service encounter can assist to make this critical task much more efficient. They do this by focusing video-enhanced specialist assessment on those at highest risk of illness progression or suicidal behaviour[7].

"Where you live" really matters. Socioeconomic and geographical disadvantages are real. The disparities in the distribution of services (urban vs. rural, wealthy vs. disadvantaged regions) have major impacts on illness course. The provision of the whole range of services from self-care right through to more specialized interventions, based largely on new technologies, may become possible for those communities that have been most neglected[8]. It will require new workforces ("digital navigators") and a much stronger commitment to telecommunication systems as essential "health" infrastructure in the 21st century.

Tied to the notion of "highly personalized" interventions is that of measurement-based care. We need smart, bidirectional and interactive systems that actively engage young people and collect data directly from service users, families, carers, clinicians and personalized devices[4]. Most importantly, these data should then be used quickly to identify those who do not respond, or deteriorate, early in the course of illness[2,3].

Rather than simply deploying new service "blocks", it may be better to focus on what a well-coordinated, regionally-organized, technology-enhanced, end-to-end "supply-chain" looks like in the 21st century. New dynamic modelling (at the population level) and discrete event approaches (at the service level) can be employed to bring rigour to national or regional health service planning[9]. It can also inform allocation of limited workforces, alongside financial and technical resources[9]. Modern, real-time data collection systems can also be used to embed clinical research within these new systems[5].

While the review by McGorry et al[1] does draw attention to the potential of new digital platforms, a less appreciated aspect of digital innovation is the large potential impact of technology-enhanced care coordination. This not only assists to put young people at the centre of the care journey, but focuses on reducing unnecessary delays in providing sophisticated clinical assessment and effective interventions[9].

In less privileged settings, we are already seeing a willingness to use new technologies that are not limited by traditional geographical barriers[7]. We can no longer simply accept the notion that specialist care is a luxury item reserved for those in developed countries, while the rest will have to make do with "universal primary care". These digitally enhanced systems have a tremendous capacity to bring more personalized, specialized and coordinated care to those who have long been neglected.

At this time, however, there is still much work to be done to determine whether new clinic-based or technology-enhanced systems, alone or in combination, can deliver substantive long-term improvements in the lives of young people with emerging mental disorders.

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Youth mental health: risks and opportunities in the digital world

McGorry et al[1] present a call to action to redesign youth mental health care and conceptualize youth psychiatry as a distinct discipline. Their proposed framework for youth mental health care contains four key elements: a) a focus on prevention and early intervention, with youth mental health services embedded in primary care and community settings; b) services co-designed with young people to be accessible, engaging and destigmatizing; c) blending the benefits of digital technology, to provide accessibility and scale, with human online and face-to-face support to promote youth engagement; d) extending the age boundary of youth mental health provision to cover the period of extended brain maturation in the "new adolescence" and the peak risk period of onset of mental disorders up to age 25.

The urgency of this task is driven by a global youth mental health crisis, and the failure of traditional models of mental health care to meet this demand. In the UK, one in eight young people have a mental health disorder, and one in four young women aged 17 to 19 have significant depression or anxiety, with half of those having self-harmed[2]. Non-suicidal self-harm has nearly tripled over the past 10 years[3], while suicide rates per 100,000 adolescents have almost doubled[4]. Depression represents the leading cause of disability-adjusted life years lost in young people, resulting in a major societal and economic burden extending across the lifespan.

The peak period for the onset of depression is adolescence and young adulthood, and most adults with recurrent depression will have first experienced it before age 25[5]. However, the growing demand for youth mental health support and intervention far outstrips the capacity of traditional mental health services to respond. In the UK, only 30% of young people with clinically significant depression or anxiety receive any help or professional support, and up to 90% of youth with mental disorders in some low-income countries receive no mental health care[6].

The youth mental health crisis has coincided with the emergence over the last decade of a new "digital environment". Digital technology presents major opportunities to scale-up and transform youth mental health services, but also potential risks for youth mental health and well-being, which, if the mechanisms were better understood, could create targets for preventive psychiatry.

In this new digital environment, young people's communication primarily takes place online or via social media. Most (83%) of UK's 12 to 15-year-olds own a smartphone, with over two-fifths of girls and one-fifth of boys aged 14 using social media for three or more hours a day[7]. For many young people who are isolated and have mental health problems, social media can be an important source of health information, knowledge and social support. However, social media use has also been linked with depression, suicide and self-harm, particularly in girls and marginalized groups[7]. Potential mechanisms include social isolation, disturbed sleep, attentional distraction, cyberbullying, pressures to conform to idealized lifestyles and body images, and the influence of screen-media activity on brain maturation.

Nevertheless, not all young people are at risk of mental health problems with social media, and currently there is little understanding of what factors make some youth more vulnerable than others. Policy initiatives and potential preventive interventions are hampered by uncertainty regarding mechanisms and the direction of effects linking use of digital technology to risks for mental health disorder in young people. The COVID-19 pandemic and resulting "lockdown" has been associated with increased mental health problems and greater online activity in young people. While the need of youth to access trusted support online is greater than ever, social media platforms are not designed to meet mental health needs of young people.

Digital technologies have the potential to transform youth mental health services through improved access to evidence-based resources and interventions, and by automating parts of diagnostic, monitoring and treatment pathways. They can connect young people with peers, mentors and therapists, potentially bridging the mental health treatment gap through novel, tailored, flexible and less stigmatizing treatments. However, this potential is still largely unrealized. Few digital interventions are included in routine care, and poor adherence is seen in those that are.

Industry-led innovations often lack a research evidence base and youth co-design (which is crucial to ensure that products fit with needs and lifestyles, and to tackle non-adherence). Numerous mental health and well-being apps exist, but most have no evidence base and some could even be harmful[8]. Meanwhile, academic-led evidence-based digital interventions are available, but few, if any, have shown sustained uptake and engagement in real-world settings. Effective, usable and accessible digital innovations could redress the imbalance of global health inequalities and ensure that evidence-based mental health interventions reach young people who need them most.

McGorry et al provide a number of examples of youth mental health services which have embraced digital technology and provide digital service platforms, such as headspace in Australia. Evidence for specific digitally-enabled, human-supported interventions is emerging, including MOST (moderated online social therapy)[9]. While youth mental health services and the associated digital interventions such as MOST were originally inspired by the aim to intervene early in the course of first-episode psychosis and other severe mental illness, the focus of these digital services has now broadened to include a wider range of youth psychopathology.

It is important to consider a number of limitations and unresolved questions facing the new systems of youth mental health care presented by McGorry et al. First, establishing these new services could result in diversion of resources away from other services for young people which fall outside their clinical remit or organizational boundaries. Second, it remains unclear how best to personalize the level of human support needed for young people who access digital mental health services, and how best to sign-post young people engaging with digital platforms to the most effective interventions. Third, a flexible, developmentally sensitive approach is needed to meet the changing psychological and social needs of youth from ages of 10 to 25. For example, younger adolescents engaging with digital interventions have been shown to benefit from parental engagement and support in their therapy, while, for older adolescents and young adults, peer-support may be of increasing relevance. Platforms and youth services need to reflect these developmental variations.

Fourth, to date, there has been little attention on interventions that focus on building young people's resilience to online harms such as cyberbullying. Youth mental health services need to address the specific challenges of the digital environment for young people with different mental health vulnerabilities, including depression, risk for self-harm, eating disorders and attention-deficit/hyperactivity disorder. As well as designing a wider digital environment that supports young people's mental health, we need services to acknowledge that youth with mental health problems may engage with the online world differently, and that they need help to develop the skills and competencies to build resilience and maximize the benefits of the digital world for their mental health and well-being.

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Peer involvement and accessibility as key ingredients for 21st century youth mental health care services

McGorry et al[1] emphasize the urgency and need to invest in (primary) mental health care services for young people. They have been an example in successfully leading the international youth mental health reform movement for many years, and managed to put youth mental health on the agenda of several policy makers worldwide, including the World Economic Forum. Moreover, they have been pioneers of an inclusive and co-designing approach with regards to service development and dissemination of their research.

The urgency of their plea has become even clearer since the COVID-19 pandemic has entered our lives. The ongoing crisis caused by the pandemic poses the greatest threat to mental health since the Second World War[2] and painfully shows that our already overstretched (mental) health care system has little flexibility and reserve capacity for unforeseen circumstances. Young people have particularly suffered from this, as demonstrated by the increasing rates not only of loneliness, suicidality and referral to specialist services, but also of drop-out from education, with possible long-lasting consequences.

Crisis situations, however, may also stimulate creativity, resulting in innovative initiatives. During this pandemic, the already ongoing digitalization of our society has overcome its last persistent hurdles, with results that have indeed been promising[3]. This offers opportunities for implementation of mHealth interventions that are transdiagnostic and empowering, probably particularly suitable for the next generation of help-seeking (emerging) adults[4], as they completely grew up in a digitalized world.

Increasing the accessibility of services, whether digital or face-to-face, is one of the crucial aspects of improving mental health care in young people. Despite great efforts and initiatives over the last decade, it remains challenging to reach young people, particularly those at risk for or with (emerging) mental disorders. This is partially due to the way traditional services have been operating, as McGorry et al[1] point out.

Several barriers are experienced by young people when in search for help for mental health problems, including (self-)stigma, worries about finances, shame, limited mental health literacy, waiting lists, and not knowing where to go or who to turn to[5].

More awareness and promotion of good mental health is essential[6]. For example, there is a need for education on mental health in collaboration with schools[7], something that has been largely ignored. Teaching on physical health is a normal part of our educational system, but this has not been the case for mental health.

Negative attitudes lead to late recognition and acceptance of mental health problems among those affected, resulting in seeking help only when these problems begin to escalate[5]. The period between the occurrence of first symptoms and related suffering until first contact with services can take up to several years. However, the first contact with health care services of a young person with mental health problems is often formally registered as the starting point of his/her journey. Mental health care professionals may thereby not always realize what journey an individual has already travelled at that point, and the amount of courage needed to step into the clinic for that first clinical assessment. Perhaps because of our focus on a medical approach of diagnosis and treatment, we may have given too little attention to the steps a young person has to make prior to reaching professional services.

To enhance early intervention, improving the accessibility of services for young people should be even higher on the agenda than it already is. McGorry et al[1] mention co-design, peer involvement and soft entry as key elements for youth mental health services, and peer support as a valuable innovation. However, peer or youth volunteer support is mainly proposed as an alternative to professional care in low-income settings or described as a strategy to cope with the shortage of mental health care professionals in general. We would like to emphasize the value of peer support and youth volunteers on their own, not only as a cheap alternative but as a crucial ingredient for lowering the threshold to seek help and facilitate disclosure of difficult topics, including suicidality and sexual abuse. Peer support results in improvements on both quantitative and qualitative measures of recovery[8], and peers represent an essential source of support for young people with mental health problems. Of course, there are some critical conditions for optimal implementation of peer support, including a clear role description of peer workers and non-peer staff, and sufficient training and supervision[8].

When implemented well, peer support is one of the most promising elements that can increase the accessibility of youth mental health services. As McGorry et al[1] point out, easy accessibility will not only attract young people with emerging mental disorders, but also young people with severe or chronic mental health problems not yet receiving appropriate help. To be able to serve young people in all stages of mental ill-health, well-organized and professionally supervised peer support should be thoroughly aligned with a broad spectrum of mental health care services.

As it may not be feasible to have this entire spectrum of services available at every youth walk-in centre, and possibly not desirable in terms of creating soft entry, we would rather speak of “first-stop” than “one-stop” shops. Deciding what services should be available on site, and who should be collaborative partners, is best done at a regional level, after close consideration of local available services and needs of young people in that specific area.

More research – qualitative as well as quantitative – into the value of peer support for accessibility and effectiveness of youth mental health services is needed. Moreover, increasing awareness amongst professionals and a change of (working) attitudes is necessary. Thus, not only the system has to change, but also our attitudes as people working in the system. In order to do this, we do need input from young people themselves, to help us make the necessary changes and see things we did not see before.

Finally, cross-domain, multidisciplinary approaches in designing integrated easy-access youth mental health services should be embraced, involving available social and educational resources. Mental health problems in young people often coexist with problems in other domains[9]. This requires collaboration with and learning from other professionals.

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Bridging between youth psychiatry and child and adolescent psychiatry

Most adults who develop a psychiatric disorder already met criteria for a diagnosis in childhood or adolescent years[1]. In addition, an early onset of psychiatric disorders is associated with greater chronicity and complexity of later psychopathology[1]. These epidemiological findings are transforming the way we study and tackle psychiatric disorders. Research and clinical practice are increasingly moving away from models prioritizing fully established, late-stage disorders to instead address their risk factors and early manifestations. Investment in prevention and early intervention for psychiatric disorders in childhood and adolescent years may achieve the greatest returns by reducing distress and impairment at key developmental stages, promoting well-being and productivity over the life course – similarly to what has been proposed for education[2]. This cultural shift has promoted renewed interest in child and adolescent psychiatry and in youth psychiatry (aka early intervention psychiatry).

The disciplines of child and adolescent psychiatry and youth psychiatry have emerged from different traditions, which are in many ways complementary and could be helpfully integrated. In particular, youth psychiatry originated from work in psychosis. Inspired by the neurodevelopmental model of psychosis, youth psychiatry has challenged the traditional system of care, focused on adult patients with chronic conditions. Instead, it has championed a novel system, focused on preventing or mitigating the onset of psychosis in adolescents and young adults through early intervention. Building on the success of the early intervention psychosis services, youth psychiatry now seeks to apply this model to address common mental disorders, including anxiety and depression[3]. The current attempts to apply the early intervention psychosis model to common mental disorders highlight both opportunities and challenges in supporting young people's mental health.

A central feature of youth psychiatry is the focus on "the transitional developmental stage from puberty to independent adulthood, which extends approximately from 12 to 25 years"[3]. This focus is justified by the early onset of psychopathology. It is also justified by the need to smooth the often-problematic transition of affected young people from child and adolescent mental health services (CAMHS) to adult services, typically set at 18 years. This age cut-off for service provision is in part related to differences in existing legal frameworks, commissioning arrangements, and educational pathways for the work with young people aged below or above 18 years. However, the cut-off produces a major bottleneck for service delivery, right at the time when young people face key personal transitions into higher education and/or employment. Some young people disengage from adult services because these are not developmentally appropriate. Other young people are not accepted by adult services because these prioritize patients who have already accumulated significant impairment.

The relaxation of the upper age cut-off championed by youth psychiatry offers a potential solution. In fact, many CAMHS have been attempting to implement this solution and increase their upper age limit beyond the 18-year cut-off, with varied results. In addition to the inertia of legal frameworks and commissioning arrangements, an important challenge to implementation has been the need to build up adequate clinical competencies, to prepare the workforce to respond to the wide range of developmental needs from childhood to young adult life. Indeed, the focus on youth psychiatry should not lead to overlook the importance of the care provided to younger, pre-pubertal populations, which is essential to ensure that prevalent psychiatric disorders with very early onset (e.g., anxiety disorders, behavioural problems) are treated timely, and that preventive interventions can effectively target early risk factors for later psychopathology[4,5].

Another important feature of youth psychiatry is its increasing focus on transdiagnostic psychopathology. This transdiagnostic focus has emerged from the epidemiological evidence that psychopathology repeatedly shifts among different successive disorders over the life course[1]. The clinical implications of this evidence are that over-reliance on diagnosis-specific clinical protocols is unhelpful[1] and that service provision should be restructured around other criteria, for example clinical staging[3].

Transdiagnostic models are also increasingly popular in child and adolescent psychiatry, for example to understand and address the consequences of childhood trauma[5]. Nevertheless, the implementation of these models presents important theoretical and practical challenges. Staging models are well established for psychosis and are increasingly emerging for bipolar, depressive and anxiety disorders[4]. However, staging models for truly cross-cutting, transdiagnostic constructs are still underdeveloped. In addition, development and empirical testing of transdiagnostic interventions are also in their infancy[6]. Establishing the validity and utility of these alternative models of psychopathology, therefore, requires further investigation prior to their widespread clinical implementation[7].

A third key feature of youth psychiatry is its focus on improving access to services. Youth psychiatry has promoted a "soft-entry" approach. Young people can self-refer to services, without the requirement for severity or impairment criteria, and access non-specialist, often peer-led support for mental health or psychosocial concerns. This approach has greatly benefited from co-design with young people, a positive-psychology ethos focused on strength building, and the development of technological/digital solutions. These services are less stigmatizing and more engaging for young people and have gained popularity worldwide[3], including in the UK (e.g., the Fund the Hubs campaign supported by the leading mental health charities Mind and YoungMinds). By removing barriers to care access and working with the voluntary sector, youth psychiatry has championed new ways to address the vast demand for youth mental health support.

However, the implementation of this "soft-entry" approach presents important challenges. To begin with, one must consider the present financial landscape. The grossly inadequate funding for CAMHS has been straining the ability to meet the raising demands from young people and their families, often limiting the focus of clinical work to only the most severe and risky cases. While the focus on prevention and early intervention in primary care can have a positive impact on the many young people with sub-threshold mental health problems[4], it is important to ensure that a "soft-entry" approach can work along with, and not in competition with, CAMHS, to avoid further reduction in the treatment opportunities for young people with established psychiatric disorders. Furthermore, the implementation of a "soft-entry" approach will require a more in-depth evaluation of its safety, effectiveness and cost-effectiveness, in the same way novel interventions have been evaluated in CAMHS[3,4].

In sum, there is much to gain from greater collaboration between child and adolescent psychiatry and youth psychiatry. The enthusiasm of early intervention services and the experience of CAMHS could drive a significant evolution in the mental health care provided to young people.

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Youth mental health care in a context of large-scale collective stress

The accelerating pace of technological and societal changes continues to impose unprecedented levels of challenges to mankind, and young people often bear the foremost impact. As well described by McGorry et al[1], globalization, climate change and technology are suggested to have incurred detectable burdens on youth mental health, and the COVID-19 pandemic has significantly added to this.

Among the different societies undergoing such challenges, Hong Kong represents a notable example where the COVID-19 pandemic coincided with social tensions, protests and unrest. The cumulative effects of these population-level stressors is only beginning to be recognized[2,3]. Symptoms of post-traumatic stress disorder (PTSD), depression and anxiety interact over time in complex manners, with the continuous unfolding of population-level distressing events aggravating outcomes. Available data suggest that the mental health of young people is being disproportionately affected[3].

In the wake of unforeseen population events, timely mental health initiatives are often unavailable. During the initial stages of an unexpected situation, interventions and research often struggle to re-orientate from their ongoing endeavours to attend to the new scenario, especially when the latter is unprecedented. There is also a "wait and see" mindset along with a hopeful anticipation that the stressor would be time-limited. As events evolve, the sense of fear and lack of trust can become another major impediment to early engagement and help-seeking.

In Hong Kong, the situation necessitated the rapid launching of simple yet engaging mental health self-help tools. A youth-friendly, locally-adapted and personalized tool was thus developed (Flow Tool, https://www.psychiatry.hku.hk/flow.html), in both Cantonese and English[2]. In-depth feedback from local young people during its development period ensured that the language and style of the tool could offer a "safe space" for feelings to be articulated. Meanwhile, discussions with clinical and research teams secured its capacity to capture sufficient information for offering individualized advice. Upon completion of the tool, areas of self-help were given to those with lower distress levels, and pathways to professional help-seeking (both online and in-person) were suggested for those with higher symptom levels. To minimize concerns about data privacy (which were particularly pronounced during crisis situations and among young people), the tool was anonymous.

Since its launch, over 70,000 responses have been gathered. Youth-friendliness, respect for confidentiality, and freedom of choice were considered to be crucial elements in successfully engaging young people who may not seek help otherwise. Data from the tool revealed high levels of depressive and PTSD symptoms as a result of the cumulative effects of COVID-19 pandemic, social unrest, and individual stressful life events[3]. Rumination about external events was identified as an important mediator between stress events and distress[3].

In the wake of intense ongoing population-level stress, interpreting heightened mental distress as an increase in "mental disorder" prevalence requires caution. The language of "symptom networks" as "reactions" to external "stressors"[4], with the possibility of transitions not only into "disorders", but also "post-traumatic growth"[5], may provide a more positive framework to support young people in distress. Particularly in a life stage of growing uncertainties and need for security, using a language which emphasizes not only intrinsic vulnerabilities but also the role of extrinsic factors, as well as the potential of the young person to regain control, can be important in instilling senses of agency and hope.

A safe physical space is particularly important during periods of uncertainty. In a city where space is difficult to come by, a new project where community "hubs" were designed for, and with, young people with mental distress was launched (*LevelMind*, https://www.levelmind.hk)[6]. As access to hubs was impeded by waves of COVID-19 pandemic, it became clear that additional online interventional services with high accessibility were needed. A free, anonymous online psychiatrist advisory service has since been launched (*headwind*, https://www.youthmentalhealth.hku.hk) and regularly serves over 100 individuals (mostly young people) every month to date.

To ensure that these initiatives are serving their intended purposes, timely evaluation is needed. Yet, the unforeseeable developments of population-level stress pose new challenges to the process of evaluation, where a significantly reduced turn-around time is demanded. In the context of limited time and resources, reverting to the simple measures of "pre" and "post" effects may be tempting. This should, however, be treated with caution, as the rapid evolution of societal stressors is expected to trigger significant fluctuations in distress and symptoms in the population, which may mask the effects of interventions. The use of appropriate comparison groups would be particularly important for controlling for background fluctuations. The skillful use of online tools (both self-administered and interview-based), combined with more adaptive evaluation designs (e.g., judicious use of planned interim analyses, multi-arm/multi-stage design, adaptive randomization)[7] are allowing more efficient evaluations.

Looking back, the series of recent events may have disrupted roadmaps and imposed new demands in this rapidly changing youth mental health landscape. Nonetheless, effective and sustainable work for young people could be made possible with quick and careful adaptations. Youth mental health training should not be overlooked, as multi-disciplinary work involving youth workers, psychologists and psychiatrists, as well as the voices of young people themselves, are keys to success. Robust future-adaptability is crucial in the shaping of an apt youth mental health platform.

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Youth mental health services: the right time for a global reach

Young people have been regarded as a predominantly healthy population group, possibly because of the relatively low prevalence of physical illnesses in this age range. This, however, is in stark contrast with the evidence concerning mental health problems: at no other time point in the lifespan do mental disorders constitute a larger share of disease-related burden than in the second and third decades. In fact, the early incidence and non-negligible persistence of these conditions have led experts to describe mental illnesses as "chronic diseases of the young"[1].

Despite the epidemiological evidence of early onset, mental disorders are typically detected only at later stages in life. To some extent, this delay is being addressed in recent years through innovative systems of youth mental health care. This set of services and strategies recognizes the needs and opportunities for prevention and clinical care from a developmentally informed perspective. As elegantly reviewed by McGorry et al[2], the case for *when* to act has been largely addressed in the literature: there are unequivocal benefits of investing in early intervention.

Equally relevant is the question of *where* action is most urgently required. Youths comprise up to one quarter of the world's population, but the geographical distribution of adolescents and emerging adults is not uniform across the globe. The vast majority of young people live in low- and middle-income countries (LMICs), where they constitute larger proportions of the population in comparison to high-income countries (HICs). In fact, even if we were able to eradicate 100% of mental disorders among 10 to 24 year-olds from HICs, this would translate into a decrease of only 15% in the overall global burden of mental disorders in this age range[3].

There is also the matter of *how*. Beyond the recognizedly similar needs of youth across the globe, there is an urgent call to enable tailored systems of care for youth mental health, which should move beyond a one-size-fits-all approach to more culturally and locally appropriated services. As a case in point, we here discuss challenges and potential opportunities of putting these strategies into practice in Brazil, a middle-income country that is home to more than 50 million youths.

Over the past three decades, Brazil has implemented one of the largest universal health care systems in the world. The publicly funded *Sistema Único de Saúde* (SUS) upscaled service coverage throughout the country, with an emphasis on the expansion of primary care. Despite remaining challenges in terms of disparities and coverage, tremendous progress has been achieved in improving the overall health of the Brazilian population[4].

As a consequence of multiple actions focusing on early childhood, Brazil surpassed the global targets of infant and child mortality reduction, being among the small number of nations to meet Millennium Development Goal 4. Importantly, this has been achieved while decreasing the inequalities among regions in the country. However, a similar advance in regard to the mental health of young people has not been achieved.

Evidence suggests that adolescents in Brazil do not frequently recognize primary care as a source of support for mental health problems, but rather rely on their own or on peer support[5]. Since physical health does not usually constitute a reason to have a regular relationship with primary care for the vast majority of young people, services are not typically designed or prepared to engage this age group. The majority of low-intensity primary care settings lack the resources required to address the developmental needs of young people, focusing mostly on younger children or older individuals. This represents an important challenge in terms of translating high-quality evidence-based models from HICs into real-world practice in LMIC environments.

For individuals with more severe clinical presentations, the SUS has implemented community-based centres (CAPS) for psychiatric treatment and psychosocial support/rehabilitation[6]. Distinct CAPS formats are still organized following a paediatric vs. adult model: paediatric services predominantly address the needs of younger children, while adult services focus on adult needs, without recognition of adolescence and emerging adulthood as relevant developmental periods and usually not addressing the domain of early intervention.

This in fact reflects a further challenge: a difficulty of the public health care system to recognize and articulate the continuum of need – from non-clinical, community- and school-based up to specialist services. Especially for the low-intensity end of the spectrum, youth-focused provision of mental health care could be integrated into youth-centered initiatives, such as education and welfare programs.

An additional gain of focusing on youth mental health and mental well-being would be the opportunity to ignite a much needed debate about mental health in the broader community, displaying the importance of this issue beyond the fields of psychiatry and psychology, with the active engagement of youths, families and the wider society. Action should therefore include not only the implementation of developmentally appropriate youth services, but integration with other stakeholders to deal with challenges such as recent actions from the federal government to inhibit discussions on diversity, gender identity, as well as sexual and reproductive health in educational and health care settings.

Across government and society (involving for example the educational system and non-governmental organizations), advocacy is essential to raise awareness, while structural measures provide material support for change — one noteworthy example being wide-scale antipoverty actions such as *Bolsa Familia*, which has operated for several years in Brazil. This conditional cash transfer program has been associated with intersectoral improvements such as increased access to food, education and primary health care, as well as reduction in child mortality and lower suicide rates[7]. Recent cash-transfer strategies implemented in the context of the COVID-19 crisis may also mitigate the negative impacts of the pandemic, as the proportion of young people not engaged in education, employment or training has been increasing in Brazil over recent years and peaked in late 2020, reaching more than one quarter of this age group[8].

It is somewhat paradoxical that, although the majority of innovative experiences to protect and promote the mental health of young people have been implemented in HICs, the largest contingent of youths live in LMICs. The creation of the SUS in Brazil paved the way for many observable achievements in a relatively short period, attesting that change in such contexts is indeed possible. Furthermore, youth leadership has played a pivotal role in building resilience in disprivileged communities during times of crisis[9].

Now is the time to acknowledge the importance of mental health needs at the point at life in which they are disproportionately burdensome, and to take advantage of many existing initiatives that can support the establishment of local youth support. With the largest cohort of young people in its history, Brazil – as many other LMICs – now faces its biggest window of opportunity to reduce the negative impacts of mental ill-health and promote the mental wealth of the next generations.

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Effectiveness of a WHO self-help psychological intervention for preventing mental disorders among Syrian refugees in Turkey: a randomized controlled trial

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Refugees are at high risk of developing mental disorders. There is no evidence from randomized controlled trials (RCTs) that psychological interventions can prevent the onset of mental disorders in this group. We assessed the effectiveness of a self-help psychological intervention developed by the World Health Organization, called Self-Help Plus, in preventing the development of mental disorders among Syrian refugees experiencing psychological distress in Turkey. A two-arm, assessor-masked RCT was conducted in two Turkish areas. Eligible participants were adult Syrian refugees experiencing psychological distress (General Health Questionnaire ≥3), but without a diagnosis of mental disorder. They were randomly assigned either to the Self-Help Plus arm (consisting of Self-Help Plus combined with Enhanced Care as Usual, ECAU) or to ECAU only in a 1:1 ratio. Self-Help Plus was delivered in a group format by two facilitators over five sessions. The primary outcome measure was the presence of any mental disorder assessed by the Mini International Neuropsychiatric Interview at six-month follow-up. Secondary outcome measures were the presence of mental disorders at post-intervention, and psychological distress, symptoms of post-traumatic stress disorder and depression, personally identified psychological outcomes, functional impairment, subjective well-being, and quality of life at post-intervention and six-month follow-up. Between October 1, 2018 and November 30, 2019, 1,186 refugees were assessed for inclusion. Five hundred forty-four people were ineligible, and 642 participants were enrolled and randomly assigned to either Self-Help Plus (N=322) or ECAU (N=320). Self-Help Plus participants were significantly less likely to have any mental disorders at six-month follow-up compared to the ECAU group (21.69% vs. 40.73%; Cramer's V=0.205, p<0.001, risk ratio: 0.533, 95% CI: 0.408-0.696). Analysis of secondary outcomes suggested that Self-Help Plus was not effective immediately post-intervention, but was associated with beneficial effects at six-month follow-up in terms of symptoms of depression, personally identified psychological outcomes, and quality of life. This is the first prevention RCT ever conducted among refugees experiencing psychological distress but without a mental disorder. Self-Help Plus was found to be an effective strategy for preventing the onset of mental disorders. Based on these findings, this low-intensity self-help psychological intervention could be scaled up as a public health strategy to prevent mental disorders in refugee populations exposed to ongoing adversities.

Key words: Refugees, prevention, common mental disorders, Self-Help Plus, psychological intervention, public health strategy, randomized controlled trial

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In 2020, the number of forcibly displaced people in the world, 80 million, was the highest since World War II[1]. Among them, 26 million fled their countries due to violence or persecution[1]. The largest group of refugees was from Syria, accounting for 6.6 million people. Around 3.6 million Syrian refugees are in Turkey, making Turkey the world's top refugee hosting country[1].

Many Syrian refugees have been exposed to potentially traumatic experiences such as bombings, threats, captivity, torture, injury, and witnessing death or injury of loved ones[2]. Moreover, they are at risk of discrimination, economic problems, and social isolation. In 2020, the COVID-19 pandemic exacerbated Syrian refugees' hardship in Turkey because of a sudden and severe deterioration in income generation opportunities and access to services and social supports[3].

Owing to potentially traumatic events, major losses and other stressors before, during and after migration, refugees are at high risk of developing common mental disorders[4]. The World Health Organization (WHO) estimates that the rates of depression, post-traumatic stress disorder (PTSD) and any mental disorder among people exposed to conflict in the previous 10 years are 10.8%, 15.3% and 22.1% respectively[5]. Evidence suggests that Syrian refugees are at high risk of developing these disorders[6].

A significant component of consensus-based humanitarian mental health policy and practice involves psychological interventions that aim to have preventive and health promotion effects[2]. However, evidence for such effects has been limited, and a recent Cochrane review did not identify any randomized studies assessing whether preventive psychological and social interventions can reduce the frequency of mental disorders in people affected by a humanitarian crisis[7].

In recent years, the WHO has developed a series of brief transdiagnostic psychological interventions, including Problem Management Plus[8] and Self-Help Plus[9], which have been tested for treatment of mental health problems among people affected by adversity[10-13]. However, they have never been evaluated as indicated preventive interventions – i.e., they have not been tested among people who are distressed, but who do not meet the criteria for any mental disorder, to see whether they can prevent the onset of mental disorders.

In the present study, we examined the effectiveness of Self-Help Plus as an indicated intervention to prevent the onset of mental disorders among distressed Syrian refugees in Turkey.

METHODS

Study design

The study was an assessor-masked, parallel-group randomized controlled trial (RCT). The trial protocol was published and registered at clinicaltrials.gov (NCT03587896)[14]. The study was approved by the WHO Ethics Review Committee and the Ethics Committees of Istanbul Sehir University and Koc University. Written informed consent was provided by all participants.

Participant recruitment occurred from October 1, 2018 to November 30, 2019 in Istanbul and Mardin, Turkey. Six-month follow-up assessments ended in June 2020.

Local non-governmental organizations (NGOs) implementing projects for refugees in Turkey were approached to identify potentially eligible participants. These NGOs provide integrated reception services that include food, housing; legal, educational, health care and social guidance and support; and programs to promote socioeconomic inclusion and integration. Participants were consecutively invited to participate by members of the research team, in agreement with local service staff, who facilitated contacts.

All research team members were Arabic-speaking. They were trained in conducting the interviews, administering the rating scales, and performing follow-up assessments, so that they were able to assist the persons in a culturally appropriate manner. Research team members followed a code of conduct, complying with the principles of neutrality, impartiality, confidentiality, demeanor, and avoiding activities that might lead to a conflict of interests. All research-related training activities were coordinated by the WHO Collaborating Centre of the University of Verona, Italy.

Randomization and masking

Participants were randomly assigned either to the Self-Help Plus arm (consisting of Self-Help Plus combined with Enhanced Care as Usual, ECAU) or to ECAU only, in a 1:1 ratio. Randomization was centralized and coordinated by the Verona WHO Collaborating Centre.

The randomization schedule was generated by Castor Electronic Data Capture (EDC) software[15], employing variable block randomization. Research team members involved in recruitment were able to access the web-based software to randomize each newly enrolled participant, but were not able to access the randomization list, and were not aware of the block size. Castor EDC software allowed random allocation only after the main information on the enrolled participant was entered, upon verification of the inclusion criteria. After random allocation, the software produced a unique identification number for each participant.

Both assessors evaluating outcomes and the statistician performing analyses were masked to participant allocation status. Outcome assessors were not involved in any activities that might reveal random allocation of study participants. A formal assessment of the success of masking was not conducted, as there is no methodological consensus on whether such tests are appropriate, reliable and truly informative[16].

Inclusion and exclusion criteria

Participants were included if they met the following criteria: a) aged 18 years or older; b) able to speak and understand Arabic; c) being under temporary protection according to Law on Foreigners and International Protection; d) experiencing psychological distress, as shown by a score of 3 or more on the 12-item General Health Questionnaire (GHQ-12)[17,18]; e) having completed oral and written informed consent to enter the study.

Exclusion criteria were: a) presence of any mental disorder according to the Mini International Neuropsychiatric Interview (MINI)[19,20]; b) evidence of acute medical conditions contraindicating study participation; c) evidence of imminent suicide risk, or suicide risk scored as “moderate or high” on the MINI; d) signs of impaired decision-making capacity emerging from responses during the clinical interview. Refugees who were excluded because of a diagnosis of a mental disorder and/or imminent suicide risk were referred for treatment to a health professional.

Experimental and control intervention

The Self-Help Plus intervention consists of a pre-recorded audio course, delivered by trained facilitators in a group setting and complemented with an illustrated self-help book adapted for the target cultural group. The intervention is based on acceptance and commitment therapy, a form of cognitive behavioural therapy. It is delivered across five 2-hour sessions. The audio material imparts key information about stress management and guides participants through individual exercises and small group discussions. The self-help book reviews all essential content and concepts.

In this study, a version of the intervention previously adapted for Syrian populations was used. The adaptation followed a WHO protocol and involved adapting the audio recordings to a colloquial form of Arabic widely understood in Syria, and culturally adapting the illustrations.

As Self-Help Plus is a pre-recorded intervention, fidelity checking primarily involved ensuring that all of the recordings were played and all activities (e.g., discussions, exercises) were completed. Fidelity forms were completed after each session by facilitators. Additionally, 20% of all sessions were checked using the same forms by external trained supervisors.

ECAU was provided to participants in both groups, and consisted of routinely delivered social support and/or care. Additionally, participants in the control arm received baseline and follow-up assessments according to the study schedule, information about freely available health and social services, and links to community networks providing support to refugees.

An independent Ethics Advisory Board, consisting of international experts giving advice on any relevant ethical issues, supervised the study.

Measures

The primary outcome was the presence of current mental disorders at six-month follow-up, ascertained by the MINI[19,20]. The MINI was also administered at baseline before randomization, and at post-intervention. All other assessment instruments measured secondary outcomes at post-intervention and at six-month follow-up.

Psychological distress was measured using the GHQ-12 questionnaire[17,18], in which items are rated on a four-point Likert scale, giving a maximum total score of 36. PTSD symptoms were assessed by the PTSD Checklist for DSM-5 (PCL-5)[21,22], a 20-item questionnaire giving a maximum total score of 80. Depression symptoms were measured by the Patient Health Questionnaire, nine-item version (PHQ-9)[23-25], which gives a maximum total score of 27. Personally identified psychological outcomes were examined using the Psychological Outcome Profiles (PSYCHLOPS)[26,27], which asks participants to describe two problems from their own perspective and rate their severity on a six-point scale (maximum score: 18).

Functional impairment and subjective well-being were assessed by the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)[28], and the WHO-5 Well-Being Index (WHO-5)[29,30], respectively. The WHO-5 contains five questions using a six-point scale (maximum score: 25). For evaluating general health, we administered the European Quality of Life 5-Dimensions 3-Level (EQ-5D-3L) questionnaire, a brief self-report measure consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression)[31-33].

Traumatic/adverse life events and environmental stressors were explored using the Harvard Trauma Questionnaire (HTQ)-Part A[34,35] and the 17-item Checklist for Post-Migration Living Difficulties (PMLD)[36]. HTQ-Part A asks for lifetime traumatic life events. The PMLD asks respondents to rate their experience of the problems during the last 12 months on a five-point scale (from "not a problem" to "a very serious problem").

Assessments were conducted as face-to-face interviews or remotely by telephone or secure online audio/video communication (for reasons of feasibility, including physical distancing requirements related to the COVID-19 pandemic). Adverse events reported spontaneously by the participants or observed by the research staff were recorded, reviewed by the Ethics Advisory Board in regular meetings, and reported to the WHO Ethics Review Committee.

Statistical analysis

We expected a frequency of mental disorders of 25% at six months in this population group[14]. We hypothesized that Self-Help Plus would show a clinically significant advantage by producing a between-groups absolute difference of 10%[14]. With these figures, to achieve at least 80% power for a 0.05 level of significance in a chi-square test, a sample size of 500 participants (250 per group) was needed. Assuming that a proportion of refugees might be lost at study endpoint (due to the specific characteristics of this population), a final sample size of 600 participants (300 per group) was planned.

Descriptive statistics were calculated on sociodemographic, pre-migration, migration and post-migration variables at baseline. Balance between treatment groups was checked calculating standardized mean differences (SMDs). SMD values of 0.1 and –0.1 were used as thresholds for imbalance[37].

We followed an intent-to-treat approach for analysis of primary and secondary outcomes. The intent-to-treat population consisted of all randomized participants who completed baseline assessment, irrespective of the number of Self-Help Plus sessions received. To check the robustness of results, the primary outcome was also analyzed using a per-protocol approach, including only participants who completed at least three Self-Help Plus sessions.

The primary outcome was compared between the two groups using Cramer's V, together with a risk ratio (RR) and its 95% confidence interval (95% CI). A multivariate secondary analysis was performed through a Poisson regression model, with a robust error variance, to estimate RRs directly, and to explore the potential confounding effect of prognostic factors controlling for variables showing imbalance at baseline.

For each secondary outcome, a mixed analysis of covariance (ANCOVA) controlling for baseline scores, with robust standard errors and distinct variances for post-intervention and six-month follow-up, was performed. In addition to mixed models, a last observation carried forward (LOCF) approach was also used to account for missing observations at six months. Standardized coefficients were estimated with the Stata "stdBeta" command.

For each questionnaire, in case of missing items, we used the corrected item mean substitution method (i.e., the item mean across participants weighted by the subject's mean of completed items)[38], using information from subjects belonging to the same treatment arm for the same follow-up time, through the Stata "hotvalue" command. The substitution was only performed if resulting in admissible values, and only for observations having less than 50% of missing items. As a sensitivity analysis, we re-ran our models without any data imputation.

The hypothesis that the experimental intervention had no effect on GHQ-12, PCL-5, PHQ-9, PSYCHLOPS, WHODAS 2.0, WHO-5 and EQ-5D-3L scores was tested by performing seemingly unrelated regression (SUR)[39], in its modification to allow for unbalanced data through the Stata "suregub" command. SUR was performed for each time point, controlling for baseline values.

Possible interactions between treatment and specific variables (gender, age, years of education, length of stay in the hosting country) were evaluated. In particular, in the case of continuous outcomes, SUR for unbalanced data on all outcomes was performed, with their value at baseline, treatment status, all potential moderators, and their interactions with treatment status as predictors. A global test on all interaction terms was implemented and, in case of significance, the same test was performed for each scale. Finally, for scales meeting the statistical significance threshold, single regressions were conducted.

As for binary outcomes, to avoid the issue of poor performance of the model in case of solutions near the boundary[40], Poisson regression models were performed with robust standard errors, setting as regressors the variable "intervention allocation", each variable separately, and their interaction with treatment. The Bonferroni correction was used to take into account multiple testing.

Multivariate analyses were performed for each secondary outcome to take confounding factors into account, again including the baseline value as a covariate. Finally, lost-to-follow-up was compared between the two groups using a chi-square or a Fisher exact test, as appropriate. All analyses were performed using Stata/SE, Release 15.1[41].

RESULTS

After screening 1,186 potentially eligible participants, 544 were excluded. A total of 123 were excluded because their level of distress was below the established cut-off, 282 because of a positive MINI, and 139 for other reasons (e.g., mental health was not a priority for them or they were not available to receive the intervention) (see Figure 1). This left 642 individuals who met the inclusion criteria, consented to be randomized, and were randomly allocated to either Self-Help Plus (N=322) or ECAU (N=320).

At six-month follow-up (primary outcome), we could not assess 95 individuals (14.8%). They were lost to follow-up because they refused to participate (N=46) or because they were not reachable and/or moved to other locations (N=49). The distribution of participants lost to follow-up was similar between the study groups (15.53% vs. 14.06%, Cramer's V=0.021, p=0.601; RR=1.104, 95% CI: 0.761-1.602).

The main sociodemographic characteristics of the included participants are shown in Table 1. Their mean age was 31.5±9.0 years; 62.9% of them were women. For 61.8% of them, primary school was the highest level of education, while 14.5% received academic education. Almost all participants came from Syria (628 of 642, 97.8%). The remaining 14 participants came from Iraq (N=11), Yemen (N=1), or occupied Palestinian territory (N=1). One additional participant did not consent to reveal this information. The mean age at departure was 27.1±10.1 years. A minority of participants (5.2%) experienced detention during their transition to Turkey.

Assessment of 20% of Self-Help Plus sessions showed that all the components of the intervention were delivered in line with

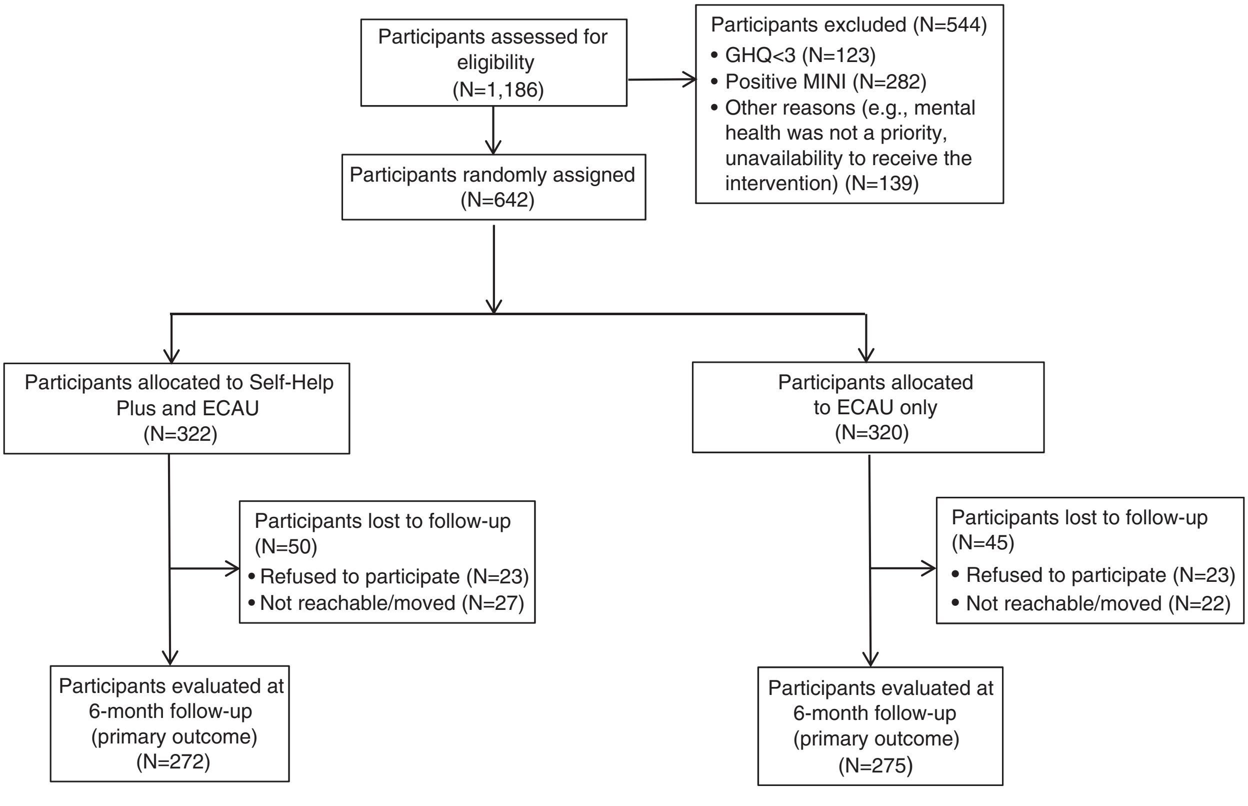

Figure 1 CONSORT flow diagram. ECAU – Enhanced Care As Usual, GHQ – General Health Questionnaire, MINI – Mini International Neuropsychiatric Interview

Table 1 Sociodemographic characteristics of Syrian refugees randomly allocated to the Self-Help Plus (SH+) and the Enhanced Care As Usual (ECAU) groups

	SH+	ECAU	Difference (standard error)	SMD
Age (years, mean±SD)	31.22±8.89	31.73±9.16	–0.508 (0.712)	–0.040
Gender (% females)	63.98	61.88	0.021 (0.038)	0.031
Education (years, mean±SD)	8.94±3.72	9.12±3.73	–0.173 (0.300)	–0.033
Type of education (%)				
Illiterate	5.28	2.50	0.028 (0.015)	0.102
Primary school	62.73	60.94	0.018 (0.038)	0.026
High school	16.46	20.00	–0.035 (0.030)	–0.065
University	14.60	14.38	0.002 (0.028)	0.004
Not reported	0.93	2.19	–0.013 (0.010)	–0.072
N. relatives (mean±SD)	5.04±3.71	4.87±2.27	0.168 (0.250)	0.039
N. children (mean±SD)	2.73±1.89	2.73±1.92	0.002 (0.157)	0.001
Age at departure (years, mean±SD)	26.91±11.13	27.20±8.96	–0.295 (0.804)	–0.021
Detention during transition (%)	5.00	5.38	–0.004 (0.018)	–0.012
Months of detention (mean±SD)	10.89±23.00	8.27±19.33	2.620 (9.051)	0.087
Total HTQ score (mean±SD)	4.35±4.00	4.12±3.56	0.229 (0.299)	0.043

SMD – standardized mean difference, HTQ – Harvard Trauma Questionnaire

the manual. No adverse events related to the study participation were reported. In addition to Self-Help Plus sessions or ECAU, participants received minimal health care during the study period, which did not differ between the two groups (see supplementary information).

Differences between study conditions on primary and secondary outcome measures are reported in Table 2. Analysis of the primary outcome revealed that Self-Help Plus arm participants were significantly less likely to meet criteria for a mental disorder at six-month follow-up (59/272, 21.69%) compared to ECAU participants (112/275, 40.73%) (Cramer's V=0.205, p<0.001, RR=0.533, 95% CI: 0.408-0.696). The mental disorders at follow-up were major depressive disorder (51/272 participants in the Self-Help Plus group and 94/275 participants in the ECAU group), PTSD (16/272 vs. 35/275), anxiety disorders (10/272 vs. 20/275), obsessive-compulsive disorder (three participants in the Self-Help Plus group) and bipolar disorder with psychotic features (one participant in the ECAU group). By contrast, at post-intervention, the frequency of any mental disorders was similar in the two groups (p=0.784) (see Table 2).

Compared with ECAU, Self-Help Plus was also associated with improvements at six-months for the secondary outcomes of depression symptoms (p<0.001), personally identified psychological outcomes (p=0.036), and quality of life (p=0.001). Psychological distress as measured with the GHQ-12 showed a significant improvement in favor of the Self-Help Plus group at post-intervention only (p=0.028) (Table 2). These results were confirmed by global statistical significance of the intervention on all secondary outcomes by performing SUR (p=0.005 at post-intervention, p<0.001 at 6 months).

The intent-to-treat analysis results were confirmed by the per-protocol analysis. Self-Help Plus arm participants were significantly less likely to meet criteria for a mental disorder at six-month follow-up (47/218, 21.56%) compared to ECAU participants (112/275, 40.73%) (Cramer's V=0.204, p<0.001, RR=0.529, 95% CI: 0.396-0.708) (see supplementary information for other results).

Results of secondary analyses of continuous outcomes conducted without any imputations of missing values were comparable to those of our main analyses. Secondary analyses accounting for baseline imbalance between groups did not identify relevant differences with respect to our main analyses on either primary or secondary outcomes (see supplementary information).

We investigated possible heterogeneity of the effect of treatment on outcomes by testing for interactions between intervention allocation and potential moderators. None of the interactions reached the statistical significance threshold for binary outcomes after applying the Bonferroni correction. By performing SUR on post-intervention secondary outcomes, a global test on all interactions of the variable "intervention allocation", with center and the potential moderators on all regressions, was not significant (p=0.292). Similarly, none of the interactions for continuous outcomes reached the significance threshold at 6 months (p>0.05 in all cases).

DISCUSSION

To the best of our knowledge, this is the first prevention RCT conducted among refugees experiencing psychological distress but without a mental disorder[7]. We found that the likelihood of

Table 2 Summary statistics of results for primary and secondary outcomes at each time point

Frequency of mental disorders	**SH+**	**ECAU**	**Cramer's V**	**p**	**RR (95% CI)**
Baseline	0/322 (0%)	0/320 (0%)			
Post-intervention	30/237 (12.66%)	36/267 (13.48%)	0.012	0.784	0.939 (0.598-1.475)
6 months (primary outcome)	59/272 (21.69%)	112/275 (40.73%)	0.205	<0.001	0.533 (0.408-0.696)
Secondary outcomes			**Coefficient**	**p**	**Standardized coefficient (SE)**
GHQ-12 score (0-36), mean±SD					
Baseline (N=642)	17.363±4.519	16.776±4.299			
Post-intervention (N=503)	12.657±4.947	13.491±5.101	–0.974	0.028	–0.096 (0.044)
Six months LOCF (N=574)	13.269±4.825	13.768±4.548	–0.578	0.139	–0.062 (0.042)
PCL-5 score (0-80), mean±SD					
Baseline (N=640)	20.724±14.904	20.138±14.278			
Post-intervention (N=504)	16.824±12.831	14.814±14.597	1.754	0.134	0.063 (0.042)
Six months LOCF (N=574)	13.991±11.454	15.085±12.855	–1.278	0.195	–0.052 (0.040)
PHQ-9 score (0-27), mean±SD					
Baseline (N=642)	6.449±4.696	6.299±4.725			
Post-intervention (N=503)	5.241±4.905	5.324±5.124	–0.196	0.648	–0.020 (0.043)
Six months LOCF (N=574)	4.928±5.048	6.694±5.455	–1.842	<0.001	–0.173 (0.040)
WHO-5 (0-100), mean±SD					
Baseline (N=642)	42.458±24.418	43.591±23.766			
Post-intervention (N=504)	50.903±24.599	48.494±23.520	2.743	0.196	0.057 (0.044)
Six months LOCF (N=574)	52.143±21.709	49.320±22.670	3.154	0.085	0.071 (0.041)
WHODAS 2.0 (12-60), mean±SD					
Baseline (N=638)	18.418±7.282	17.924±7.089			
Post-intervention (N=501)	15.380±4.705	15.561±6.477	–0.205	0.665	–0.018 (0.041)
Six months LOCF (N=570)	14.804±4.787	14.269±4.261	0.488	0.190	0.054 (0.041)
PSYCHLOPS score (0-20), mean±SD					
Baseline (N=488)	9.422±5.592	8.911±5.269			
Post-intervention (N=388)	6.230±5.727	6.890±5.640	–1.071	0.104	–0.091 (0.056)
Six months LOCF (N=543)	4.852±5.375	6.168±6.499	–1.215	0.036	–0.100 (0.047)
PMLD score (0-68), mean±SD					
Baseline (not measured)	-	-	-	-	-
Post-intervention (N=501)	16.569±11.022	18.864±12.689			
Six months (N=524)	13.422±10.451	12.322±11.536	1.824	0.075	0.080 (0.045)
EQ-5D-3L score, mean±SD					
Baseline (N=627)	0.718±0.275	0.720±0.282			
Post-intervention (not measured)	-	-	-	-	-
Six months (N=513)	0.857±0.218	0.799±0.250	0.067	0.001	0.147 (0.044)

SH+ – Self-Help Plus, ECAU – Enhanced Care As Usual, RR – risk ratio, SE – standard error, LOCF – last observation carried forward, GHQ-12 – General Health Questionnaire, 12-item version, PCL-5 – PTSD Checklist for DSM-5, PHQ-9 – Patient Health Questionnaire, 9-item version, WHO-5 – WHO-5 Well-Being Index, WHODAS 2.0 – WHO Disability Assessment Schedule 2.0, PSYCHLOPS – Psychological Outcome Profiles, PMLD – Checklist for Post-Migration Living Difficulties, EQ-5D-3L – European Quality of Life 5-Dimensions 3-Level

having a mental disorder at six-month follow-up was approximately half for Self-Help Plus vs. ECAU participants, and that such risk reduction appeared to be consistent across the most common diagnoses, i.e. depression, PTSD and anxiety disorders. Consistent with this, Self-Help Plus participants also showed improvements in depression symptoms, personally identified psychological outcomes, and quality of life at six-month follow-up. We did not detect significant differences between the Self-Help

Plus and control groups on any outcome measure immediately post-intervention, with the exception of psychological distress.

Four out of ten participants in the control group developed a mental disorder. This very high frequency may be explained by events occurring during the study. First, before completion of six-month assessments, in October-November 2019, Operation Peace Spring was launched in northern Syria at the border with Mardin, a Turkish area where most study participants lived. The aim was to create a safe zone where Syrian refugees could be resettled[42]. However, this event caused fears of deportation, and this stressor may have increased the risk for mental disorders. Second, many six-month follow-up assessments were completed during the first lockdown period to control COVID-19 pandemic in 2020, which led to the cutting off of core services and income generating activities for refugees, causing severe economic hardships and adversity[43].

Though there is limited information on the psychological effects of COVID-19 pandemic among refugees in Turkey, a prospective study with displaced populations in Iraq indicated a substantial increase in their depression, anxiety and PTSD during the pandemic[44]. Refugees settled in countries where existing services have not been well-established are even more vulnerable to financial and psychosocial problems when new crises arise. Within this context, the Self-Help Plus intervention may have been particularly beneficial in tackling severe and ongoing stress and adversities.

The positive impact of Self-Help Plus at six-month follow-up is in line with previous studies indicating an incubation effect in acceptance and commitment therapy trials[45,46]. However, an RCT among asylum seekers and refugees resettled in Western European countries, conducted following a similar protocol on a smaller sample of participants, did not report this pattern of findings, possibly because it did not reach the target sample size[47]. In addition, participants in the Western European trial might have faced different stressors as compared with the present sample, which was exposed to severe and persistent stress throughout the follow-up period.

The results of the present study consolidate recent research evidence showing that prevention programs can be effective in reducing mental health problems. For example, a recent meta-analysis of 50 prevention trials indicated that psychological interventions can reduce the incidence of depressive episodes by 19%[48].

This study has some limitations. First, as for most RCTs of psychological interventions, a double-blind design was not feasible. However, outcome assessors were masked, and they were not involved in any trial phase that might reveal random allocation. In addition, both participants and assessors were instructed not to mention any interventions received during the study. Second, we had to switch from face-to-face to remote (online or telephone) assessments due to the COVID-19 pandemic during follow-up. It is unclear if this change, which equally applied to both study arms, might have affected the participants' responses. Even though several studies documented that a careful and culturally appropriate use of available instruments is feasible and allows a standardization of the screening process and a systematic recognition of psychological distress and psychiatric diagnoses[6], formal studies on online or telephone use of these tools in refugee groups are lacking. Third, at baseline we did not assess the history of any previous mental disorder. Consequently, mental disorders at follow-up could include both new cases and recurrences of previous mental disorders.

Considering the size of the effect observed in the present study, and that Self-Help Plus can be provided by briefly trained peer non-specialist facilitators in large groups of up to 30 participants at a time, we suggest that it could be offered to forced migrants to support and improve their functioning, and to decrease the pressure on mental health services. Moreover, the use of an illustrated guide and audio recording for delivery decreases the need for extensive training and supervision of facilitators, while increasing intervention fidelity.

In the light of these advantages, Self-Help Plus could be scaled up as a public health strategy to prevent mental disorders in refugee populations exposed to ongoing adversities. Since the intervention does not address the determinants of the refugees' mental health problems, it should be applied in tandem with strong advocacy for protection of those who face adversity, and for services that address their social, physical and broad mental health needs.

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Community-based social interventions for people with severe mental illness: a systematic review and narrative synthesis of recent evidence

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People living with severe mental illness (SMI) are one of the most marginalized groups in society. Interventions which aim to improve their social and economic participation are of crucial importance to clinicians, policy-makers and people with SMI themselves. We conducted a systematic review of the literature on social interventions for people with SMI published since 2016 and collated our findings through narrative synthesis. We found an encouragingly large amount of research in this field, and 72 papers met our inclusion criteria. Over half reported on the effectiveness of interventions delivered at the service level (supported accommodation, education or employment), while the remainder targeted individuals directly (community participation, family interventions, peer-led/supported interventions, social skills training). We identified good evidence for the Housing First model of supported accommodation, for the Individual Placement and Support model of supported employment, and for family psychoeducation, with the caveat that a range of models are nonetheless required to meet the varied housing, employment and family-related needs of individuals. Our findings also highlighted the importance of contextual factors and the need to make local adaptations when "importing" interventions from elsewhere. We found that augmentation strategies to enhance the effectiveness of social interventions (particularly supported employment and social skills training) by addressing cognitive impairments did not lead to transferable "real life" skills despite improvements in cognitive function. We also identified an emerging evidence base for peer-led/supported interventions, recovery colleges and other interventions to support community participation. We concluded that social interventions have considerable benefits but are arguably the most complex in the mental health field, and require multi-level stakeholder commitment and investment for successful implementation.

Key words: Social interventions, severe mental illness, community-based interventions, supported accommodation, supported education, supported employment, community participation, family interventions, peer-supported interventions, social skills training

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The high social and economic costs of severe mental illness (SMI) are well recognized, with clear negative impacts on patients, their families and the wider society[1,2]. The World Economic Forum has estimated that mental ill-health will account for more than half the global economic burden attributable to non-communicable diseases by 2030[3]. People with SMI are at greater risk of poverty, unemployment and poor housing, factors which impact negatively on their social inclusion and exacerbate mental ill-health. Consequently, clinicians, policy-makers and many other stakeholders are interested in improving social outcomes for this group. Yet, this has proved to be a very challenging task.

The World Health Organization (WHO) Mental Health Action Plan (2013-2030)[4] specifically emphasizes the need to implement comprehensive, integrated and responsive mental health and social care services in community-based settings so that "persons affected by these disorders are able to exercise the full range of human rights and to access high-quality, culturally-appropriate health and social care in a timely way to promote recovery, in order to attain the highest possible level of health and participate fully in society and at work, free from stigmatization and discrimination". Similarly, the Australian Government's Productivity Commission (2020)[5] states that "housing, employment services and services that help a person engage with and integrate back into the community, can be as, or more, important than healthcare in supporting a person's recovery".

However, despite these and many other calls and concerted efforts over recent decades to develop services that can enable people with severe mental health problems to integrate into their local communities, these people remain one of the most excluded groups in society[6]. In the second national survey of psychosis in Australia, only one third of people experiencing a psychotic disorder was employed, and these people were more than twice as likely to report loneliness compared with the general population[7].

Whilst this situation is in part due to stigma and discrimination, as well as inadequacies in service provision and mental health systems that continue to institutionalize individuals with more complex problems[8,9], symptoms of the illness itself also contribute. Around a third of people diagnosed with schizophrenia have positive symptoms (delusions and hallucinations) that do not respond to medication[10,11], and negative symptoms and cognitive impairments associated with more severe psychosis impair people's motivation and social skills. These problems create barriers for social inclusion by impacting on the person's ability to build and sustain relationships and to engage in work, education and other community activities[12-14].

Nevertheless, there is a growing body of consumer-oriented literature which validates the importance of personal recovery from mental illness, which is not defined by the presence or absence of symptoms but by valued social roles and relationships[15,16]. There is, therefore, an obvious need to address the social impact of SMI and thus interrupt its bidirectional, negatively reinforcing relationship with social exclusion. Yet, the evidence base to support investment in social interventions has tended to lag behind that concerning pharmacological and psychological therapies, possibly due to their complex nature and the associated challenges they pose in terms of robust study design. Furthermore, due to their complexity, even when supported by good evidence, social interventions are typically more difficult to implement in practice compared with pharmacological (and even psychological) therapies and require commitment and support from multiple stakeholders across the policy and provider spectrum[17].

Perhaps a more fundamental issue is the lack of clarity about exactly what is meant by a "social intervention". For example, the UK National Institute for Health and Care Excellence (NICE) guideline on the prevention and management of psychosis and schizophrenia in adults[18] categorizes family interventions under psychological therapies (along with cognitive behavioral therapy and art therapies) in one section and under "psychosocial interventions" in another, but does not use the terms "psychosocial" or "social" in relation to its section on interventions that enable employment, education and occupational activities.

These difficulties with nomenclature are understandable but problematic. If we consider the example of family interventions, these need to be delivered by well-trained professionals (often, but not exclusively, clinical psychologists) and draw on underpinning psychological theories, and it seems reasonable, therefore, to consider them as psychological interventions. However, they target the individual's immediate social network and aim to impact positively on social outcomes for both service users and carers (for example, through better family relationships and reducing the emotional strain experienced by family members). The term "psychosocial" addresses this issue, but has tended to be used as a catch-all for any intervention that is not a medicinal or biomedical one.

This term also often conflates models of care with interventions that more specifically target the individual. For example, intensive case management is a well-described, manualized and internationally recognized model of community-based multidisciplinary support provided to people with severe mental health problems who are high users of inpatient care. Its effectiveness in reducing inpatient service use is well established (particularly when implemented in settings that have high levels of provision of inpatient services and less developed community services)[19]. However, it is not a psychological or social intervention in itself, but rather a vehicle for the delivery of pharmacological, psychological and social interventions. Despite this, it is often referred to as a psychosocial intervention. Other models of care (such as supported accommodation and supported employment) appear more obviously "social" both in content and in what they aim to achieve and thus, arguably, have a better fit with the term "social intervention".

Adding to the complexity, there is an increasing interest in peer-led or co-led interventions for people with mental health problems, which, by definition, have a "social" component (the "peer" element) but are not commonly described as "social" interventions, despite an emphasis on promoting choice, control and agency.

An additional problem for researchers is that social outcomes are not always well defined, which impacts on how reliably they can be measured. More objective outcomes, such as employment or stable housing, can be operationalized relatively easily, but concepts such as quality of life tend to be more subjective and thus more difficult to assess, not least because they can be confounded by symptoms of the mental illness itself[20].

A further issue is context. Whilst the belief that schizophrenia and other SMI has a better social prognosis in non-industrialized societies is no longer universally accepted[21], there are major challenges associated with the delivery of effective social interventions to enhance social outcomes in less economically developed settings, including sociocultural factors such as the availability of family support, the impact of industrialization, stigma, discrimination, inadequate protection of human rights, and limited access to services[22]. Furthermore, there are even greater barriers to providing and researching social interventions in low- and middle-income (LAMI) than higher-income countries, due to the limited availability of human and financial resources.

Given these multiple considerations, we focused this review on interventions that were clearly social in content *and* aimed to improve social outcomes; specifically, those that aimed to improve social and economic participation for people with SMI. We included studies conducted in LAMI countries as well as those from high-income countries.

METHODS

We conducted a systematic review of the recent literature on models of care and interventions for individuals with SMI for the Australian Royal Commission into Victoria's Mental Health System[23]. The present review includes a subset of identified studies that reported on the effectiveness and/or cost-effectiveness of community-based models of care and interventions that had the overarching aim of supporting social inclusion.

Search strategy, inclusion and exclusion criteria

Our search was conducted in July 2020 using Medline, EMBASE, PsycInfo, CINAHL and Cochrane databases, and included peer-reviewed papers published between January 2016 and July 2020. Our search terms (key words and MeSH terms) reflected three central concepts: "severe mental illness", "models of care and/or interventions", and "outcome and experience measurement" (full search string available on request). We limited our search to publications in English and available in full text. Authors were contacted for relevant papers if the full text could not be accessed.

Inclusion criteria for the original search were: a) models of care for adults aged 18 to 65 years with severe and persistent mental illness; b) group or individual interventions that could be delivered alone or through an identified model of care. For example, Individual Placement and Support is a model of care (a form of supported employment), whereas family psychoeducation is an intervention. Additional inclusion criteria for the present review were: c) community-based models and interventions that aimed to improve social inclusion (i.e., supported accommodation, supported education, supported employment, community participation interventions, family interventions, peer-supported/developed/led interventions; social skills training interventions); d) studies that evaluated models of care or interventions for people with SMI, defined as a primary diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or other severe and enduring psychotic disorder. Studies reporting on models of care or interventions that also comprised a peer component were included within the relevant category. The separate peer-led/supported interventions category included studies where the peer component was not delivered as part of one of the other included models of care or interventions.

Exclusion criteria were: a) studies conducted in environments other than the community, for example inpatient units or prisons; b) studies that focused on individuals with a primary diagnosis of personality, depressive or anxiety disorder, substance use disorder, acquired brain injury, intellectual disability, or trauma due to natural disasters or military service; c) studies where fewer than 50% of the sample met our SMI diagnostic inclusion criteria (see above); d) studies that did not report on any relevant social outcomes; e) publications that did not report primary empirical data, such as reviews, editorials and commentaries.

Social outcomes were broadly defined to include any indicator of improved social or economic participation. For example, for studies evaluating supported accommodation, we included those reporting on housing stability or progression to more independent accommodation; for studies of supported employment or supported education, we included those reporting outcomes related to gaining or sustaining employment in a competitive, paid or unpaid post, or engagement in mainstream or supported study or volunteering. Outcomes of interest for studies of family interventions included measures of family functioning such as expressed emotion and carer burden. Whilst not measured at the individual service user level, these are appropriate to the aims of this review since supportive, healthy family relationships are crucial to most people's recovery and social and community participation[24]. In addition, it is well established that high expressed emotion within the family is a risk factor for relapse and is highly correlated with carer burden[25]. Thus, family interventions often aim to reduce one or both of these. For other interventions, outcomes included measures of social skills, social functioning, engagement in community-based activities, social connection, self-efficacy, hope and empowerment.

Study selection

Results of the original search undertaken for the Victorian Royal Commission were screened using the Covidence online software (https://www.covidence.org). After duplicates were removed, reviewers screened by title, abstract and full text. All disagreements were resolved through consulting with the project lead.

The Royal Commission review identified 313 papers. For the present review, an additional 15 papers reporting on studies conducted in LAMI countries (that were excluded from the Royal Commission review) plus eight hand-searched papers were included in the pool, giving a total of 336 papers.

Publications were selected from these 336 using Covidence on the basis of the inclusion and exclusion criteria described above. A team of six reviewers screened by title, abstract and full text, with each study requiring two "yes" votes at each stage to be included. All conflicting votes were resolved by an independent third reviewer.

Quality of evidence

Primary papers were evaluated by the Kmet standard criteria to assess methodological quality of both quantitative and qualitative research[26]. Quantitative papers were rated on 14 items and qualitative papers on 10 items, related to the study design, participant selection, data analysis methods, and the clarity and interpretation of results. Each paper was rated by one reviewer and validated through discussion between reviewers at weekly meetings to ensure consistency in rating. Total scores were reported out of 100 (i.e., as percentage equivalents) to take account of non-applicable items.

We developed a data extraction table and guidance notes to assist consistency in the synthesis of findings from studies in each of the seven models of care/community interventions. One co-author produced a textual summary for each social intervention category, and each summary was then reviewed by both first authors. The textual summaries were then refined and finalized through consensus discussion within the author group.

Narrative synthesis

Given the range of models of care and interventions included, we chose a narrative synthesis approach to summarize our findings. Narrative synthesis includes: a preliminary synthesis to identify patterns of findings across included studies; exploration of whether effects of an intervention vary according to study population; identification of factors that may influence the results within individual studies and explain difference in findings between studies; development of a theoretical framework underpinning specific intervention effects; assessment of the robustness of the synthesis based on the strength of evidence; discussion of the generalizability of conclusions to wider populations and contexts[27].

Since our review included multiple social interventions, we did not aim to address the development of a theoretical framework underpinning the effects of each intervention. However, factors that might be relevant to the effectiveness and implementation across our included social interventions were summarized.

RESULTS

We identified 72 studies meeting our eligibility criteria (see Figure 1).

Over half (41/72) of the included studies reported on the effectiveness of social interventions delivered at the service level (supported accommodation, supported education, supported employment), and the remainder evaluated interventions targeting people with SMI directly (community participation, family interventions, peer-developed/led/supported interventions, social skills training). A summary of the characteristics and quality ratings of included studies is provided in Tables 1-3.

Social interventions delivered at the service level

Supported accommodation (see Table 1)

There were 16 eligible studies in this domain, nine of which were quantitative[28-36] and seven qualitative[37-43]. The stud-

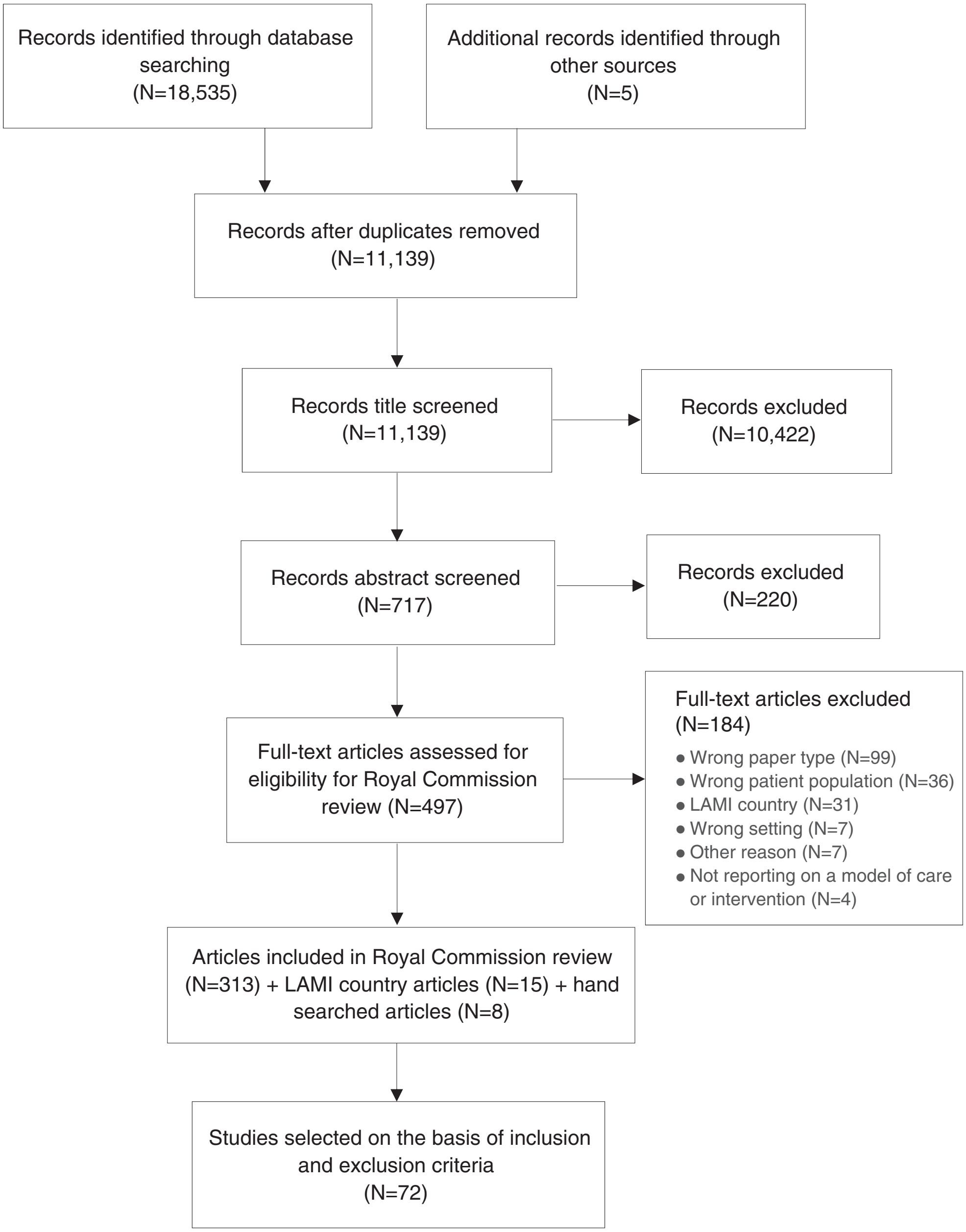

Figure 1 PRISMA flow chart. LAMI – low- and middle-income

ies were conducted in eight different countries: six in Canada[28,35-37,42,43], three in the UK[31,33,34], two in the US[30,41], and one each in Australia[32], France[39], India[38], the Netherlands[29] and Norway[40].

The quantitative studies comprised four randomized controlled trials (RCTs)[28,29,35,36], two case-control studies[30,31], one pre-post uncontrolled study[32], one national survey[33], and one national naturalistic prospective cohort study[34].

The mean Kmet quality assessment score for quantitative papers was 83 (out of 100) and ranged from 100[33,34] to 45[31,32]. The mean quality assessment score for the qualitative papers was 85 and ranged from 100[39] to 40[38].

Table 1 Characteristics of included supported accommodation and supported education studies

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Supported accommodation studies							
Aubry et al[28]	Canada	Non-blinded RCT comparing HF+ACT with TAU	Homeless adults with SMI	92		Outcomes at 24 months. Primary: housing stability. Secondary: community integration.	HF+ACT group had greater housing stability. No difference between groups in community functioning.
Bitter at al[29]	The Netherlands	Non-blinded cluster RCT comparing supported housing staff training in recovery-based practice with TAU	Adults with SMI	92		Outcomes at 20 months. Primary: social functioning and personal recovery. Secondary: empowerment, hope, self-efficacy.	No difference between groups in outcomes.
Brown et al[30]	US	Pre-post case-control study comparing HF+ ACT with TAU	Homeless adults with SMI	91		Housing stability over the 12 months before and after intervention or TAU period.	HF+ACT group had greater housing stability.
Gutman et al[31]	UK	Case-control study comparing supported housing transition program with TAU	Homeless men with SMI	45		Primary outcome at 6 months: successful move to supported housing.	Intervention group more likely to have successful move to supported housing.
Holmes et al[32]	Australia	Retrospective non-controlled pre-post evaluation of supported housing	Homeless adults with mental health problems	45		Housing stability and evictions 2 years before and after moving to the project.	Those with SMI less likely to be evicted than other clients.
Killaspy et al[33]	UK	National survey of supported accommodation services in England	Adults with SMI	100		Cross-sectional survey. Primary: autonomy and social inclusion. Secondary: costs of care.	Residential care (RC) and supported housing (SH) had clients with more severe mental illness than floating outreach (FO). Autonomy greatest for SH. SH and FO more socially included than RC. RC most expensive.
Killaspy et al[34]	UK	Cohort study of participants surveyed in Killaspy et al[33]	Adults with SMI	100		Outcomes at 30 months. Primary: successful move to more independent accommodation. Secondary: costs of care.	41% moved-on successfully with associated lower inpatient and community mental health service costs. Move-on was most likely for FO clients.
Somers et al[35]	Canada	Non-blinded RCT comparing HF+ACT (scattered housing) vs. HF+ACT (congregate housing) vs. TAU	Homeless adults with SMI	92		Outcomes at 24 months. Primary: housing stability. Secondary: community integration.	HF+ACT in both scattered and congregate site groups had greater housing stability than TAU. Community integration better than TAU for congregate HF+ACT group.

Table 1 Characteristics of included supported accommodation and supported education studies *(continued)*

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Stergiopoulos et al[36]	Canada	Non-blinded RCT comparing HF+ACT with TAU	Homeless adults with SMI	92		Outcomes at 24 months. Primary: housing stability. Secondary: community integration.	HF+ACT group had greater housing stability and community integration.
Macnaughton et al[37]	Canada	Qualitative process evaluation of HF implementation in six regions	HF staff and stakeholders, training and process documents		92	Implementation of HF in different contexts.	Training and support critical for HF staff. Training flexible enough to accommodate different contexts and policy imperatives.
Padamaker et al[38]	India	Qualitative study of move from long-term institution to supported housing	Women with SMI and focus group with staff		40	Service user and staff experiences of the move.	Gradual improvement in women's functioning and confidence and acceptance by neighbours.
Rhenter et al[39]	France	Qualitative study of participants of RCT comparing HF with TAU	Homeless adults with SMI who received HF		100	Housing and recovery experiences before and after move to HF service.	Importance of stable housing as "a refuge" that prompts reflection and instils hope.
Roos et al[40]	Norway	Qualitative study of sheltered housing services	Adults with SMI		90	Clients' experiences of the services.	Clients liked having self-contained apartment plus shared space to socialize and do activities with others. Main issue was time-limited nature of service.
Stanhope et al[41]	US	Qualitative study of supportive housing projects	Staff of services for homeless adults with SMI		85	Case managers' views on purpose and delivery of the service.	Staff were overly focused on medication management.
Stergiopoulos et al[42]	Canada	Qualitative process evaluation of implementation of HF	HF managers, housing providers and case managers		90	Facilitators and barriers to implementation of HF.	Facilitators: shared commitment to HF philosophy; shared caseload; monitoring fidelity. Barriers: lack of housing availability; inadequate frequency of client contacts; lack of service user involvement.
Worton et al[43]	Canada	Qualitative process evaluation of implementation of HF in six regions	HF staff and stakeholders, training and process documents		92	Facilitators and barriers to implementation of HF in different contexts.	Facilitators: stakeholders engaged; resources; local champions; staff trained and supervised, able to adapt model to local context; outcome monitoring. Barriers: lack of structures to align key agencies; staff resistance.
Supported education studies							
Ebrahim et al[46]	UK	Non-controlled, mixed methods pre-post evaluation of a recovery college	Recovery college students	55	40	Outcomes assessed through feedback forms at end of each course: empowerment, well-being, confidence and free-text comments.	Students felt more empowered and experienced improved well-being and confidence. College was enabling, promoted hope and social connection.

Table 1 Characteristics of included supported accommodation and supported education studies *(continued)*

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Hall et al[47]	Australia	Co-produced, non-controlled, mixed methods evaluation of a recovery college	Recovery college students, staff, other key stakeholders	41	85	Experiences of the recovery college	College facilitated learning and growth; was inspiring, encouraging and compassionate; a "stepping-stone" to mainstream education.
Sommer et al[48]	Australia	Non-controlled pre-post evaluation of a recovery college	Recovery college students	91		Primary outcome: achievement of goals identified in initial learning plan.	70% of goals achieved at least partially. Most common goals related to education, physical health, social and personal relationships, mental health, and employment.
Sutton et al[49]	UK	Non-controlled pre-post evaluation of a recovery college	Recovery college students	86		Primary outcome: economic benefits of attending the recovery college.	Attendance associated with higher chance of subsequent employment and increase in personal income.
Wilson et al[50]	UK	Non-controlled, mixed methods, pre-post evaluation of a recovery college	Recovery college students	77	80	Primary outcomes at 6 months: well-being, social inclusion.	Improvement in students' well-being and social inclusion, supported by qualitative findings.

RCT – randomized controlled trial, HF – Housing First, ACT – assertive community treatment, TAU – treatment-as-usual, SMI – severe mental illness, quant. – quantitative, qual. – qualitative

Housing First

Five of the quantitative studies and four of the qualitative studies (53% of all the supported accommodation studies) evaluated the Housing First (HF) model. This approach evolved in the US and Canada to address the high rate of homelessness amongst people with SMI, many of whom also have comorbid substance misuse problems. It involves the provision of rent supplements and support from a clinical team assisting persons to find, move into and sustain a tenancy, and helping them address their mental health issues using a recovery-oriented framework[44].

A robust, five centre RCT in Canada ("Chez Soi") found HF to be associated with greater housing stability compared with treatment-as-usual (TAU) at 2-year follow-up (74% of HF clients were in stable housing compared to only 41% of those receiving standard care)[45], but no differences were found between the groups in community functioning or secondary clinical and social outcomes. Our review included five high-quality studies, two quantitative[28,36] and three qualitative[37,42,43], associated with the Chez-Soi trial.

A high-quality (Kmet 91) case-control study[30] in Seattle, US reported better housing outcomes for those receiving HF, with a lower percentage homeless and fewer days of homelessness at 12-month follow-up compared to standard care. A non-blinded RCT versus TAU (Kmet 92)[28] reported findings from Moncton, Canada, where the clinical input to HF tenants was provided through assertive community treatment (ACT). Housing outcomes were better for HF recipients than those in the standard care group, with large effect sizes, but there was no difference between groups in community functioning or clinical outcomes.

A sub-analysis of data from the Chez-Soi trial's Toronto site[36] (Kmet 92), which provided HF plus intensive case management, adapted to the city's ethnically diverse population, reported that housing stability and community functioning were greater for those who received HF compared to controls. Similar positive results were obtained in a three-arm RCT conducted in Vancouver[35] (Kmet 92) that compared HF provided to people with SMI (mainly psychosis and co-occurring substance misuse problems) in scattered tenancies without on-site staff, versus support provided in 24-hour staffed congregate housing, and versus standard care. Both forms of supported accommodation (HF and on-site staffing) were associated with greater housing stability than standard care, but clients in the congregate staffed housing rated their sense of community integration and personal recovery higher than the other two groups.

Using data from preparatory meetings, training events, supervision and focus groups with key stakeholders at HF implementation sites in the Chez-Soi trial, two qualitative studies[37,43] (both with Kmet scores of 92) investigated the barriers and facilitators to successful implementation of the HF model.

Facilitators included: a) site readiness (i.e., ensuring that local stakeholder organizational policies were aligned to support implementation; that ring-fenced and adequate resources were available; and that local champions were in place); b) organizing stakeholder sessions to frame the problem (homelessness) in a way that was congruent with different organizations' values and allowed them to collaborate to address it; c) ensuring that all key players were included and engaged in the process; d) ensuring that housing providers and clinicians were trained and supervised to deliver the key elements of the HF model; e) identifying and addressing obstacles to local implementation (e.g., providing rent subsidies to use private tenancies to address shortages in housing supplies); f) providing forums for staff to share and solve implementation problems, build knowledge and avoid burnout; g) allowing flexibility in the model to fit with local context; h) using data to highlight successful outcomes and expand the programme.

Barriers to implementation included: a) lack of consensus about target client group; b) seeing homelessness as a housing problem rather than a wider health and societal problem; c) lack of consensus on how to organize the various structures of the HF approach; d) staff resistance to change and the (false) belief that they were already delivering HF; e) lack of existing structures to bring agencies together; f) financial disincentives (e.g., organizations competing for the same funds); g) housing stability being seen as an end in itself rather than a vehicle to support clients' ongoing recovery; h) lack of training and supervision to ensure that staff adopted a recovery-oriented approach.

A qualitative evaluation of the implementation of HF at the Chez-Soi Toronto site[42] was also conducted through interviews with HF senior managers, housing providers and case managers (Kmet 90). Model fidelity assessments were used to identify services with lower fidelity for further exploration of the barriers to implementation. Three main obstacles were identified: lack of housing availability; inadequate frequency of client contacts (the target was weekly contact, but this proved challenging due to staff time constraints and clients declining visits); and a lack of service user involvement in the HF programme. Facilitators to implementation included: a shared commitment to the HF philosophy across providers, senior managers and case managers; and using a shared team caseload approach to provide staff with peer support. The authors concluded that monitoring model fidelity was helpful to identify and then address implementation challenges.

A further robust (Kmet 100) qualitative study of clients of HF services conducted in France[39] reported benefits that went beyond the concrete outcome of housing stability reported in the quantitative studies. These included the deep sense of security that came from having a permanent home and how this provided a base to access adequate resources, build a routine, reclaim a previous identity or build a new one. However, the findings also highlighted the scale of the challenge for individuals in doing so. The authors noted that, whilst the effects of HF are considerable, they are often insufficient to break negative cycles and may only be able to "cushion" downward trajectories. They also observed that housing stability should not be considered a success in and of itself, but rather a basis for ongoing recovery.

Other models of supported accommodation

A national survey of mental health supported accommodation services in England[33] and a subsequent naturalistic cohort study[34] (both with a Kmet score of 100) identified three main types of service: a) residential care homes that provided congregate facilities, staffed 24 hours, where day-to-day needs were addressed (e.g. meals, supervision of medication and cleaning) and places were not time limited; b) supported housing that comprised shared or individual self-contained, time-limited tenancies with staff based on-site up to 24 hours a day to assist individuals to gain skills to move on to less supported accommodation; and c) floating outreach services that provided visiting support for a few hours a week to people living in time-unlimited, self-contained, individual tenancies, with the aim of reducing support over time.

Quality of care was best in supported housing, and floating outreach was the cheapest of the three service types, but client characteristics differed significantly. Although two-thirds of participants had some form of psychosis, those in residential care and supported housing had more severe mental health problems than those receiving floating outreach. However, across all services, 57% had a history of severe self-neglect and 37% were considered vulnerable to exploitation.

After adjusting for differences in clinical characteristics, supported housing clients had greater autonomy than those of the other two service types. Clients of supported housing and floating outreach services were more socially included than those in residential care, but experienced more crime.

At 30-month follow-up, 41% of participants had successfully moved on to more independent accommodation (or, for those receiving floating outreach, were managing with fewer hours of support). After adjustment for clinical characteristics, this was most likely for floating outreach clients compared to clients of the other two service types, and more likely for those in supported housing than those in residential care.

Adjusted multilevel models revealed that clients who progressed to more independence had significantly lower community and inpatient mental health service costs than those who did not. Two aspects of service quality were associated with successful progression to more independence: promotion of human rights and recovery-based practice. Those with more unmet needs, those with higher ratings of vulnerability to self-neglect or exploitation, and those who had been living at the supported accommodation service longer were less likely to move on. The authors concluded that there were pros and cons of the various models and that different service types tailored to individual need were required, rather than investing only in the cheapest type (i.e., floating outreach).

Group and individual qualitative interviews were carried out with residents of a sheltered housing project in Trondheim, Norway[40] (Kmet 90), that provided self-contained bedsits, with some communal areas for socializing, and staff on site 24 hours a day. Residents felt that this model provided them with a good balance of independence and support. They liked not having to share facilities with others, felt safe having staff on site, and reported being supported to gain confidence with daily living skills and social activities. The only drawback was the time-limited nature of the project (residents were expected to move on after a few years).

A six-week group programme comprising twice weekly sessions with an occupational therapist to prepare people to move to a floating outreach service was evaluated through a small (Kmet 45) case-control study[31]. More of those who attended the group sustained their supported housing at six-month follow-up, suggesting that structured preparatory work for housing transition may be beneficial, but the methodological problems with this study limit the strength of its findings.

Whilst a number of studies identified the importance of supported accommodation services providing a recovery-oriented approach[34,37,43], this may prove difficult to implement. A cluster RCT[29] (Kmet 92) in the Netherlands evaluated a recovery-based practice training intervention for staff of supported accommodation services. The intervention encompassed the use of a collaborative and strengths-based approach to support service users to identify and work towards individualized goals, but no differences were found between intervention sites and standard services on the primary outcomes of personal recovery, quality of life or social functioning.

Nevertheless, a small qualitative study in Chennai, India[38] (Kmet 40), exploring the experiences of women who moved from a longer-term mental health institution to a staffed group home, highlights the importance of supported accommodation to people's recovery. The move allowed the women to begin to develop an individual identity and to gain a sense of belonging in the local community for the first time.

Supported education (see Table 1)

Five papers evaluating supported education were identified[46-50], all of which focused on recovery colleges: a recovery-based mental health education program that uses peer learning advisors to facilitate individual student learning plans[48] and where students are people with lived experience of mental health problems. Two of the studies were quantitative[48,49] and three employed mixed methods[46,47,50]. Three were conducted in the UK[46,49,50] and two in Australia[47,48].

Although a number of studies reported that attendance at a recovery college inspired students to consider looking for work, only one – a self-report survey of a college in the UK[49] (Kmet 86) – reported data to show a significant positive association between attendance and being in paid or self-employment at nine-month follow-up.

A recovery college in Australia, where students were supported to develop learning plans and identify up to three specific goals, which were reviewed at least annually, was evaluated using routinely collected data on 64 students[48] (Kmet 91). The most commonly cited goals were education, physical health, social and personal relationships, mental health, and employment.

Student engagement in the college courses (including the number of courses enrolled in and the number of classes attended) was found to be associated with goal attainment, but active involvement in the college for over 685 days was negatively associated with goal attainment. The authors concluded that this could be due to a higher severity of mental health needs amongst longer-term students and a possible need for additional support. The main factors that were reported to impede goal attainment included physical health problems, external stressors/life events, and dependency on others to access the college.

Simpler goals with a relatively short-time frame appeared easier to achieve than more complex or longer-term ones. Employment goals were less likely to be achieved than other types of goals, whereas education related goals were the most likely, followed by mental health, social, and physical health goals.

Mixed methods evaluations of recovery colleges of varying quality conducted in the UK[46,50] and Australia[47] have shown consistently positive findings in terms of student satisfaction, improvements in mental well-being, confidence and reduced social isolation. Many students reported that they were planning to attend mainstream courses, volunteer or gain paid employment in the future[46,50], and some described the college as a "stepping-stone" to mainstream education[47]. Some colleges provided employment opportunities themselves by involving students in the formulation and facilitation of courses on a paid or voluntary basis, and some signposted students to peer-support positions elsewhere[47].

Supported employment (see Table 2)

We identified 20 studies that addressed interventions targeting employment or voluntary work, of which 15 were quantitative[51-65], one used mixed methods[66] and four were qualitative[67-70].

The mean Kmet quality assessment score for quantitative papers was 82 and ranged from 100[51,54,61] to 50 (quantitative component of a mixed methods study)[66]. The mean quality assessment score for the qualitative papers was 66 and ranged from 100[68] to 35[66] (qualitative component of a mixed methods study).

Seven studies were conducted in the US[52,54,55,57-59,64], three in the UK[63,66,69], two each in China[65,70], Denmark[51,67], Norway[56,60] and Spain[61,68], and one each in Australia[62] and the Netherlands[53].

The interventions studied could be grouped into three main types: Individual Placement and Support (IPS), characterized by rapid individualized job searching for competitive employment, integrated with mental health support, welfare benefits counselling, and on-the-job support[71]; other forms of competitive or sheltered employment with employment specialists providing on-the-job support; and vocational rehabilitation, that typically focused on pre-vocational training, interview and preparation of a curriculum vitae.

Two high-quality studies (Kmet 100[51] and Kmet 85[60]) compared IPS with usual care, both reporting more favourable employment outcomes achieved through IPS, supporting the international evidence that IPS delivers improved employment outcomes compared to traditional vocational rehabilitation[72].

A further study[53] (Kmet 77) investigated the longitudinal association between IPS fidelity and employment outcomes among 27 IPS programmes that reported outcomes quarterly to a central registry in the Netherlands. A positive association was found between improvement in IPS fidelity and employment rates over time, with employment outcomes showing the greatest improvement after 18 months of implementation.

Based on emerging evidence that enhanced cognitive func-

Table 2 Characteristics of included supported employment studies

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Christensen et al[51]	Denmark	Assessor-blinded RCT comparing IPS with enhanced IPS (E-IPS) or TAU	Adults with SMI seeking employment or education	100		Outcomes at 18 months. Primary outcome: competitive employment or education.	More of those receiving IPS (59.1%) or E-IPS (59.9%) achieved competitive employment or education than TAU group (46.5%), but advantage for E-IPS over IPS.
Cook et al[52]	US	Multisite controlled trial comparing SE with TAU	Adults with SMI from four US regions	85		Social security data on employment over 13 years.	32.9% of participants were employed at some point. This was almost three times more likely for SE recipients.
De Winter et al[53]	The Netherlands	Non-controlled longitudinal study of IPS	Clients of 27 IPS programs (23 targeted adults with SMI)	77		IPS fidelity and employment assessed quarterly over five years.	Greatest improvement in employment outcomes seen after 18 months of IPS. Positive association between IPS fidelity and employment.
Glynn et al[54]	US	Non-blinded RCT comparing IPS with IPS + work skills training	Adults with SMI	100		Primary outcomes at 2 years: employment and job tenure.	63% of all participants gained employment. No differences between groups.
Kern et al[55]	US	Pooled results from two RCTs comparing IPS with IPS + errorless learning	Adults with SMI	77		Primary outcomes at 12 months: achievement of employment and job tenure.	32% of all participants obtained jobs (mostly minimum wage and part-time). The IPS + errorless learning group had greater job tenure.
Lystad et al[56]	Norway	Multi-site non-blinded RCT comparing VR+CR with VR+CBT	Adults with SMI	62		Primary outcome at 2 years: employment, hours worked.	Employment and hours worked increased in both groups. No difference between groups in outcomes.
McGurk et al[57]	US	Non-blinded RCT comparing enhanced VR (E-VR) with E-VR+CR	Adults with SMI for whom previous VR was ineffective	85		Outcomes at 3 years. Primary: employment rate. Secondary: engagement in work related activity.	No differences in employment rate between groups, but E-VR+CR group more likely to engage in work-related activity.
McGurk et al[58]	US	Pre-post feasibility study of VR+CR	Adults with SMI	64		Feasibility (uptake and completion).	Intervention feasible (79% of participants completed at least 6/24 sessions).
Puig et al[59]	US	Sub-analysis of one arm of RCT comparing IPS with and without cognitive training	Adults with SMI receiving the cognitive training intervention	82		Outcomes at 2 years: cognitive skills and competitive employment.	Improved attention and age (younger and older participants) were associated with achieving competitive employment.
Reme et al[60]	Norway	Multicentre non-blinded RCT comparing IPS with TAU	Adults with severe and moderate mental illness	85		Outcomes at 12 and 18 months. Primary: competitive employment.	IPS group more likely to be in competitive employment. Similar employment rates for people with severe and moderate mental illness.

Table 2 Characteristics of included supported employment studies *(continued)*

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Rodriguez Pulido et al[61]	Spain	Non-blinded RCT comparing IPS with IPS+CR	Adults with SMI	100		Outcomes at 2 years. Primary: employment and hours worked/ week.	IPS +CR group more likely to gain employment and worked more hours.
Scanlan et al[62]	Australia	Non-controlled prospective study of recovery-based IPS service	Adults with SMI	83		Outcomes at 2 years: competitive or voluntary employment, job tenure, education engagement.	49.5% gained competitive employment, mean duration 151 days. 63.9% gained employment or engaged in education or voluntary work.
Schneider et al[63]	UK	Feasibility RCT comparing IPS + work-focused CBT with IPS alone	Adults with SMI	81		Outcomes at 6 months. Primary: hours in competitive employment. Secondary: participation in education, training or volunteering.	34% participants gained employment. No differences between groups in outcomes.
Twamley et al[64]	US	Non-blinded RCT comparing IPS + cognitive training with E-IPS	Adults with SMI	96		Outcomes at 2 years. Primary: number of weeks worked. Secondary: job attainment, hours worked, wages earned.	No difference between groups in outcomes.
Zhang et al[65]	China	Non-blinded RCT comparing IPS with VR or IPS + work-related social skills training (E-IPS)	Adults with SMI	88		Outcomes at 2 years. Primary: job attainment Secondary: job tenure, hours per week worked.	Higher job attainment and longer job tenure in the E-IPS group than IPS alone. IPS and E-IPS both had better employment outcomes than VR.
Hutchinson et al[66]	UK	Mixed methods evaluation of IPS implementation in six regions	Community mental health services for adults with SMI	50	35	Outcomes at 18 months. Primary: competitive employment. Qualitative: factors influencing implementation.	5 of the 6 sites achieved target of supporting 60 clients into competitive employment. Service resource pressures, stakeholder support and achievement of targets influenced programme sustainability.
Gammelgaard et al[67]	Denmark	Phenomenological study of IPS	Adults with SMI participating in RCT evaluating IPS		80	How IPS and employment might influence recovery, through a "reflective lifeworld approach".	Employment specialists adopted recovery-based practice. Employment boosted self-esteem, skills, routines and financial security.
Perrez-Corrales et al[68]	Spain	Phenomenological study of volunteering programs	Adults with SMI working in volunteer roles		100	Experiences of volunteering and its impact on the recovery process.	Volunteering enabled people to build a valued identity; having responsibility through volunteering helped people feel they had a "normal" life.

Table 2 Characteristics of included supported employment studies *(continued)*

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Talbot et al[69]	UK	Descriptive qualitative study of IPS in forensic mental health setting	Adults with SMI under community forensic services		60	Implementation of IPS in community forensic mental health service.	Implementation required robust collaboration with internal and external agencies. Barriers: negative staff attitudes and difficulty engaging employers. Facilitators: support of service managers and outside groups.
Yu et al[70]	China	Qualitative process evaluation of E-IPS recipients in RCT reported above[65]	Adults with SMI who received E-IPS and gained employment plus their family members		55	Participant and family views of the E-IPS intervention.	Participants reported benefits from work-related social skills training and valued social connections made at work. Participants valued having choice about jobs whereas carers valued financial benefits more than job fit.

RCT – randomized controlled trial, IPS – Individual Placement and Support, SE – supported employment, CBT – cognitive behavioral therapy, TAU – treatment-as-usual, SMI – severe mental illness, VR – vocational rehabilitation, CR – cognitive remediation, quant. – quantitative, qual. – qualitative

tioning could further improve the outcomes achieved from supported employment[73], eight studies investigated the effectiveness of enhancements to supported employment interventions. Six of these supplemented IPS[51,54,61,63,64,65], and two supplemented another form of supported employment[56,57]. Enhancements included: cognitive remediation computer-assisted training via CogPack[61]; manualized compensatory cognitive training[64]; cognitive remediation (CIRCUITS computer software) in combination with social skills (Thinking Skills for Work)[51]; computer-assisted cognitive remediation (CogPack) plus Thinking Skills for Work[56,57], generic work skills training (Workplace Fundamentals)[54]; work-related social skills training (10 sessions of behavioral rehearsal plus *in vivo* problem solving)[65]; and work-focused cognitive behavioral therapy (3-6 sessions matched to need)[63].

The supplemental interventions were offered at varying levels of intensity, ranging from three to 30 sessions. However, not all studies described in detail the degree of participant engagement, and those which did suggest less than optimal engagement. Twamley et al[64] (Kmet 96) reported a mean of 8.23±4.88 weekly sessions of cognitive training attended in the first 12 weeks of IPS. Christensen et al[51] (Kmet 100) described the enhanced IPS intervention as comprising 30 sessions of cognitive remediation, but 24% of participants did not attend any sessions and the mean attendance was fewer than 10 sessions. In Glynn et al's RCT[54] (Kmet 100), comparing IPS versus IPS plus work skills training, 22% of participants attended none of the work skills classes (an "as-treated" analysis that removed those participants did not reveal any additional benefits from the supplemental intervention).

While some neurocognitive improvement was described in most of the studies that augmented IPS with a cognitive intervention, only two[61,65] demonstrated significant between-group findings on employment outcomes. In a Spanish study[61] (Kmet 100), participants in the IPS plus cognitive remediation group achieved significantly greater employment rates and hours worked than those receiving IPS alone. Although well conducted, this was quite a small study, and findings should be interpreted with some caution. In a study carried out in China, Zhang et al[65] (Kmet 88) found that the group receiving IPS plus work-related social skills training had significantly higher employment rates (63%) than a standard IPS group (50%) and a vocational rehabilitation group who engaged in sheltered work (33%). They suggested that the success of the enhanced IPS intervention might be associated with cultural factors (such as the importance that Chinese employers place on social competence) and concluded that the augmented IPS intervention was a good cultural fit for the Chinese context.

Two studies supplemented supported employment (not IPS) with enhancements that included cognitive remediation[56,57]. McGurk et al[57] (Kmet 85) focused their intervention on people who had not previously benefited from vocational services. They randomized participants to either enhanced vocational rehabilitation alone (where participants were supported to identify and address specific cognitive difficulties relevant to the workplace) or enhanced vocational rehabilitation plus computer-based cognitive remediation (24 sessions) and work-related coaching (Thinking Skills for Work). There were no between-group differences on employment outcomes, although the authors noted between-group differences in education levels at baseline that may have influenced the results.

In Norway, Lystad et al[56] (Kmet 62) investigated the JUMP vocational rehabilitation programme, where participants were offered 10 months of intensive vocational support in sheltered or competitive work environments in addition to either cognitive remediation (40 hours of computer-based training and coaching, similar to the Thinking Skills for Work intervention), or 40 hours of work-related cognitive behavioral therapy. Both groups improved in cognitive skills, but no between-group differences were found in employment outcomes.

Kern et al[55] (Kmet 77) examined how job tenure and work behaviors were impacted by errorless learning (structured training where work behaviors that were causing challenges were broken into elements and addressed hierarchically using cues, prompts, modelling and self-instruction until high levels of performance were achieved). Data from two studies were combined in the reported paper: a study of 74 veterans with schizophrenia or schizoaffective disorder and a study of 106 participants living in the community with a diagnosis of SMI and memory impairment. Participants all received IPS and were randomized at the point of obtaining a job to either continue IPS alone or to receive IPS plus errorless learning. In total, 58 (32%) participants obtained jobs that were mostly minimum wage and part-time, and the errorless learning group had significantly better job tenure (41% were still working at the end of 12-month follow-up compared to 14% of the IPS alone group). There were no differences in hours worked or wages earned.

Overall, of the eight studies that evaluated supplementing IPS or another form of supported employment, only two found that the augmented approach improved employment outcomes[61,65], despite most of the interventions being associated with improved neurocognitive performance. In addition, Kern et al[55]'s errorless learning enhancement, predominantly targeting social skills in the workplace, demonstrated enhanced job tenure. Furthermore, a subsequent analysis of participants in the trial conducted by Twamley et al[64] who received IPS and compensatory cognitive training, found that those who were younger or older benefited more in comparison with middle-aged participants, and that improving attention significantly predicted work attainment[59] (Kmet 82).

Employment outcomes in the included studies were assessed over different periods, up to two years, with the most effective intervention reporting 63% employed and most studies reporting around 50%. These data demonstrate that targeted interventions can be effective in helping a large proportion of people with SMI achieve employment. However, the definition of employment varied and could involve as little as one hour per week in a low wage job over a short period of time.

One study took a longer view, using social security data to understand the impact of engagement in a supported employment programme in the US over many years[52] (Kmet 85). The supported employment programme was not IPS, but comprised employment specialists embedded within multidisciplinary teams coordinating clinical and employment supports and aiming to place people in competitive jobs matched to their preferences. Data on 449 individuals over 13 years showed that a third earned some income and 13% achieved economic self-sufficiency at least some of the time. Compared to the control group receiving usual care, participants in this study were almost three times more likely to gain employment.

Several studies provided insights into implementation issues. The difficulties of addressing negative staff and employer attitudes, and ensuring that supplemental interventions are delivered by adequately skilled trainers, the contextual challenges of the local labour market and welfare systems, and organizational factors – including the separation of employment and mental health services – have been previously identified[72] and were again highlighted in the included studies.

A mixed methods study of a UK demonstration project to embed IPS into six health service sites[66] (quantitative Kmet 50, qualitative Kmet 35) used various strategies to address barriers to implementation (operational and strategic management, data monitoring, alignment of reporting, use of champions, and learning communities), and many participants gained employment. However, funding was not sustained at several sites, in the context of cost pressures in the health system, highlighting how external factors can undermine implementation efforts. A qualitative evaluation of the implementation of IPS in a forensic context (Kmet 60)[69] identified additional barriers for this client group, such as stigma and restrictions on employment relating to participants' criminal history.

McGurk et al[58] demonstrated that it was feasible for front-line staff to engage clients with more complex SMI in their Thinking Skills for Work intervention, prior to referring them to mainstream employment support (Kmet 64). The intervention was tailored to each site, with staff trained via two workshops focused on understanding the cognitive challenges of people with SMI and supporting clients to use a computerized cognitive training software programme. Sites with easier access to mainstream employment support had better employment outcomes, and the authors highlighted the relevance of local contextual factors to the successful implementation of supported employment interventions.

An Australian study[62] (Kmet 83) provided detail on how job coaches used the theory and practice guidance of the Collaborative Recovery Model[74] to underpin their implementation of IPS, including how they engaged with people, instilled hope and built on individuals' strengths and values. The authors concluded that a recovery-based approach appeared to enhance the structured activities of high-fidelity IPS, but the findings warrant further investigation under controlled conditions.

Qualitative studies also provided additional insights into the need to consider cultural factors, personal experiences and family perspectives in implementation. A phenomenological investigation of 12 participants receiving IPS explored how the intervention influenced recovery for people with SMI[67] (Kmet 80). Some participants described the importance of the relationships that they established with employment specialists leading to increased self-esteem and changes to life patterns, while others identified employment itself as most influential in their recovery. They highlighted how the individualized approach of IPS made them more hopeful about employment, especially in comparison with previous experiences with mainstream employment centres.

The experiences of 15 people with schizophrenia who received the IPS enhanced with social skills training intervention in the study conducted in China described earlier[65] were explored qualitatively[70] (Kmet 55). The findings highlighted the importance of sociocultural factors, such as the legal and moral responsibility of families in mainland China for caring for those with mental illness. The authors identified differences in perspectives between caregivers, who wanted their family member to attain the "best" job, and their relatives with schizophrenia, who wanted to find a job they liked. They concluded that, in collectivist cultures, provision of vocational interventions may benefit from taking a family-oriented rather than individualistic approach.

Countering the focus on competitive employment as the only important outcome for people with SMI, a high-quality Spanish study explored volunteering as a vocational intervention[68] (Kmet 100). People with SMI reported that volunteering provided them with a role and responsibilities and supported them in rebuilding a valued identity and sense of a "normal life", affirming that vocational activities deliver benefits beyond earning an income.

Social interventions delivered at the group or individual client level (see Table 3)

Community participation

Nine studies evaluating interventions aimed to improve the community participation of people with SMI were identified, three of which were quantitative[75-77], five qualitative[78-82], and one employed mixed methods[83]. Three of the studies were conducted in the US[76,79,83], two in Canada[80,82], and one each in Australia[78], China[75], Hungary[77] and the UK[81].

A high-quality RCT[77] (Kmet 92) conducted in Hungary investigated the impact of two types of community-based psychosocial intervention (a community social club and case management) on social cognition and functional outcomes compared to a matched TAU control group. The authors reported a significant improvement in functional outcomes for participants in both intervention groups at six-month follow-up, with the most significant gains in social cognition found amongst those allocated to the community-based club. They concluded that the club's "supportive social milieu" enabled consumers to engage in more social interactions and practice new social roles, which they posited would, in turn, enable greater societal engagement.

A well-established, internationally recognized approach to bringing people with SMI together in a "supportive social milieu" to promote community participation is the Clubhouse. This has a strong peer-led ethos, whereby members are responsible for the everyday running of the programme and mutually supported within the peer structure to achieve a wide range of psychosocial goals, including social and work-based skills.

An RCT conducted in China[75] (Kmet 75) reported greater improvements in social functioning and self-determination in participants randomly allocated to join a Clubhouse compared to a standard care control group at six-month follow-up.

The Clubhouse approach has also been evaluated through robust qualitative studies. Prince et al[79] (Kmet 85) first identified the key features of the approach through focus groups involving 20 Clubhouse members. These features were then assessed for importance through interviews with a further 150 members. Respondents particularly valued the flexibility of the Clubhouse structure, which they attributed to the lack of organizational hierarchy, the variety of activities provided to support the development of social skills, and the availability of activities outside, as well as within, office hours.

In addition, a large qualitative study of a Clubhouse in Canada[80] (Kmet 95) found that the co-leadership by peers and staff was fundamental to its culture. Other critical aspects included unconditional acceptance, promotion of self-efficacy and mutual respect. Members reported that being part of the Clubhouse reduced social isolation and stigma and provided them with a sense of purpose, accomplishment and belonging.

A variety of other activity-based group programmes aiming to improve people's confidence and community participation have also been studied. The Gould Farm programme, described as providing "recovery-focused, milieu treatment on a 700-acre working farm, that integrates counselling and medication with a work program providing opportunities for the development of daily living, social, and work skills as well as mental and physical

Table 3 Characteristics of included studies on social interventions delivered at the group or individual client level

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Community participation studies							
Chen et al[75]	China	Non-blinded RCT comparing Clubhouse model with standard care	Adults with SMI	75		Outcomes at 6 months. Primary: social functioning and self-determination.	Clubhouse group had greater improvement in social functioning and self-determination.
Heatherington et al[76]	US	Non-controlled pre-post study evaluating a residential farm program	Adults with SMI	86		Outcomes at 6 and 36 months: clinical and personal recovery; community participation.	Improved community participation at 36 months.

Table 3 Characteristics of included studies on social interventions delivered at the group or individual client level *(continued)*

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Varga et al[77]	Hungary	Non-blinded RCT comparing community social club with case management or TAU	Adults with SMI	92		Outcomes at 6 months: social functioning and social cognition.	Community social club and case management groups had better social function than TAU. Community social club group also had better social cognition.
Moxham et al[78]	Australia	Qualitative evaluation of Recovery Camp	Adults with SMI		85	Participants' personal goals and whether met during the camp.	Goals: connectedness; developing healthy habits; challenging myself; personal recovery. Most goals reported as met.
Prince et al[79]	US	Qualitative exploration of Clubhouse model	Clubhouse members (adults with SMI)		85	Exploration of benefits of Clubhouse membership and most helpful features.	Benefits: improved social skills, gaining confidence, social connection. Features: flexible, non-judgmental culture; equality of members and staff; evening and weekend activities; skills acquisition; sharing experiences; outreach support.
Rouse et al[80]	Canada	Participatory qualitative evaluation of Clubhouse model	Clubhouse members (adults with SMI) and staff		95	Explored how Clubhouse structures and ethos facilitated members' recovery.	Structures/ethos: mutual respect, promoting self-efficacy and autonomy, opportunities for social connection, providing purpose. Recovery: building identity and self-respect, acquiring skills, being part of an empowered community.
Saavedra et al[81]	UK	Qualitative evaluation of creative workshops in local art gallery	Adults with SMI, mental health staff, and workshop facilitator		95	Exploration of impact of workshop participation.	Main benefits: learning about artistic process; social connection; greater psychological well-being; challenging institutional attitudes; breaking down barriers between service users and staff.
Whitley et al[82]	Canada	Qualitative evaluation of a participatory video project	Adults with SMI		80	Exploration of participants' experiences of the project.	Project well received. Main benefits: skill acquisition; connectedness; meaningful focus; empowerment; personal growth.
Smidl et al[83]	US	Non-controlled, mixed methods pre-post evaluation of a therapeutic gardening project	Adults with SMI and staff	45	60	Outcomes at 3 months: motivation, social skills. Qualitative data from participants' journals.	Motivation ratings improved. Most participants and staff felt the project helped with social connection and skills. Qualitative: the project gave people a sense of purpose and pride.
Family intervention studies							
Kumar et al[84]	India	Assessor-blinded RCT comparing a brief psychoeducation programme with nonspecific control intervention	Key relatives of adults with SMI	69		Outcomes at completion of sessions. Primary: carer burden.	Intervention group experienced greater reduction in carer burden.
Martin-Carrasco et al[85]	Spain and Portugal	Multicentre, assessor-blinded RCT comparing psychoeducation intervention programme with TAU	Primary family caregivers of adults with SMI	96		Outcomes at end of intervention (4 months) and 4 months later. Primary: subjective and objective carer burden.	Intervention group experienced reduced subjective carer burden at both follow-ups. No difference between groups in objective carer burden.

Table 3 Characteristics of included studies on social interventions delivered at the group or individual client level *(continued)*

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Mirsepassi et al[86]	Iran	Implementation study of a psychoeducation service	Adults with SMI and their family members	60		Programme development, implementation and sustainability.	Implementation affected by: low referral rate; limited resources; poor literacy; excessive distance to travel to access service.
Perlick et al[87]	US	Assessor-blinded RCT comparing carer-only adaptation of family focused therapy with standard health education	Relatives of adults with SMI	88		Outcomes at end of intervention and 6 months later. Primary: carer burden.	Intervention group experienced greater improvement in carer burden at both follow-ups.
Al-HadiHasan et al[88]	Jordan	Qualitative process evaluation, nested within an RCT	Adults with SMI and their primary caregivers who received the family intervention		85	Impact of family psychoeducation intervention on recipients.	Carers reported improved health, well-being and coping. Service users reported better motivation. Both groups experienced improved self-confidence and social interaction.
Edge et al[89]	UK	Mixed methods, feasibility cohort study	African-Caribbean adults with SMI, their relatives or "proxy" family	65	65	Feasibility of delivering a culturally appropriate family intervention to "proxy families" (peer supporters or volunteers if no family).	Intervention highly acceptable. Most service users reported improved family relationships. Relatives' communication with service users and health professionals improved.
Higgins et al[90]	Ireland	Sequential mixed methods, single group, pre-post pilot evaluation of EOLAS programmes	Adults with SMI and their family members	45	55	All outcomes at programme completion. Service users and families: hope for the future and self-advocacy. Family members: perceptions of available social support.	No significant changes in quantitative outcomes. Qualitative: most participants found hearing other members' stories was helpful. Co-facilitation by peer support workers viewed positively, but some clinician facilitators appeared to lack skills to enable peer support worker co-facilitators to participate equally.
Higgins et al[91]	Ireland	Sequential mixed methods, single group, pre-post evaluation of EOLAS programmes	Relatives of adults with SMI	59	50	All outcomes at programme completion: confidence in ability to cope and to access help for relative; self-advocacy; hope for the future.	Participants experienced increased confidence and hope and were satisfied/very satisfied with the program. Qualitative: increased awareness of communication within the family; value of peer support.
Lobban et al[92] and Lobban et al[93]	UK	Assessor-blinded RCT comparing online psychoeducation + resource directory (RD) with RD alone; mixed methods evaluation and economic analysis	Relatives and close friends of adults with SMI. Qualitative sample: intervention group only	100 100	65 50	Outcomes at 12 and 24 weeks. Primary: carer well-being and experience of support. Secondary: costs of intervention and health and social care; experiences of the intervention.	No differences between groups in carer well-being and support. Intervention cost more than RD alone and delivered no better health outcomes. Qualitative: intervention positively received. Proactive support from the peer supporters particularly appreciated.

Table 3 Characteristics of included studies on social interventions delivered at the group or individual client level *(continued)*

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Nguyen et al[94]	Vietnam	Non-controlled, mixed methods, pre-post evaluation of family intervention and cost analysis	Adults with SMI and their caregivers	68	45	Outcomes at 1 year. Quantitative: service user functioning. Qualitative: intervention acceptability and feasibility. Cost analysis: service user and family income.	High participation (98%) and acceptability. Service user functioning improved, and one quarter secured a paid job. Financial burden on family decreased.
Peer-led/supported intervention studies							
Agrest et al[95]	Chile	Qualitative evaluation of peer supported intervention promoting recovery	Adults with SMI		80	Feasibility and acceptability of the intervention.	Peer support workers well received and helped engagement with community resources.
Beavan et al[96]	Australia	Self-report survey of Hearing Voices Network	Adults with SMI who attended network meetings	85	75	Cross-sectional data only. Descriptive and free-text responses.	Positive benefits included reduced isolation, gaining social skills and improved self-esteem.
Easter et al[97]	US	Non-blinded RCT comparing facilitation of advance directive by a peer-support worker or a clinician	Adults with SMI under the care of an ACT team	69		Outcomes at 6 weeks. Primary: empowerment. Secondary: self-esteem.	Modest advantage of using peer support workers in terms of empowerment and attitudes toward treatment.
Mahlke et al[98]	Germany	Assessor-blinded RCT comparing peer support + TAU with TAU alone	Adults with SMI	96		Outcomes at 6 months. Primary: self-efficacy.	Self-efficacy greater for intervention group.
O'Connell et al[99]	US	Assessor-blinded RCT comparing peer mentor + TAU with TAU alone	Adult inpatients with SMI, substance misuse and recurrent admissions	85		Outcomes at 9 months. Secondary: social function and sense of community.	Greater improvement in social function for intervention group.
Salzer et al[100]	US	Non-blinded RCT and qualitative evaluation of addition of peer support workers to community mental health services	Adults with SMI	69	60	Outcomes at 12 months: community participation, empowerment, therapeutic alliance. Qualitative: content of peer support.	Peer support group had greater community participation days.
Thomas et al[101]	US	Sub-analysis of intervention arm of RCT comparing peer support with TAU	Adults with SMI receiving the peer support intervention	89		Outcomes at 6 and 12 months: therapeutic alliance, empowerment and satisfaction.	Therapeutic alliance between participants and peer workers was high and positively associated with empowerment and satisfaction.
Social skills intervention studies							
Favrod et al[102]	France	Non-controlled pre-post evaluation of Positive Emotions Program for Schizophrenia	Adults with schizophrenia and severe negative symptoms	86		Follow-up assessment point not specified. Primary: social function.	Social function improved.

Table 3 Characteristics of included studies on social interventions delivered at the group or individual client level *(continued)*

	Country	Study design	Study population	Kmet score/100 (quant.)	Kmet score/100 (qual.)	Social outcomes investigated	Key findings
Hasson-Ohayon et al[103]	Israel	Non-blinded RCT comparing social cognition and interaction training (SCIT) vs. therapeutic alliance focused therapy (TAFT) vs. TAU	Adults with SMI under a psychiatric rehabilitation service	75		Outcomes at end of 6 month intervention and 3 months later. Primary: social function.	No difference between groups in social functioning.
Horan et al[104]	US	Non-blinded RCT comparing social cognitive skills training (SCST) delivered *in vivo* with SCST delivered in clinic or active control intervention	Adults with SMI	93		Outcomes at 3 months. Primary: social cognition. Secondary: social functioning.	SSCT groups both improved in social cognition. No between-group differences in social functioning.
Kayo et al[105]	Brazil	Assessor-blinded RCT comparing social skills training with an active control intervention	Adults with treatment resistant schizophrenia receiving clozapine	93		Outcomes at 20 weeks and 6 months. Primary: negative symptoms. Secondary: social skills.	No between-group differences in social skills or negative symptoms.

RCT – randomized controlled trial, TAU – treatment-as-usual, SMI – severe mental illness, quant. – quantitative, qual. – qualitative

health" was evaluated through an uncontrolled, pre-post study[76] (Kmet 86). Participants showed improvements in psychosocial functioning of medium effect size, and maintenance of gains six months after finishing the programme. At 36-month follow-up, it was reported that participants had subsequently been able to gain work or volunteering positions, attend mainstream education, or participate in hobbies.

A five-day "Recovery Camp" for people with SMI in Australia, staffed by mental health professionals, their students and a peer support worker, providing a range of recreational pursuits including physical, creative and relaxing activities, was evaluated qualitatively[78] (Kmet 85). Attendees identified specific goals at the start of the camp that the authors grouped into four main themes: feeling more connected, developing healthy habits, challenging oneself, and personal recovery. The findings suggested that the camp activities were particularly helpful in supporting individuals to make social connections and build on their existing strengths, resulting in them attaining many of the goals they had set.

A series of six-week creative art workshops for people with SMI and mental health staff in the UK, hosted in a local art gallery, was evaluated through a robust qualitative study[81] (Kmet 95). The workshops included guided gallery exhibitions, group discussion and making art. Participants described very positive experiences of the workshops and reported that their social networks, communication skills and confidence improved as a result. There was also a positive change in how staff and clients viewed each other, with greater mutual respect.

In Canada, a two-year group intervention for people with SMI provided training in video editing and production, and participants then worked in groups to make a film[82]. Across three cities, 23 participants produced 26 videos and 1,500 people viewed these at 49 community screenings. A qualitative evaluation at the end of the programme (Kmet 80) found that participants valued the opportunity to acquire new skills, and that the programme helped them feel more socially connected and enabled personal growth.

Similar benefits were reported from a therapeutic gardening project for people with SMI in the US[83]. The authors of this small, non-controlled, mixed methods, pre-post study used quantitative feedback (Kmet 45) and qualitative evaluation of participant journals (Kmet 60) to assess experiences of the project. At three-month follow-up, there was an improvement in participants' motivation and social interactions, and many experienced positive gains in respect of personal responsibility and achievement.

Family interventions

In total, 11 papers assessing family interventions were identified, of which four reported on quantitative studies[84-87], three of which were RCTs[84,85,87], and one described a programme development and implementation[86]. One study was qualitative in design[88], and the remaining six employed mixed methods[89-94].

Of the mixed methods papers, two reported on the EOLAS (Eolas is the Irish word for knowledge) family information programme study[90,91], and two on the REACT (Relatives' Education And Coping Toolkit) RCT[92,93]. Two studies were conducted in the UK[89,92,93], and one each in India[84], Iran[86], Ireland[90,91], Jordan[88], Spain and Portugal[85], the US[87] and Vietnam[94].

The mean Kmet score for quantitative papers was 75 and ranged from 100[92,93] (one study) to 45[90]. The mean score for qualitative papers was 59 and ranged from 85[88] to 45[94].

The evaluated family interventions were varied, although all included psychoeducational elements. A number also included cognitive behavioral strategies[85,87,89,92,93]. The interventions were typically delivered in secondary or tertiary community care settings, mostly outpatient or community clinics[84-87,89-91]. One of the UK interventions was virtual[92,93]; the Jordanian family intervention was carried out in the family home[88]; and one paper described an intervention delivered at the local community level to residents of a rural commune in Vietnam[94]. Two studies evaluated family interventions that were co-facilitated by peers alongside clinicians[90-93].

Carers receiving a family intervention showed significantly reduced caregiver burden compared with carers in the control group in three RCTs of high[85,87] to moderate[84] quality. The two high-quality trials each evaluated psychoeducational programmes based on a cognitive-behavioral approach. One of them (Kmet 96), conducted across 23 centres in Spain and Portugal, targeted families of people diagnosed with schizophrenia or schizoaffective disorder[85]. The other (Kmet 88) was carried out across three US centres and comprised a caregiver-only adaptation of family focused therapy versus standard health education for relatives of people diagnosed with bipolar I or II disorder[87]. Both trials reported sustained decreases in carer burden at four and six months follow-up respectively.

The third RCT (Kmet 69) evaluated a brief psychosocial family intervention in a LAMI setting (Northern India)[84]. This intervention consisted of two initial psychoeducation sessions for families of people with schizophrenia, followed by six multi-family group sessions. The burden of care was significantly reduced at the completion of sessions. The authors postulated that the involvement of multiple families in the sessions, along with psychoeducation, might explain their positive outcomes compared with negative studies from elsewhere in India. Poor confidence in psychosocial treatments amongst the general public in the country was cited as a possible reason for the high rate of treatment dropout[84].

Relatives or close friends of people with psychosis or bipolar disorder participated in a high-quality (quantitative Kmet 100) mixed methods study, including an RCT, comparing an online family intervention (REACT plus access to a resource directory) with a control intervention comprising access to the resource directory only[92,93]. The REACT intervention consisted of 12 online psychoeducation modules, alongside a group forum and a confidential direct messaging service, that were both moderated by REACT supporters (trained relatives with lived experience of supporting someone with SMI). There were no significant between-group differences in social outcomes, and both groups showed improved well-being and experience of support[92,93].

A pre-post uncontrolled proof-of-concept mixed methods study of moderate quality[94] (quantitative Kmet 68) trialled a community-based family intervention for Vietnamese people with SMI and their families. Staff from a local social organization, the Women's Union, facilitated psychoeducation group meetings over 12 months, alongside community awareness activities (e.g., talent shows and a summer programme for school students in the commune). The authors reported a significant positive impact on the personal functioning of service user participants, with approximately one quarter achieving a paid job[94].

Several qualitative studies of varying quality reported that family interventions were associated with potential improvements in social inclusion for all participants, service users and family members alike[88,89,91]. An Irish study of an information programme for families of people with SMI[89] (qualitative Kmet 50) and a British study of a culturally-adapted family intervention for African-Caribbean people diagnosed with schizophrenia and their families[91] (qualitative Kmet 65) both reported that participants learnt more constructive ways of communicating with each other and experienced better family relationships. A high-quality (Kmet 85) Jordanian study[88] reported that service user and family participants gained skills that made them feel more equipped to cope with daily life and/or caregiving and improved confidence and empowerment, leading to an enhanced social life.

Only two papers[92,94] reported on cost analyses. A health economic analysis found that the virtual family intervention delivered in the UK (REACT) incurred higher costs and resulted in no better health outcomes than the comparison, making it very unlikely that the intervention was cost-effective at a standard willingness-to-pay threshold of £20,000[92]. In contrast, a health economic analysis based on pre-post data reported in the Vietnamese study[94] showed a significant increase in the annual income of service user participants (from nearly US$80 to around US$120), with an associated reduction in the annual financial burden on the family (from around US$1500 to US$1100).

Two studies were specifically designed to explore the implementation of family interventions for people with SMI: the above-mentioned Vietnamese study[94] (qualitative Kmet 45) and a study in Iran[86] (Kmet 60). Referral rates were low in the Iranian study of a psychoeducation service (comprising eight service user group sessions and six multiple family group sessions in parallel), despite the provision of information on the programme to hospital clinicians[86]. The authors concluded that poor awareness and negative attitudes towards psychosocial treatments amongst clinicians were major implementation barriers requiring cultural and organizational change. In addition, obstacles to families' participation included the need to travel long distances to access the sessions, as well as poor literacy amongst a substantial minority[86].

Several facilitators of implementation were reported in the Vietnamese study[94], although it should be noted that this component of the study was of low quality. A good fit between the characteristics of the family intervention and the facilitators (Women's Union staff employed in a community-based "task-shifting" approach) was highlighted as especially suitable for resource-constrained settings. The importance of providing facilitators with training and ongoing supervision, to ensure that they had adequate confidence and skills to provide the family intervention, was also emphasized[94]. Finally, the "whole community" nature of the intervention and the fact that meetings took place in participants' houses in each village at a time decided by participants was thought to facilitate the very high participation rate (98%).

Both UK studies provided useful insights into optimal delivery and implementation of family interventions[89,92,93]. In the above-mentioned uncontrolled feasibility trial of a culturally adapted family intervention for African-Caribbean people diagnosed with schizophrenia and their families[89], the most frequently cited barriers to implementation were resource constraints and service pressures (demanding caseloads and the need to prioritize emergencies over routine care) that curtailed therapists' capacity to deliver therapeutic interventions. Difficulties were also noted in recruiting suitably qualified and experienced therapists. Competing demands also hindered relatives' engagement in the REACT virtual family intervention[92], and some reported difficulty processing the new information provided during the intervention due to feeling too stressed.

Peer-led and peer-supported interventions

Seven publications evaluating peer-led or peer-supported interventions that did not fit into any of the other six intervention categories were identified[95-101]. Five studies were quantitative[97-101], four of which were randomized trials[97-100], one was qualitative[95], and two used mixed methods[96,100]. Four were conducted in the US[97,99-101], and one each in Australia[96], Chile[95] and Germany[98].

A robust RCT in Germany[98] (Kmet 96) found that one-to-one peer support provided over six months within a community mental health service was associated with greater self-efficacy for participants who received the intervention compared to those who did not. The mean number of meetings between participants and peer support workers (12.2±9.6) and the high retention rate (75% versus 60% in the comparison group) also suggested that the intervention was highly acceptable.

In the US, a randomized trial[99] (Kmet 85), evaluating the addition of peer mentors to standard care for people with SMI who were high users of inpatient care, found that it led to greater improvement in social functioning (as well as reduction in symptoms, substance abuse and inpatient service use) compared to standard care at nine-month follow-up. However, one third of those assigned a peer mentor had no contact with him/her during the study period. Participants who engaged with their peer mentor differed from those who did not (they were more likely to be white, had completed more years of formal education, had fewer psychiatric symptoms and physical health problems, and used less alcohol), thus limiting the strength and generalizability of the findings.

A community-based intervention delivered by peer workers and community mental health workers in Chile[95] (Kmet 80) aimed to promote recovery and community reintegration by strengthening the individual's engagement with community resources, family and friends. Qualitative evaluation showed that the intervention was feasible, but concerns were expressed about its time-limited nature, and some participants were worried that their neighbours would know they were being treated for a mental illness when they saw staff visiting them at home. Nevertheless, most participants reported that they enjoyed meeting with the peer support worker. The intervention helped people gain a greater understanding of the importance of participating in community activities and reconnecting with their social supports. Peer workers were also reported to facilitate better relationships between clients and mental health staff.

The addition of certified peer specialists to community-based mental health services was investigated in the US through a trial (Kmet 69) that included a qualitative component[100] (Kmet 60). Those who received the intervention did not differ from controls in their community participation or empowerment at six or 12-month follow-up. However, of the 50 participants allocated to receive the intervention, only 29 met with their peer worker more than once. In a post-hoc analysis at 24-months follow-up, participants who did engage with their peer supporter spent more days participating in community activities compared to those who did not. The qualitative findings showed that the peer workers provided the expected support, including help with using public transport, addressing substance misuse issues, and accessing community activities. The authors suggested that the poor engagement with the intervention may have been due to participants finding it too intrusive or assertive, but they also commented that non-engagement could represent positive self-determination.

A related sub-study[101] reported a strong positive association between the quality of the working alliance between the peer support worker and the participant (rather than the number of contacts made) and participants' empowerment and satisfaction with the service.

A trial assessed the use of peer support workers to facilitate advance directives[97] (Kmet 69). Clients of an ACT team were randomly assigned to draw up an advance directive in collaboration with either a peer support worker or a mental health clinician. The advance directive aimed to prevent involuntary treatment during a future mental health crisis by clarifying preferences and plans prior to the crisis. The authors reported a modest advantage of using peer support workers in terms of ratings of service users' empowerment and attitudes towards treatment, but no differences between peer support or clinician facilitated directives in preventing involuntary admission.

Finally, a small mixed methods evaluation of peer-led Hearing Voice Network groups in New South Wales, Australia[96] (quantitative Kmet 85, qualitative Kmet 75) found that the groups helped attendees feel less socially isolated and gain a better understanding of their voice-hearing experiences.

Social skills interventions

Only four papers evaluating social skills training interventions for people with SMI that met our inclusion criteria were identified[102-105], all of which were quantitative. The studies were conducted in the US[104], Brazil[105], France[102] and Israel[103].

Three of the papers reported on RCTs[103-105], each investigating a different social skills training intervention. A three-arm trial[104] (Kmet 93) investigated whether the inclusion of some *in vivo* community-based sessions within a 24-session social cognitive skills training programme enhanced the generalization of improvements in social cognition to "real world" social functioning. Although both forms of social skills training (clinic-based or *in vivo* enhanced) were associated with greater improvements in emotional intelligence, facial emotional recognition and empathy than an active control intervention, there were no differences between the three trial arms in any measure of functioning. The authors suggested that their results could be due to the low sensitivity of their outcome tools.

However, similar findings were reported from an RCT[103] (Kmet 75) evaluating social cognition and interaction training, a manualized group-based intervention, versus therapeutic alliance focused therapy or TAU delivered over six months to patients of psychiatric rehabilitation services. Unlike the previous trial, the primary outcome in this study was social functioning rather than social cognition. Although both intervention groups showed greater improvement in various aspects of social cognition compared to TAU controls, there was no difference between groups in social functioning at three-month follow-up. Of note, only around one third of participants completed all the intervention sessions.

A small but high-quality (Kmet 93) trial[105] compared a 20-week, group-based social skills training programme, including role play and homework exercises, with an active control intervention for people with treatment-resistant schizophrenia receiving clozapine therapy. The study was designed to assess improvement in negative symptoms, with social skills as a secondary outcome. No between-group differences were found in social skills (or negative symptoms) at the end of the intervention or at six-month follow-up. The authors noted that their measure of social skills had not been formally standardized with people with SMI and thus potential benefits may have been missed.

In contrast to the findings of these three trials, significant improvements in negative symptoms and social functioning were reported in a small, pre-post study[102] (Kmet 86) assessing the Positive Emotions Program for Schizophrenia. The intervention comprised eight weekly group sessions to address anhedonia and apathy amongst people with SMI through reinforcing positive emotions and developing positive thinking. Apart from the study design limitations, participants were relatively young compared to the other studies described in this section, which may partially account for the more positive findings.

NARRATIVE SYNTHESIS

Overall pattern of findings

We identified an encouraging level of recent research evaluating social interventions for people with SMI. We included interventions with a more established evidence base (supported accommodation, supported employment, and family interventions) as well as those at an earlier stage of development (supported education, peer led/supported interventions, and interventions aiming to improve social skills or community participation). Although we found higher numbers of studies evaluating supported accommodation and supported employment compared to the other interventions, most of which were of high quality, we also identified a growing evidence base for peer-led/supported interventions. However, there was a paucity of recent studies assessing the cost-effectiveness of the interventions.

Our results corroborate previous studies indicating the value of investing in the HF model of supported accommodation[45,106], the IPS model of supported employment[72], and family psychoeducation interventions[107], but we also identified research showing that a range of supported accommodation, supported employment and family interventions should be available, to allow tailoring to individuals' needs and context rather than adopting a "one size fits all" approach[108-110].

We also noted considerable research interest in augmentation strategies to enhance outcomes from social interventions, particularly supported employment and social skills training, where supplements to the standard interventions mainly focused on addressing the cognitive impairments associated with SMI. However, results are rather disappointing so far: despite their success in improving cognitive ability, most of these augmentation strategies do not seem to lead to transferable "real life" skills. Nevertheless, this is an ongoing area of research, and we identified two studies where augmentation of supported employment (training in social skills for the workplace, and a behavioral psychological approach, "errorless learning")[55,65] appeared to be associated with better outcomes.

The majority of studies that investigated peer-led/supported interventions reported positive findings, including four randomized trials[97-100]. The addition of peer workers in the delivery of some of the other social interventions included in our review was also commonly noted, including as staff of recovery colleges[46-50] and co-facilitators of family interventions[90-93], providing knowledge and experience distinct from that of health professionals. Peer involvement was noted to be particularly helpful for people in building confidence and social connections[47,50], gaining a better understanding of their mental health issues[96], and improving engagement with mental health services[95].

Our review also identified a number of common facilitators of successful implementation of social interventions. These included ensuring that relevant stakeholders were authentically supportive of the plans, and that local policies and resources were in place to support the intervention; and providing training for those delivering the intervention, and ongoing supervision and discussion forums to support staff, share ideas and prevent mission drift. Monitoring fidelity and progress through the collection of routine metrics or outcome data was also considered helpful in sustaining the intervention, and the identification of local champions to keep everyone focused was commonly recommended[37,42,43,66].

Several barriers to implementation were also identified. For example, in supported accommodation studies, barriers included poor local housing availability, and stakeholder policies that did not align with the plans or obstructed implementation. In supported employment studies, barriers included high local unemployment rates, and welfare benefits systems that disincentivized or prevented people taking up part-time paid employment. In studies of family interventions, obstacles included negative referrer attitudes and practical obstacles such as sessions being held too far from where people lived[86].

Factors that influenced findings

Context

Many of the studies highlighted the importance of considering the influence on the results of the context in which the studies were conducted. This is particularly relevant to the supported accommodation literature, since housing policy varies from one setting to another (for example, in the supply of social housing and the rules pertaining to eligibility) and there are major international differences in the way in which mental health care has evolved in the post-deinstitutionalization era.

Many of the supported accommodation studies we identified focused on HF, which has been shown to be effective in facilitating stable housing for homeless people with mental health problems, usually SMI, but whose impact on other outcomes is less clear[45,111]. The HF model is popular in the US and Canada because of the high levels of homelessness amongst those with SMI, secondary to deficiencies in health, social care and welfare benefits coverage[112], whereas other countries that have more universal access to these systems (such as the UK) have, historically, seen far lower levels of homelessness amongst people with SMI. The UK's approach has evolved over recent decades into providing a range of types of supported accommodation, organized into graduated pathways, with the expectation that people progress from higher to lower supported settings. This has the disadvantage that people have to make repeated moves as they progress in their recovery.

The impact of HF even varied from one Canadian city to another. Stergiopoulos et al[36] concluded from their trial in Vancouver that, for those with psychosis, HF should be combined with ACT to be effective, whereas Aubry et al[28] did not find this combination to be effective in improving community functioning in a smaller Canadian city.

The study of enhanced IPS conducted in China[65,70] noted that cultural factors specific to the local context influenced the success of the intervention. Likewise, cultural factors were found to be relevant in some of the family intervention studies we included, with both the community-based intervention developed for the Vietnamese context[94] and the culturally-adapted intervention for African-Caribbean people in the UK[89] showing promise. For the latter, it was concluded that the greatest adaptation should be in its "ethos of delivery", and that this would rely on the family therapists' cultural competency and skills. Similarly, the inclusion of group therapy sessions facilitated by a proactive moderator within a brief psychosocial family intervention in India was considered a useful cultural adaptation[84].

In contrast, specific challenges may arise in certain contexts, such as those identified in relation to the implementation of a supported employment programme in a forensic setting[69], including stigma and the difficulty of gaining employment when an individual has a criminal history.

Taken together and consistent with the implementation literature[113], these findings highlight the need to consider all relevant contextual factors and make appropriate, specific adaptations when "importing" social interventions from other countries or settings.

Inconsistent terminology

Our interpretation of the evidence was challenged by the lack of a consistent terminology used to describe the interventions. This was particularly obvious in the supported accommodation studies. This issue has been previously acknowledged, and a common taxonomy has been proposed[114,115]. However, our findings suggest that researchers are not yet following this suggestion.

Whilst the evidence for HF appears strong in regard to improving housing stability outcomes, a number of studies used this term to describe models of supported accommodation that did not appear to reflect the classic HF model, with staff on-site rather than visiting[32,41], or with accommodation provided in congregate rather than self-contained settings[35]. Of note, the high-quality trial conducted by Somers et al[35] found no difference in housing outcomes for those who received the classic version of HF (visiting support) compared to those who had on-site support. This suggests that further trials comparing different models are warranted, although the logistic difficulties of doing so have been highlighted recently[116].

Heterogeneity of the target population

We attempted to minimize variation in the target population by selecting those studies where the majority of participants had SMI. However, this was not always clearly described, particularly in studies reporting on supported education and peer-led/supported interventions, possibly due to ideological considerations about diagnostic "labels" and the methodological distinctions between quantitative and qualitative studies.

In addition, the difficulties in taxonomy mentioned above also extended sometimes to the target population for a specific intervention. For example, the HF model of supported accommodation is very similar to the UK's "floating outreach" services, but the latter tend to target people with less severe mental health problems[33].

Content of interventions

In general, the studies described the specific intervention being evaluated relatively well. However, there was considerable heterogeneity in the range of interventions evaluated within each of our seven categories. Some were more established and well defined (e.g., HF, IPS, family psychoeducation), whereas others (most notably in the community participation and peer-led/supported categories) were more varied and not at a stage of development where internationally accepted models or fidelity criteria exist (an exception being the Clubhouse). Nevertheless, most studies included a description of how staff were trained and supported to deliver the intervention and, where relevant, most included an assessment of fidelity.

There was, however, considerable variation in the length of the intervention phase in different studies evaluating the same intervention (or the same type of social intervention). This was particularly noted in the peer-led/supported group of studies and raises questions about the optimum duration of interventions resulting in positive outcomes.

Strength of the evidence

The aggregation of findings of the studies we identified was confounded by some limitations, including the heterogeneity in what constituted a positive outcome, the range of measures and metrics used to assess similar outcomes, the use of bespoke tools that lacked psychometric testing, the use of varying follow-up periods, and the variation in what constituted usual care in comparison groups. For example, amongst supported employment studies, success could refer to the achievement of competitive employment, sheltered employment or other vocational activity, and various outcome metrics were reported (employment rates, duration of employment, hours worked, and wages earned).

Bearing these limitations in mind, our findings provided good evidence that HF is effective at improving housing stability for homeless people with SMI; IPS is effective at improving employment outcomes; and family interventions facilitate better social connections and relationships, improved functioning and reduced carer burden. We also found consistent good evidence for peer-led/supported interventions. We identified a number of well-conducted trials evaluating cognitive interventions aimed to enhance people's social skills or outcomes from supported employment but, whilst these led to improvement on measures of cognition, they rarely translated to better social functioning.

Studies evaluating interventions to enable people's community participation were diverse in approach and of lower quality, but they reported similar benefits: improved social function, reduced social isolation and increased confidence and empowerment.

All the studies investigating supported education reported on evaluations of a single recovery college and had significant limitations, including small sample sizes, lack of control groups and sampling biases. Nevertheless, consistently positive findings are promising and suggest that these interventions can assist some people to achieve personal and educational goals.

Generalizability

Most of the studies we identified were conducted in high-income countries, with only 11 (out of 72) coming from outside the US, Canada, Europe or Australia, limiting generalizability to other settings. The contextual considerations and variability in target populations detailed above also limit the generalizability of findings.

The majority of participants in the studies were male, and this may mean that findings are less relevant for women. In addition, when the interventions were delivered alongside existing mental health services, the latter were often not described at all. This applied particularly to peer involvement studies, limiting generalizability.

Further issues, common to all complex intervention research, include the fact that the implementation of many of the interventions we examined was driven by a local enthusiast and supported by the framework of a research study, and therefore wider implementation may be less successful.

DISCUSSION

Our review highlights the value of investment in supported accommodation, supported employment and family psychoeducation for people with SMI, in order to foster their social and economic participation, and provides evidence of positive outcomes associated with peer involvement in the development and delivery of social interventions. It also indicates that greater consistency in the parameters and methods of studies evaluating the same intervention (such as the core elements, the length of the intervention, the outcomes assessed, and the time frames over which data are collected) is required to improve the evidence base. The development of a shared language to describe participants with SMI will also be important in future research, given the reluctance to use clinical "diagnosis" in some of the papers we included.

Despite the various limitations of the studies we identified, there was considerable high-quality evidence for several of the interventions examined. However, our findings particularly emphasize that social interventions, whether delivered at the service or individual level, need to be tailored to the person and context specific. This is unsurprising, since their aim is to influence positively the individual's social world. In other words, social interventions are, perhaps, the most complex of all mental health interventions.

Furthermore, although studies of the same or similar interventions may report similar "positive" findings, this may obscure a more nuanced interpretation. In regard to supported employment, there is increasing concern as to whether being employed for minimal hours in a low wage job is delivering the secondary gains and "material or ontological security" anticipated from competitive employment[117]. This highlights the need for a more critical review of what is considered a success in this field. In addition, despite the evidence supporting IPS, its success rate in facilitating competitive employment has not improved since 2011[118].

Similarly, the supported accommodation literature is dominated by studies of HF. Yet, housing stability, the primary outcome used to assess its effectiveness, whilst clearly important, does not appear to provide the platform for consistent improvement in other social benefits. Studies of other forms of supported accommodation report on different important outcomes, such as successful progression to more independent settings, reflecting the different systems that operate in different countries, but the impact on social (and clinical) functioning has been less commonly studied.

Killaspy et al[33,34] concluded, from their national research programme into mental health supported accommodation in the UK, that a range of different types of accommodation should be provided to allow for tailoring of the most appropriate setting and support for people with different needs, rather than investing in only one model such as HF. They also highlighted the importance of considering the safety of individuals when making decisions about the most suitable type of accommodation, given the high prevalence of severe self-neglect and vulnerability to exploitation amongst this group. In addition, a qualitative meta-synthesis of the experiences of people living in mental health supported housing[119] highlighted that people supported through the HF approach had quite varied experiences of reconnecting within their community, with some reporting social exclusion.

The supported employment studies also highlighted an important element in terms of international adoption: collectivist versus individualistic cultural context. In particular, the study from China by Zhang et al[65] suggested that the intervention could (and should) not target the individual alone, but rather the whole family. This is also relevant in the supported accommodation field, where the vast majority of research has been conducted in Western settings with a culturally congruent goal of achieving independent living, while this may be far less important in countries or communities with stronger family-based cultures.

The extent to which other social interventions should take cultural considerations into account remains relatively unexplored, but the potential relevance of cultural adaptations for the implementation of these interventions has been acknowledged[120] and, for people with SMI, it appears to have been considered most often in relation to family interventions[121].

A number of studies highlighted the benefits of delivering social interventions within a recovery-oriented framework[45-50,62,76,78]. In supported accommodation settings in the UK, recovery-based practice has been shown to assist individuals to progress to more independent accommodation[34]. However, few staff training approaches have proved effective in improving recovery-based practice[29,122,123]. As highlighted by Agrest et al[95] in their study from Chile, one element that may assist services with recovery orientation is the use of peer support workers. The first step is to allow adequate time and flexibility for a trusting, therapeutic alliance to be established between the peer worker and the service user[101].

Our findings concerning the benefits of peer-led/supported interventions in the delivery of mental health services synergize well with the results of a previous Cochrane review[124]. However, attrition was quite high in some of these studies, suggesting poor acceptability. Of course, poor engagement can be due to a range of personal or practical issues (such as illness severity or service accessibility). Nevertheless, positive "chemistry" in the relationship between peer support worker and client appears critical to successful implementation[101]. Perhaps more work is needed to develop processes for increasing compatibility and "matching" between the two parties to maximize uptake.

Despite their robust evidence base, the implementation of family interventions in mental health services continues to present a challenge, often secondary to resource constraints[89]. In LAMI countries, negative attitudes towards people with SMI and a lack of understanding of the potential benefits of psychosocial approaches may further hinder take-up, alongside practical issues such as illiteracy and inaccessibility[86]. Our evidence suggested that family psychoeducation is gaining popularity, possibly due to it being perceived as more feasible to deliver. However, surprisingly, we identified only one study evaluating an online family psychoeducation package for people with SMI[92,93], a format which appears to be gaining traction for other groups such as children and adolescents[125].

We found that interventions aiming to support the community participation of people with SMI demonstrated a high degree of innovation, with promising initial results. This is clearly an area of growing interest, although research into which types of interventions are most effective and how to address implementation challenges is at a fledgling stage of development[126]. However, one of the main strengths of these interventions is their diversity and creativity, so it may well be counterproductive to "over-operationalize". Nevertheless, further research can help to identify critical ingredients such as the structural and relational components that provide the opportunity for peer support, social connection and personal growth.

This might be assisted by learning from studies of the Clubhouse approach. We identified considerable benefits for this approach, in keeping with a recent review[127] which concluded that Clubhouse programmes are worthy of support as one component of a spectrum of rehabilitative services for people with SMI, providing a highly acceptable and useful vehicle for increasing social integration and social competence. The authors also noted that further trials are needed to compare the effectiveness of these programmes with IPS in terms of employment outcomes[127].

We identified surprisingly few studies evaluating social skills training programmes that assessed social outcomes relevant to this review. Most evaluated cognitive interventions[103-105] which were also assessed for their ability to enhance supported employment[51,54,56,57,63,64]. The results were disappointing, with improvements in cognitive function rarely generalizing to social outcomes such as employment or social functioning. Whilst this may have been due to poor uptake[51,54,103], a recent, robust trial of social cognition and interaction training for people with schizophrenia[128] reported no differences in social cognition or social functioning at three-month follow-up compared with an active control group. Sub-analysis of those who attended at least half the planned sessions did not alter these negative findings.

Although we excluded studies that reported only on quality of life rather than any of our social outcomes of interest, we did not exclude health economic papers on this basis, since most use quality of life for the calculation of Quality Adjusted Life Years. Nevertheless, we identified very few health economic studies. The main exception was in research into family interventions[92,93]. We also identified a study showing that, as people move from higher to lower supported accommodation, the total costs of care decrease[34], presumably since the move signifies gains in the person's ability to manage in a more independent setting.

Our review was wide-ranging in scope and included seven domains of social intervention that targeted people with SMI. A strength of our approach was the use of narrative synthesis to summarize a diverse range of quantitative, qualitative and mixed methods research reporting on both effectiveness and implementation of interventions. However, the difficulties in defining social interventions, as noted in our introduction, may have led to exclusion of relevant studies.

We restricted our search to studies that focused on people with SMI to ensure the relevance of our findings for this group. However, studies that targeted other diagnostic groups or that did not report the diagnoses of participants, and were thus excluded, may also have findings relevant to those with SMI. Similarly, studies that did not report on social outcomes within our scope were excluded and, again, may provide evidence relevant to people with SMI.

To address these issues, we employed an iterative approach to ensure consistency in the decision-making process for study inclusion, with each paper considered by two assessors and a third assessor where agreement was not reached, alongside frequent meetings of the authorship group to discuss decisions. In addition, each paper was assessed for quality using a robust assessment tool which allowed us to emphasize findings with greater validity.

Finally, as we only included papers published in the English language, we may have excluded significant contributions produced in other languages, and studies from LAMI countries may have been under-represented.

CONCLUSIONS

Our review identified an encouraging level of interest in research into social interventions for people with SMI. Of note, the service level interventions with the strongest evidence (supported accommodation and supported employment) have often been fostered by specific policy and government investment (e.g., HF in Canada and the US; IPS in the US, UK and Australia), which has facilitated their widespread adoption and ongoing research, whilst other effective interventions, such as family interventions, have struggled with implementation.

This may be due to policy-makers being more receptive to the potential cost benefits of some interventions (for example, through reduced use of inpatient care and greater employment) than others. However, these kinds of "hard outcomes" do not always reflect the authentic success of an intervention. Many of the studies we included reported positive but "softer" outcomes, such as gaining confidence and building social connections. This invites the question as to whether such outcomes, whilst clearly valued by people with SMI, are valued enough by society to convince governments to invest in the relevant interventions.

In addition, we aimed to identify the social interventions that are most effective in increasing the social and economic participation of people with SMI, yet many of the studies reported on interventions that took place within settings where participants mixed mainly with other service users. Whether this represents social participation depends on the definition of the term. There is growing evidence to suggest that loneliness is a driver of poor health and social outcomes and therefore any opportunities to support social connection should be valued[129].

The research we identified on supported education is also relevant here. All the studies we identified evaluated recovery colleges. Yet, only a few years ago, research in this field focused on interventions to support individuals in mainstream educational settings[130]. Perhaps this indicates a growing awareness that specialist mental health settings should be considered part of the "mainstream", or certainly an important component of the whole system of services that facilitates "mainstream" participation.

A further tension in this field is the lack of priority given to the use of social interventions compared to pharmacological and, to some degree, psychological interventions. Whilst relatively small benefits from medication are often tolerated amongst those with longer-term SMI, there appears to be a higher threshold for the expected effectiveness of social interventions. The low uptake of some of the interventions we identified was concerning, but no worse than other treatments that are widely considered essential aspects of multidisciplinary care. A recent systematic review[131] reported non-adherence to psychotropic medication amongst people with SMI at 49%[131], and uptake of psychological interventions amongst this group in the UK is under 20%[132]. Our findings suggest that greater consumer involvement during the development of interventions may assist acceptability and uptake.

Finally, our review identified a number of recommendations for future research in this field. First, a clear definition of what constitutes a social intervention is needed. Similarly, agreement on relevant, high-level social outcomes to be reported in studies of different types of social intervention should be considered. A standard taxonomy should be adopted by journals publishing studies on specific models of care, such as supported accommodation and supported employment, to enable easier interpretation and comparison of results. Further discussion is also needed on how to address the lack of detailed description of participants' diagnoses, particularly in the qualitative and peer support literature. Finally, given the limitations of the studies we identified and the influence of contextual issues, further multisite RCTs are needed, even for the interventions for which we found the strongest evidence.

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Increased risk for COVID-19 breakthrough infection in fully vaccinated patients with substance use disorders in the United States between December 2020 and August 2021

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Individuals with substance use disorders (SUDs) are at increased risk for COVID-19 infection and for adverse outcomes of the infection. Though vaccines are highly effective against COVID-19, their effectiveness in individuals with SUDs might be curtailed by compromised immune status and a greater likelihood of exposures, added to the waning vaccine immunity and the new SARS-CoV-2 variants. In a population-based cohort study, we assessed the risk, time trends, outcomes and disparities of COVID-19 breakthrough infection in fully vaccinated SUD patients starting 14 days after completion of vaccination. The study included 579,372 individuals (30,183 with a diagnosis of SUD and 549,189 without such a diagnosis) who were fully vaccinated between December 2020 and August 2021, and had not contracted COVID-19 infection prior to vaccination. We used the TriNetX Analytics network platform to access de-identified electronic health records from 63 health care organizations in the US. Among SUD patients, the risk for breakthrough infection ranged from 6.8% for tobacco use disorder to 7.8% for cannabis use disorder, all significantly higher than the 3.6% in non-SUD population (p<0.001). Breakthrough infection risk remained significantly higher after controlling for demographics (age, gender, ethnicity) and vaccine types for all SUD subtypes, except for tobacco use disorder, and was highest for cocaine and cannabis use disorders (hazard ratio, HR=2.06, 95% CI: 1.30-3.25 for cocaine; HR=1.92, 95% CI: 1.39-2.66 for cannabis). When we matched SUD and non-SUD individuals for lifetime comorbidities and adverse socioeconomic determinants of health, the risk for breakthrough infection no longer differed between these populations, except for patients with cannabis use disorder, who remained at increased risk (HR=1.55, 95% CI: 1.22-1.99). The risk for breakthrough infection was higher in SUD patients who received the Pfizer than the Moderna vaccine (HR=1.49, 95% CI: 1.31-1.69). In the vaccinated SUD population, the risk for hospitalization was 22.5% for the breakthrough cohort and 1.6% for the non-breakthrough cohort (risk ratio, RR=14.4, 95% CI: 10.19-20.42), while the risk for death was 1.7% and 0.5% respectively (RR=3.5, 95% CI: 1.74-7.05). No significant age, gender and ethnic disparities for breakthrough infection were observed in vaccinated SUD patients. These data suggest that fully vaccinated SUD individuals are at higher risk for breakthrough COVID-19 infection, and this is largely due to their higher prevalence of comorbidities and adverse socioeconomic determinants of health compared with non-SUD individuals. The high frequency of comorbidities in SUD patients is also likely to contribute to their high rates of hospitalization and death following breakthrough infection.

Key words: Substance use disorders, COVID-19 breakthrough infection, vaccination, cannabis use disorder, cocaine use disorder, comorbidities, socioeconomic determinants of health

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Substance use disorders (SUDs) are common: ~10.8% of adults in the US have had a problem with drug use[1,2]. SUDs are often associated with multiple comorbid conditions that are known risk factors for severe outcomes of COVID-19 infection, including cardiovascular, cerebrovascular, immune, hematological, pulmonary, metabolic, oncological, hepatic, renal, infectious, neurological and psychiatric diseases[3-11]. Additionally, studies from the early pandemic showed that patients with SUDs – including alcohol use disorder, cannabis use disorder, cocaine use disorder, opioid use disorder, and tobacco use disorder – were at increased risk for COVID-19 infection and associated severe outcomes, especially among African Americans[6].

In the US, three vaccines have been approved since December 2020: two mRNA vaccines developed by Pfizer-BioNTech and Moderna, and an adenovirus vaccine by Johnson & Johnson. Clinical trial data showed an efficacy of 95% for the Pfizer-BioNTech[12], 94.1% for the Moderna[13] and 66.3% for the Johnson & Johnson vaccine[14] in preventing COVID-19 infection. Clinical trials for COVID-19 vaccines did not explicitly include SUD patients, though they did include – for example, in the clinical trial for Pfizer-BioNTech vaccine – participants with a range of other diseases, including cancers, cardiovascular diseases, human immunodeficiency virus (HIV) infection, and renal diseases[12]. Currently, there are no systematic studies examining the real-world effectiveness of COVID-19 vaccines in populations with various SUDs. Vaccines are very effective, but breakthrough infections have been recorded[15-18], highlighting the need to identify populations that might be most vulnerable, as we have entered a worrisome new phase of the pandemic.

Studies have shown that individuals with compromised immune function, such as organ transplant recipients and cancer patients, have limited rates of SARS-CoV-2 IgG seroconversion[19-23]. Drugs and alcohol affect immune function, which is likely to contribute to the higher risk for infections in individuals with SUDs[3,6,24,25]. Thus, we hypothesized that individuals with SUDs could be at increased risk for vaccine breakthrough COVID-19 infection.

In this study, we estimated the risk for breakthrough COVID-19 infection among vaccinated patients with various SUDs compared to matched vaccinated individuals without SUDs. We also examined how the rate of breakthrough cases changed between December 2020 and August 2021.

METHODS

Study population

We used the TriNetX Analytics network platform[26], which allows access to de-identified data of 84.5 million unique patients from 63 health care organizations in the US, among whom 15 million (age ≥12 years) had medical encounter(s) with health care organizations since December 1, 2020.

The study population comprised 579,372 individuals who fulfilled the following inclusion criteria: a) they had medical encounter(s) with health care organizations since December 1, 2020; b) they had documented evidence of full vaccination in electronic health records (i.e., they had received a second dose of Pfizer-BioNTech or Moderna vaccine, or a single dose of Johnson & Johnson vaccine) between December 1, 2020 and August 14, 2021; and c) they had not contracted COVID-19 infection prior to vaccination.

The fully vaccinated study population included 30,183 patients with SUD and 549,189 patients without SUD. Among the fully vaccinated population with SUD, 7,802 patients had a diagnosis of alcohol use disorder, 2,058 of cannabis use disorder, 1,011 of cocaine use disorder, 2,379 of opioid use disorder, and 21,941 of tobacco use disorder.

TriNetX Analytics provides web-based real-time secure access to patient electronic health records from hospitals, primary care and specialty treatment providers, covering diverse geographic locations, age groups, ethnic groups, and income levels. Though the data are de-identified, end-users can use the platform built-in functions working on patient-level data for cohort selection and matching, analyzing incidence and prevalence of events in a cohort, and comparing characteristics and outcomes between matched cohorts. Multiple studies have used TriNetX to study risk, disparity, sequelae, temporal trends, clinical characteristics, and outcomes of COVID-19 infection[27-30].

The status of COVID-19 infection was based on the ICD-10 diagnosis code of "COVID-19" (U07.1) or lab-test confirmed presence of "SARS coronavirus 2 and related RNA" (TNX:LAB:9088). The status of full vaccination was based on the Current Procedural Terminology (CPT) relevant codes for Pfizer-BioNTech (0002A), Moderna (0012A) and Johnson & Johnson (0031A) vaccines.

The status of SUD was based on the ICD-10 diagnosis code of "mental and behavioural disorders due to psychoactive substance use" (F10-F19). The status of alcohol use disorder was based on the ICD-10 diagnosis code of "alcohol related disorders" (F10); that of cannabis use disorder on the code of "cannabis related disorders" (F12); that of cocaine use disorder on the code of "cocaine related disorders" (F14); that of opioid use disorder on the code of "opioid related disorders" (F11); and that of tobacco use disorder on the code of "nicotine dependence" (F17). Other subtypes of SUD, such as methamphetamine use disorder, were not examined due to their small sample sizes.

For breakthrough outcome measures, the status of hospitalization was based on the CPT code "hospital inpatient services" (013659), while the status of death was based on the vital status code "deceased" that TriNetX regularly imports from the Social Security Death index.

Procedures

We tested whether fully vaccinated SUD patients had higher risk for breakthrough infection than non-SUD patients. Separate analyses were performed for alcohol use disorder, cannabis use disorder, cocaine use disorder, opioid use disorder, and tobacco use disorder.

The cohorts of SUD and non-SUD patients were created by propensity score matching for demographics (age, gender, ethnicity); adverse socioeconomic determinants of health (including "problems related to education and literacy", "problems related to employment and unemployment", "occupational exposure to risk factors", and "problems related to housing and economic circumstances", according to the ICD-10); lifetime comorbidities (hypertension, heart diseases, cerebrovascular diseases, obesity, type 2 diabetes, cancers, chronic respiratory diseases, chronic kidney diseases, liver diseases, blood diseases and disorders involving immune mechanisms, HIV infection, dementia, depression, and psychotic disorders), and vaccine types (Pfizer, Moderna and Johnson & Johnson).

The TriNetX built-in propensity score matching function was used (1:1 matching using a nearest neighbor greedy matching algorithm with a caliper of 0.25 times the standard deviation). The outcome was COVID-19 infection at least 14 days after patients received the second dose of Pfizer-BioNTech or Moderna vaccine or a single dose of Johnson & Johnson vaccine. Kaplan-Meier analysis was performed to estimate the probability of breakthrough infection from day 14 after full vaccination to August 28, 2021. Comparisons between cohorts were made using a log-rank test (a built-in function in TriNetX). The hazard ratio (HR) was used to describe the relative risk of breakthrough infection based on comparison of time to event rates, and was calculated using a proportional hazard model (a built-in function in TriNetX). The proportional hazard assumption was tested using the generalized Schoenfeld approach.

We tested whether fully vaccinated patients who received Pfizer-BioNTech vaccine had a different risk of developing breakthrough COVID-19 infection compared with a matched cohort of patients who received Moderna vaccine. Johnson & Johnson vaccine was not examined due to small sample size. The Pfizer and Moderna cohorts were propensity-score matched for demographics, adverse socioeconomic determinants of health, and comorbid medical conditions. Kaplan-Meier analysis was used to estimate the probability of breakthrough infection from day 14 after full vaccination to August 28, 2021. Separate analyses were performed for SUD, SUD subtypes, and non-SUD individuals. HR was calculated to compare the relative risk of breakthrough infection in two matched cohorts.

We explored how the rates of breakthrough infection in fully vaccinated SUD and non-SUD populations, measured by cases/person-day for each month, evolved between December 2020 and August 2021. TriNetX built-in functions were used for calculating proportion rates.

We tested whether fully vaccinated patients with breakthrough infection had different risk for hospitalization and death compared with a matched cohort without breakthrough infection. Breakthrough and non-breakthrough cohorts were propensity-score matched for demographics, adverse socioeconomic determinants of health, comorbid medical conditions, and vaccine types. For the breakthrough cohort, overall risks of hospitalization and death were calculated from the day of infection to August 28, 2021. For the non-breakthrough cohort, overall risks of hospitalization and death were calculated from day 14 after full vaccination to August 28, 2021. Relative risk (RR) was used to compare matched cohorts. Separate analyses were performed for SUD and non-SUD populations.

We investigated how the risks for breakthrough infection in fully vaccinated patients differed by age, gender and ethnicity. The case cohort comprised fully vaccinated patients with one of the following demographic factors: female, older (age ≥65 years), or African American. The comparison cohort comprised matched vaccinated SUD patients with one of the following corresponding factors: male, younger (age <65 years), or Caucasian. Two cohorts were propensity-score matched on other demographics, adverse socioeconomic determinants of health, comorbid medical conditions, and vaccine types. Kaplan-Meier analysis was performed to estimate the probability of breakthrough infection from day 14 after full vaccination to August 28, 2021 in matched cohorts. HR was used to compare the relative risk of breakthrough infection between matched cohorts. Separate analyses were done for SUD, non-SUD and each SUD subtype.

We examined how the timing of recent medical encounters for SUD diagnosis was associated with the risk of breakthrough infection among fully vaccinated SUD patients. Four cohorts of SUD patients were used: a) "Ever" (all SUD patients, irrespective of when they had a medical encounter for their diagnosis, thus including both recovered patients and those with active SUD); b) "February 2019" (patients who had a medical encounter for their SUD diagnosis after February 2019); c) "February 2020" (patients who had a medical encounter for their SUD diagnosis during the pandemic, i.e. any time after February 2020); and d) "December 2020" (patients who had a medical encounter for their SUD diagnosis after the COVID-19 vaccine was approved, thus most likely having a currently active SUD). The "Ever" group was used as the reference one to which the risk of breakthrough infection in the other groups was compared. Separated analyses were conducted for each SUD subtype.

Statistical tests were conducted with significance set at $p<0.05$ (two sided) using R, version 3.6.3.

RESULTS

The demographic characteristics of the fully vaccinated patients and the sample sizes as a function of SUD subtype are shown in Table 1. Among vaccinated SUD patients, 75.6% received Pfizer-BioNTech, 21.1% Moderna, and 3.3% Johnson & Johnson vaccine. Among vaccinated non-SUD population, 88.2% received Pfizer-BioNTech, 10.6% Moderna and 1.2% Johnson & Johnson vaccine.

Patients with SUD were older (mean age: 59.3±14.4 years) than those without SUD (54.7± 19.8 years). There were more men in the SUD population (51.4% vs. 43.1%), and the percentage of African Americans was higher in the SUD (26.2%) than in the non-SUD (14.3%) sample. The prevalence of adverse socioeconomic determinants of health was also higher in the SUD population than in patients without SUD (7.9% vs. 1.2%). Vaccinated patients with SUD had a higher lifetime prevalence of all comorbidities, as well as of transplants (all $p<0.001$).

Among the vaccinated population, the risk of breakthrough infection ranged from 6.8% for tobacco use disorder to 7.8% for cannabis use disorder, all significantly higher than the 3.6% in the non-SUD population ($p<0.001$). The HRs between SUD and non-SUD cohorts after propensity score matching for demographics (age, gender, ethnicity) and vaccine types remained significantly higher for all SUD subtypes except for tobacco use disorder, being highest for cocaine use disorder and cannabis use disorder (HR=1.17, 95% CI: 1.01-1.35 for alcohol; HR=1.92, 95% CI: 1.39-2.66 for cannabis; HR=2.06, 95% CI: 1.30-3.25 for cocaine; and HR=1.31, 95% CI: 1.00-1.71 for opioids) (see Table 2).

After controlling for adverse socioeconomic determinants of health and comorbid medical conditions, the risk for breakthrough infection no longer differed in SUD compared to non-SUD cohorts, except for patients with cannabis use disorder, who remained at significantly increased risk (HR=1.55, 95% CI: 1.22-1.99) (see Table 3).

Among SUD and non-SUD populations, the risk for breakthrough infection was higher in individuals who received the Pfizer than the Moderna vaccine, after matching for demographics, adverse socioeconomic determinants of health, and comorbid medical conditions (HR in SUD cohort: 1.49, 95% CI: 1.31-1.69; HR in non-SUD cohort: 1.45, 95% CI: 1.38-1.53). The same trend was observed in SUD subtypes (see Table 4).

The rate of breakthrough infection in the SUD population steadily increased from 0 cases/person-day in January 2021 to 0.001 cases/person-day in June 2021 to 0.0025 cases/person-day in August 2021 (2.5 times faster than in June 2021). A similar trend was observed in the non-SUD population: the rate of breakthrough infection steadily increased from 0 cases/person-day in January 2021 to 0.0009 cases/person-day in June 2021, and then reached 0.0049 cases/person-day in August 2021 (5.4 times faster than in June 2021) (see Figure 1).

Within the SUD population, the overall risk for hospitalization was 22.5% in the breakthrough cohort compared to 1.6% in the matched non-breakthrough cohort (RR=14.4, 95% CI: 10.19-20.42). The overall risk for death was 1.7% in the breakthrough cohort, compared to 0.5% in the matched non-breakthrough cohort (RR=3.5, 95% CI: 1.74-7.05).

Within the non-SUD population, the overall risk for hospitalization was 17.5% in the breakthrough cohort compared to 0.5% in the matched non-breakthrough cohort (RR=34.2, 95% CI: 28.05-41.67). The overall risk for death was 1.1% in the break-

Table 1 Characteristics of substance use disorder (SUD) and non-SUD vaccinated populations

	AUD	CUD	CocaineUD	OUD	TUD	SUD	Non-SUD
Total number of patients	7,802	2,058	1,011	2,379	21,941	30,184	549,189
Age (years, mean±SD)*	59.3±14.4	47.9±16.3	55.1±12.2	59.1±14.2	59.6±13.5	59.3±14.4	54.7±19.8
Gender (% male)*	61.8	60.1	61.5	45.7	50.3	51.4	43.1
Ethnicity (%)							
White	69.0	57.7	41.9	62.8	62.1	63.2	63.4
African American*	21.9	33.4	50.1	29.6	28.5	26.2	14.3
Hispanic/Latino	5.0	4.6	5.0	3.2	3.8	4.3	12.3
Asian	1.2	1.1	1.0	1.0	2.2	2.0	8.6
Unknown	7.4	7.4	6.7	6.0	6.9	7.2	12.6
Adverse socioeconomic determinants of health (%)*	10.8	18.7	22.6	14.1	7.8	7.9	1.2
Lifetime medical conditions (%)							
Hypertension*	63.3	50.8	66.8	67.2	62.9	61.6	22.8
Heart diseases*	19.6	17.0	24.2	21.0	21.5	20.1	5.3
Cerebrovascular diseases*	15.0	13.0	19.6	15.0	13.3	13.2	3.6
Obesity*	27.7	31.1	33.4	36.6	31.2	30.4	9.3
Type 2 diabetes*	21.6	19.9	28.9	30.7	25.7	24.6	8.4
Cancers*	48.8	40.9	46.6	44.5	45.2	44.9	16.2
Chronic respiratory diseases*	30.1	35.1	44.8	39.7	38.7	34.7	7.6
Chronic kidney diseases*	11.9	11.5	18.8	15.7	10.8	11.3	3.5
Liver diseases*	26.3	18.0	29.2	21.9	15.4	16.9	3.2
Blood diseases and disorders involving immune mechanisms*	41.1	40.0	50.1	49.8	34.3	35.6	10.5
HIV infection*	3.3	8.4	12.5	7.1	3.1	3.2	0.3
Dementia*	2.2	0.9	1.6	2.2	1.2	1.4	0.5
Major depression*	37.0	51.8	52.3	48.0	29.2	30.9	6.0
Psychotic disorders*	4.7	12.9	16.9	6.3	3.5	3.6	0.3
Lifetime organ transplants (%)*	3.9	3.7	3.8	3.4	1.8	2.6	0.7

*Significant difference between SUD and non-SUD populations, $p<0.001$. AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

through cohort compared to 0.2% in the matched non-breakthrough cohort (RR=6.0, 95% CI: 4.20-8.66).

No significant age, gender and ethnic disparities of breakthrough infections were observed in SUD patients after matching for other demographics, adverse socioeconomic determinants of health, comorbid medical conditions and vaccine types, except for patients with cannabis use disorder, among whom African Americans had higher risk than matched Caucasians (HR=1.63, 95% CI: 1.06-2.51). Among vaccinated non-SUD population, older individuals (age ≥65 years) were more likely to have breakthrough infections than younger patients after matching for gender, ethnicity, adverse socioeconomic determinants of health, and comorbid medical conditions (HR=1.08, 95% CI: 1.04-1.13); women had lower risk than matched men (HR=0.87, 95% CI: 0.84-0.90); and African Americans had higher risk than matched Caucasians (HR=1.12, 95% CI: 1.07-1.18) (see Figure 2).

Within the SUD population, the risk for breakthrough infection was higher for patients who had recent medical encounters for their SUD diagnosis, ranging from 7.0% in the "Ever" group to 10.5% in the "December 2020" group ($p<0.001$ between these two groups). The same trends were observed for SUD subtypes (see Table 5).

DISCUSSION

In this population-based cohort study, we report that the overall risk for breakthrough infection in vaccinated SUD patients ranged from 6.8% for tobacco use disorder to 7.8% for cannabis use disorder, all significantly higher than the 3.6% in the vaccinated non-SUD population. After matching for demographics (age, gender, ethnicity) and vaccine types (Pfizer,

Table 2 Risk of breakthrough COVID-19 infection in propensity-score matched (demographics and vaccine types) substance use disorder (SUD) and non-SUD populations

Cohort	Patients in cohort	Risk in cohort	Risk in matched non-SUD cohort	Hazard ratio (95% CI)
AUD	7,802	7.2%	3.7%	1.17 (1.01-1.35)
CUD	2,055	7.8%	2.3%	1.92 (1.39-2.66)
CocaineUD	1,011	7.7%	2.4%	2.06 (1.30-3.25)
OUD	2,379	7.1%	3.2%	1.31 (1.00-1.71)
TUD	21,935	6.8%	3.9%	1.06 (0.98-1.15)

AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

Moderna, Johnson & Johnson), patients with SUD – with the exception of those with tobacco use disorder – still had higher risks for breakthrough infection compared with matched non-SUD cohorts, with the highest risks for those with cocaine use disorder (HR=2.06, 95% CI: 1.30-3.25) and cannabis use disorder (HR=1.92, 95% CI: 1.39-2.66).

Matching for adverse socioeconomic determinants of health and comorbid medical conditions removed the differences in breakthrough infection between SUD and non-SUD populations, suggesting that the increased risk in SUD patients was driven by their high prevalence of a diverse set of comorbidities. Patients with cannabis use disorder, who were younger and had less comorbidities than the other SUD subtypes, had higher risk for breakthrough infection even after they were matched for adverse socioeconomic determinants of health and comorbid medical conditions with non-SUD patients (HR=1.55, 95% CI: 1.22-1.99). This may indicate that additional variables, such as behavioral factors or adverse effects of cannabis on pulmonary and immune function[31], could contribute to the higher risk for breakthrough infection in this group.

The rate of severe COVID outcomes in vaccinated individuals with breakthrough infections is known to be much lower than in infected unvaccinated individuals[32]. However, the outcome analyses in our study showed that hospitalization and

Table 3 Risk of breakthrough COVID-19 infection in propensity-score matched (adverse socioeconomic determinants of health and comorbid medical conditions, in addition to demographics and vaccine types) substance use disorder (SUD) and non-SUD populations

Cohort	Patients in cohort	Risk in cohort	Risk in matched non-SUD cohort	Hazard ratio (95% CI)
AUD	7,754	7.2%	6.9%	1.09 (0.96-1.22)
CUD	2,032	7.8%	5.4%	1.55 (1.22-1.99)
CocaineUD	991	7.7%	7.5%	1.15 (0.83-1.58)
OUD	2,360	7.0%	7.6%	0.94 (0.76-1.16)
TUD	21,757	6.8%	6.8%	1.03 (0.96-1.11)

AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

Table 4 Risk of breakthrough COVID-19 infection in propensity-score matched (demographics, adverse socioeconomic determinants of health, and comorbid medical conditions) substance use disorder (SUD) and non-SUD populations receiving Pfizer and Moderna vaccine

Cohort	Risk in patients receiving Pfizer	Risk in patients receiving Moderna	Hazard ratio (95% CI)
SUD	8.7%	6.3%	1.49 (1.31-1.69)
AUD	8.9%	7.1%	1.41 (1.10-1.80)
CUD	8.2%	7.3%	1.16 (0.68-1.97)
CocaineUD	7.3%	4.9%	2.78 (1.08-7.16)
OUD	9.7%	6.6%	1.56 (1.01-2.42)
TUD	9.0%	5.8%	1.69 (1.46-1.97)
Non-SUD	5.4%	4.7%	1.45 (1.38-1.53)

AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

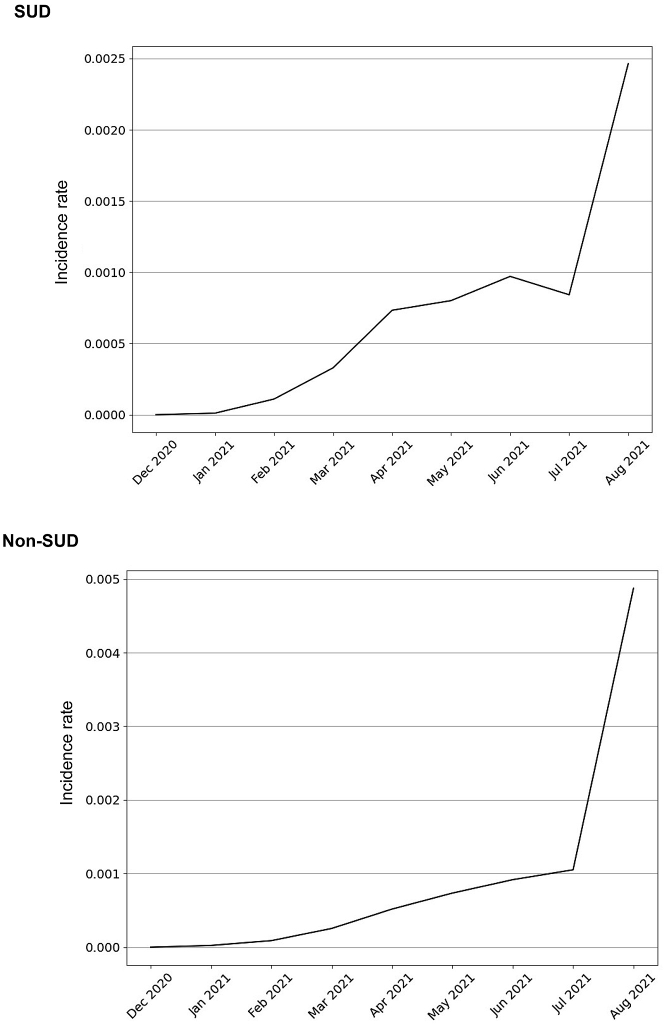
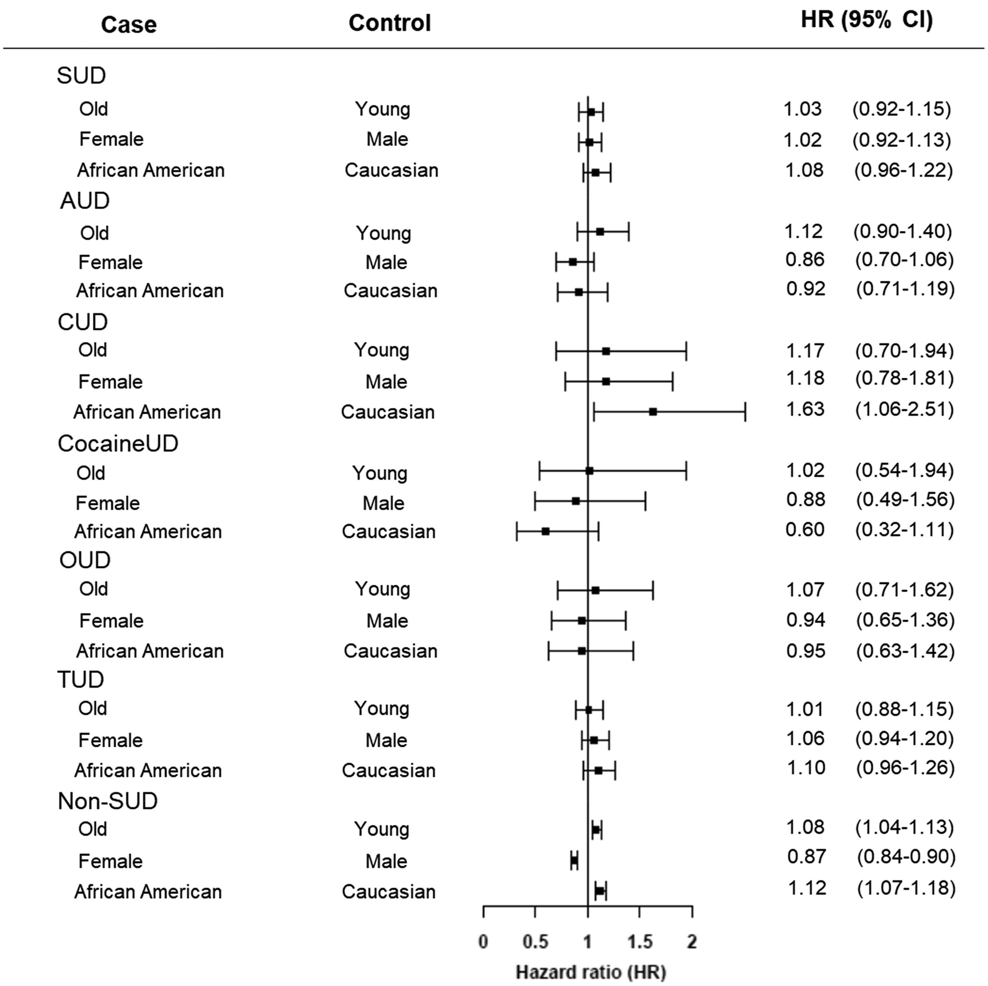


Figure 1 Time trend of incidence rates (cases/person-day) of breakthrough COVID-19 infection in patients with and without substance use disorder (SUD)



Case	Control	HR (95% CI)
SUD		
Old	Young	1.03 (0.92-1.15)
Female	Male	1.02 (0.92-1.13)
African American	Caucasian	1.08 (0.96-1.22)
AUD		
Old	Young	1.12 (0.90-1.40)
Female	Male	0.86 (0.70-1.06)
African American	Caucasian	0.92 (0.71-1.19)
CUD		
Old	Young	1.17 (0.70-1.94)
Female	Male	1.18 (0.78-1.81)
African American	Caucasian	1.63 (1.06-2.51)
CocaineUD		
Old	Young	1.02 (0.54-1.94)
Female	Male	0.88 (0.49-1.56)
African American	Caucasian	0.60 (0.32-1.11)
OUD		
Old	Young	1.07 (0.71-1.62)
Female	Male	0.94 (0.65-1.36)
African American	Caucasian	0.95 (0.63-1.42)
TUD		
Old	Young	1.01 (0.88-1.15)
Female	Male	1.06 (0.94-1.20)
African American	Caucasian	1.10 (0.96-1.26)
Non-SUD		
Old	Young	1.08 (1.04-1.13)
Female	Male	0.87 (0.84-0.90)
African American	Caucasian	1.12 (1.07-1.18)

Figure 2 Hazard ratios of breakthrough COVID-19 infection in fully vaccinated substance use disorder (SUD) and non-SUD populations: female vs. male; older (age ≥65 years) vs. younger (age <65 years); African American vs. Caucasian. Two demographic-stratified cohorts were propensity-score matched based on other demographics (age, gender, ethnicity), adverse socioeconomic determinants of health, comorbid medical conditions, and vaccine types. AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

death risks were significantly different between vaccinated SUD patients with breakthroughs and those without breakthrough, after matching for demographics, adverse socioeconomic determinants of health, comorbid medical conditions, and vaccine types. The risk for hospitalization in vaccinated SUD patients with breakthrough infection was 22.5%, compared to 1.6% in matched SUD patients without breakthrough infection (RR=14.4, 95% CI: 10.19-20.42). The risk for death in vaccinated SUD patients with breakthrough infection was 1.7%, compared to 0.5% in matched SUD cohort without breakthrough infection (RR=3.5, 95% CI: 1.74-7.05). This was also the case for fully vaccinated non-SUD population. We were unable to determine whether the hospitalizations and deaths in the breakthrough cases were due to COVID-19 or were associated with other medical conditions, but the large and significant differences between breakthrough and matched non-breakthrough cases indicate that COVID-19 infection contributed.

Outcome analysis for hospitalization between breakthrough and non-breakthrough cohorts may have suffered from ascertainment bias, as patients with moderate to severe breakthrough infections are more likely to visit health care organizations than asymptomatic or mild breakthrough cases, resulting in overrepresentation of the more severe breakthrough cases in the electronic health record data. On the other hand, the analysis for death outcomes is less prone to ascertainment bias, as the death data were regularly imported from the Social Security Death index. Overall, our results suggest that vaccine breakthrough infections can result in significant adverse outcomes, including death, based on the analysis of the fully vaccinated population from a nationwide real-time electronic health record database.

Clinical trials and real-world studies have demonstrated that both Pfizer-BioNTech and Moderna vaccines are highly effective for preventing COVID-19 infection and its severe outcomes[12,13,33-35]. Two recent reports showed that Pfizer-BioNTech may be less effective than Moderna vaccine during periods of Alpha and Delta variant prevalence[36], and that elderly nurs-

Table 5 Risk of breakthrough COVID-19 infection among fully vaccinated substance use disorder (SUD) patients who had medical encounters for their diagnosis at different time cutoffs

	Medical encounter for SUD	Patients on cohort	Patients with infection	Risk of infection	p
SUD	Ever	30,183	2,113	7.0%	Ref.
	Feb. 2019	4,185	366	8.7%	0.003
	Feb. 2020	13,621	1,181	8.7%	<0.001
	Dec. 2020	9,041	946	10.5%	<0.001
AUD	Ever	7,802	563	7.2%	Ref.
	Feb. 2019	4,185	366	8.7%	0.003
	Feb. 2020	2,959	294	9.9%	<0.001
	Dec. 2020	1,858	222	11.9%	<0.001
CUD	Ever	2,058	160	7.8%	Ref.
	Feb. 2019	1,019	91	8.9%	0.270
	Feb. 2020	667	72	10.8%	0.015
	Dec. 2020	403	56	13.9%	<0.001
CocaineUD	Ever	1,011	78	7.7%	Ref.
	Feb. 2019	422	41	9.7%	0.211
	Feb. 2020	293	30	10.2%	0.168
	Dec. 2020	176	25	14.2%	0.005
OUD	Ever	2,379	170	7.1%	Ref.
	Feb. 2019	1,449	114	7.9%	0.409
	Feb. 2020	1,078	84	7.8%	0.500
	Dec. 2020	783	67	8.6%	0.193
TUD	Ever	21,941	1,490	6.8%	Ref.
	Feb. 2019	13,450	1,029	7.7%	0.002
	Feb. 2020	9,790	832	8.5%	<0.001
	Dec. 2020	6,485	678	10.5%	<0.001

Ever – all SUD patients, irrespective of when the diagnosis was made (reference group); Feb. 2019 – patients who had a medical encounter for SUD after February 2019; Feb. 2020 – patients who had a medical encounter for SUD during the pandemic, i.e. any time after February 2020; Dec. 2020 – patients who had a medical encounter for SUD after vaccines were approved. AUD – alcohol use disorder, CUD – cannabis use disorder, CocaineUD – cocaine use disorder, OUD – opioid use disorder, TUD – tobacco use disorder

ing home residents in Ontario produced stronger immune responses with the Moderna than the Pfizer BioNTech vaccine[37]. We observed a higher risk for breakthrough infection in patients who received the Pfizer-BioNTech than in those receiving the Moderna vaccine in the whole population of 579,372 vaccinated patients, with HR=1.49 (95% CI: 1.31-1.69) for the SUD population, and HR=1.45 (95% CI: 1.38-1.53) for the non-SUD population.

Our study covered months when the Delta variant appeared in the US, including July and August 2021, when it caused more than 90% of new cases[38]. Vaccine effectiveness against the Delta variant is lower than for the Alpha variant[39-42]. Evidence also suggests that vaccine efficacy against COVID-19 may wane over time[32,43]. The trend analyses in our study showed that the rate of new COVID-19 infections, measured by cases/person-day, steadily increased in vaccinated SUD patients from January to June 2021, and then accelerated and reached 0.0025 cases/person-day in August 2021 (2.5 times faster than in June 2021). A similar trend was observed for fully vaccinated non-SUD patients. As the vaccination time could be any time between December 2020 and August 2021, the increasing rates of breakthrough infections with time may reflect a possible decline in vaccine-induced immunity for those vaccinated early, especially in older persons. The rapid increase after June 2021 may be due to the emergence of the Delta and other variants and the relaxation of prevention measures.

The lack of variant sequencing information in electronic health records did not allow us to assess the contribution of the Delta variant to breakthrough infections, including differences observed between Pfizer and Moderna vaccines. Future studies are warranted to further understand how much of the breakthrough infections are contributed by waning vaccine efficacy or by the Delta variant, separately and combined. The accelerated increase in incidence rate after June 2021 highlights the importance of follow-up studies to continuously monitor incidence rates of breakthrough infections.

In our previous study during the early stage of the pandemic (February to June 2020), when vaccines were not available, we reported ethnic and gender disparities in COVID-19 risk in individuals with SUD, with African Americans at greater risk than Caucasians and women at greater risk than men[6]. In the present study, no significant age, gender and ethnic disparities of breakthrough infections were observed in vaccinated SUD patients, after matching for other demographics, adverse socioeconomic determinants of health, comorbid medical conditions, and vaccine types. This may be due to small sample sizes, as we observed age, gender and ethnic disparities in fully vaccinated non-SUD population: older individuals (age ≥65 years), African Americans and men were more likely to have breakthrough infections than matched younger patients, Caucasians or females, respectively. The age disparity might reflect age-related decline in immunity, that not only would increase susceptibility to infection but also reduce the prophylactic efficacy of vaccinations[44,45]. The reasons for gender and ethnic disparities for breakthrough infections warrant further investigation.

Among vaccinated SUD patients, the risk for breakthrough infection was higher in patients who had a recent medical encounter for their SUD diagnosis (after December 2020), who were likely patients with current SUD. These results suggest that SUD itself, apart from the contribution of comorbid medical conditions, may have increased the risk for COVID-19 infection, even among the vaccinated population. The higher rate of breakthrough infection in active SUD patients might in part be due to behaviors that place them in situations of greater infection risk, or to the effects of the drugs, such as respiratory depression with opioid consumption or the adverse impact of cannabis on immune function.

Our study has several limitations. First, although widely used and accepted for observational studies on health care utilization, drug utilization, epidemiology (incidence/prevalence), risk factors, and safety surveillance, patient electronic health record data may suffer from under-/over-/mis-diagnosis, and do not include all possible confounding factors. Second, the TriNetX database represents people who had medical encounters with health care systems, and does not necessarily represent the entire US population, for example patients from rural areas, healthy population, undocumented immigrants. Third, vaccinations made outside of health care organizations, for example at mass vaccination centers, drug stores or recreational centers, are not necessarily captured in patient electronic health records. Fourth, we were unable to determine whether the breakthrough COVID-19 cases were asymptomatic, symptomatic or severe, or whether they were caused by the Delta variant. Further studies utilizing other data resources are needed to examine these questions.

Future studies should: a) continue to evaluate the long-term effectiveness of COVID-19 vaccines, as the infection caused by the Delta variant has become dominant and the efficacy of immunization may wane after several months; b) monitor outcomes, including hospitalization and mortality, associated with breakthrough infection; c) compare outcomes of COVID-19 infection in vaccinated versus unvaccinated SUD populations, which is important as vaccine hesitancy remains high worldwide[46]. Factors independently associated with vaccine hesitancy include age, ethnicity and lower educational attainment[47], and these factors disproportionally affect SUD populations[48,49].

In our study, the overall risk of COVID-19 infection among vaccinated SUD patients was low, highlighting the effectiveness and the need for full vaccination in this population. However, our findings document that this group remains a vulnerable one even after vaccination, confirming the importance for vaccinated patients with SUD to continue to take protective preventive measures against the infection.

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The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses

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Mental disorders represent a worldwide public health concern. Psychotherapies and pharmacotherapies are recommended as first line treatments. However, evidence has emerged that their efficacy may be overestimated, due to a variety of shortcomings in clinical trials (e.g., publication bias, weak control conditions such as waiting list). We performed an umbrella review of recent meta-analyses of randomized controlled trials (RCTs) of psychotherapies and pharmacotherapies for the main mental disorders in adults. We selected meta-analyses that formally assessed risk of bias or quality of studies, excluded weak comparators, and used effect sizes for target symptoms as primary outcome. We searched PubMed and PsycINFO and individual records of the Cochrane Library for meta-analyses published between January 2014 and March 2021 comparing psychotherapies or pharmacotherapies with placebo or treatment-as-usual (TAU), or psychotherapies vs. pharmacotherapies head-to-head, or the combination of psychotherapy with pharmacotherapy to either monotherapy. One hundred and two meta-analyses, encompassing 3,782 RCTs and 650,514 patients, were included, covering depressive disorders, anxiety disorders, post-traumatic stress disorder, obsessive-compulsive disorder, somatoform disorders, eating disorders, attention-deficit/hyperactivity disorder, substance use disorders, insomnia, schizophrenia spectrum disorders, and bipolar disorder. Across disorders and treatments, the majority of effect sizes for target symptoms were small. A random effect meta-analytic evaluation of the effect sizes reported by the largest meta-analyses per disorder yielded a standardized mean difference (SMD) of 0.34 (95% CI: 0.26-0.42) for psychotherapies and 0.36 (95% CI: 0.32-0.41) for pharmacotherapies compared with placebo or TAU. The SMD for head-to-head comparisons of psychotherapies vs. pharmacotherapies was 0.11 (95% CI: –0.05 to 0.26). The SMD for the combined treatment compared with either monotherapy was 0.31 (95% CI: 0.19-0.44). Risk of bias was often high. After more than half a century of research, thousands of RCTs and millions of invested funds, the effect sizes of psychotherapies and pharmacotherapies for mental disorders are limited, suggesting a ceiling effect for treatment research as presently conducted. A paradigm shift in research seems to be required to achieve further progress.

Key words: Psychotherapies, pharmacotherapies, mental disorders, randomized controlled trials, meta-analyses, effect sizes, meta-analytic evaluation

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Mental disorders represent a worldwide public health concern[1,2]. Psychotherapies and pharmacotherapies are recommended as first line treatments[3,4]. However, evidence has recently emerged suggesting that the efficacy of both types of treatment may have been overestimated, due to several shortcomings of clinical trials, such as publication bias, researcher allegiance, or use of weak comparison groups (in particular, waiting list)[5-16]. A realistic estimate of the efficacy of psychotherapies and pharmacotherapies is important to obtain.

Meta-analyses and systematic reviews of randomized controlled trials (RCTs) are thought to provide the highest level of evidence[17]. However, not only individual RCTs but also meta-analyses may be affected by the above-mentioned biases[6,18,19]. To avoid overestimating treatment efficacy, meta-analyses need to take risk of bias systematically into account[6,18-20]. Furthermore, estimates of efficacy depend upon the comparator against which treatments are tested. Waiting list conditions, for example, represent a relatively weak comparator, leading to larger effect sizes[6,8,21,22]. Comparisons with placebo or treatment-as-usual (TAU) provide better estimates of the true efficacy of a treatment [6,22].

The most recent comprehensive review of meta-analyses of both psychotherapies and pharmacotherapies in mental disorders, including 61 meta-analyses, was published in 2014, reporting a medium effect size (standardized mean difference, SMD=0.50)[8]. Some of the included meta-analyses, however, used waiting list comparisons in the assessment of overall efficacy. In addition, the authors seem to have just averaged the extracted effect sizes, without performing a meta-analytic evaluation including weighting effect sizes. Furthermore, a large number of studies and meta-analyses have been published since 2014.

For all these reasons, we carried out an up-to-date umbrella review of recent meta-analyses of psychotherapies and pharmacotherapies for the main mental disorders in adults which used placebo or TAU as comparison groups and formally assessed risk of bias or quality of studies. As the primary outcome, we used the effect size for target symptoms of the relevant disorder.

METHODS

The study protocol of this umbrella review was registered in advance at PROSPERO (International Prospective Register of Systematic Reviews), registration number: CRD42020155452.

Inclusion criteria

Meta-analyses of RCTs comparing psychotherapies or pharmacotherapies to placebo or TAU in adults with mental disorders published since 2014 were eligible. We also considered meta-analyses comparing psychotherapies vs. pharmacotherapies head-to-head, or their combination to either monotherapy. Only meta-analyses which formally assessed risk of bias or quality of studies were included. If multiple meta-analyses fulfilling the inclusion criteria were available for one condition, all of them were included. Reporting of SMD or other measures of between-group effect size was required.

All types of pharmacotherapy or psychotherapy were eligible for inclusion. Meta-analyses examining specific subgroups (e.g., treatment resistant depression, primary care patients, the elderly), psychiatric or somatic comorbidities (e.g., depression in cancer patients), specific settings (e.g., group therapy only, or inpatient therapy) or augmentation strategies (e.g., psychostimulants added to antipsychotic drugs in schizophrenia), or focusing on secondary outcomes (e.g., quality of life in depression) were not included. These inclusion criteria are consistent with the above-mentioned 2014 review[8], except for excluding waiting list comparisons and requiring meta-analyses to have assessed risk of bias or quality of studies. Both standard and network meta-analyses were eligible.

Combining data of patients receiving TAU or placebo with those of patients on waiting list has been shown to inflate effect sizes[8,22,23]. On the other hand, mixing data of patients on TAU with those receiving specific therapies (e.g., cognitive-behaviour therapy, CBT) can be expected to underestimate the effect size of the treatment in question. Therefore, meta-analyses mixing data of TAU or placebo with waiting list or active treatments were excluded.

Search for studies

We searched PubMed and PsycINFO and individual records of the Cochrane Library for meta-analyses of RCTs of psychotherapies and/or pharmacotherapies for mental disorders in adults published between January 2014 and March 2021.

Four reviewers independently searched for studies. Decision on inclusion was made by consensus including another rater. Search terms were meta-analy* or metaanaly* combined with the thesaurus of the individual databases concerning each disorder. To provide comparable results, we used the syntax applied in the previous most comprehensive review[8].

Data extraction

We focused on effect sizes and 95% confidence intervals (CIs) for the target symptoms of the relevant disorder (primary outcome). We extracted between-group SMDs and related measures (Cohen's d, Hedges' g) as reported in the meta-analyses. Odds ratios (ORs) and hazard ratios (HRs) were converted to SMDs[24,25]. Data on relative risk (RR) were extracted as reported. We used Cohen's convention of d=0.2, d=0.5 and d=0.8 as indicating small, medium and large effect sizes[26], corresponding to success rate differences of 11%, 28% and 43%; numbers needed to treat of 9, 4 and 2; ORs of 1.43, 2.48 and 4.25; RRs of 1.22, 1.86 and 3.00; and HRs of 1.3, 1.9 and 2.8[24,25,27-29]. Intention-to-treat data were preferred whenever available.

If meta-analyses took risk of bias into account by, for example, additionally reporting data separately for low risk of bias studies or correcting for publication bias, we listed all reported effect sizes but preferably focused on the corrected or high quality data for interpreting results.

Rates of remission and response were included as secondary outcomes when available. Dichotomous variables have some limitations[30], but complementarily to SMDs they can provide useful information about efficacy.

One author extracted data (type of treatment and disorder, number of studies, number of participants, type of comparator, risk of bias, adverse events/side effects, and effect sizes). Data were cross-checked independently by two raters each.

Quality assessment

The quality of the included meta-analyses was independently assessed by two raters. For the purpose of this review, we used the items 1 to 9 of the Checklist for Systematic Reviews and Research Syntheses[31,32], complemented by item 12 of AMSTAR 2[20] ("Was the impact of risk of bias in individual studies on results of the meta-analysis taken into account?") and an additional item addressing whether the meta-analysis was registered. In case of disagreement between raters, consensus ratings were used.

Data synthesis

The results of the largest meta-analyses for each condition, i.e. those including most RCTs, are presented and evaluated separately. Additionally, these independent meta-analyses were included in second-order meta-analyses combining their summary effect sizes across all the different mental disorders[33]. This allowed to obtain a weighted effect of psychotherapy or pharmacotherapy across all mental disorders, and weighted effects for the benefits of combined therapy, and for the comparative efficacy of psychotherapy vs. pharmacotherapy. The analysis was performed by Comprehensive Meta-Analysis (CMA, Version 3) using a random effects model based on SMDs and their CIs via the CMA analysis option "generic estimates".

Heterogeneity was assessed using the I^2 statistic. If meta-analyses did not report an overall effect size, but effect sizes for specific treatments and comparisons, the effect sizes of the relevant comparisons were aggregated by CMA and the resulting overall SMDs were entered into the second-order meta-analyses across disorders. Only effect estimates based on at least two primary RCTs were used.

RESULTS

Included meta-analyses

The search retrieved 23,601 items, reduced to 19,500 after removing duplicates, which were screened by titles and abstracts. Full-text evaluation was carried out for 319 papers. One hundred and two meta-analyses fulfilled the inclusion criteria (see Figure 1 and supplementary information). These encompassed 69 meta-analytic comparisons of pharmacotherapies with placebo or TAU, 26 comparisons of psychotherapies with placebo or TAU, 11 comparisons of psychotherapies vs. pharmacotherapies head-to-head, and 13 comparisons of combined psychotherapy and pharmacotherapy to either monotherapy[6,12,13,34-134]. The 102 meta-analyses encompassed 3,782 RCTs (range: 2 to 522) and 650,514 patients (range: 65 to 116,477) (see supplementary information).

Across all meta-analyses, the mean number of positively rated items in the quality assessment was 8.71±1.43 (range: 4 to 11). The items 10 (item 12 of AMSTAR 2, addressing whether the meta-analyses took the impact of bias on results into account) and 11 (study registration) were the least frequently fulfilled (48% and 47%, respectively). The quality of meta-analyses was not significantly different between psychotherapies and pharmacotherapies (mean of positively rated items: 8.95±1.12 for psychotherapies, 8.68±1.54 for pharmacotherapies, t=0.74, p=0.46).

Psychotherapies and pharmacotherapies vs. TAU or placebo

In the largest meta-analyses, the effect sizes of both psychotherapies and pharmacotherapies in comparison to TAU or placebo were small (SMD<0.50) for most disorders and treatments (see Figure 2 and supplementary information). Medium effect sizes were found only for pharmacotherapies of obsessive-compulsive disorder (OCD) (SMD=0.56)[72], bulimia nervosa (SMD=0.61)[80], and somatoform disorders (SMD=0.50)[91], and for psychotherapies of post-traumatic stress disorder (PTSD) (SMD=0.54)[54] and borderline personality disorder (SMD=0.57)[93]. Large effect sizes were only reported for psychotherapy of OCD (SMD=1.03)[74], with, however, a substantial proportion of patients taking concomitant pharmacotherapy[72,74]. Overall, risk of bias was often high (see Figure 2 and supplementary information).

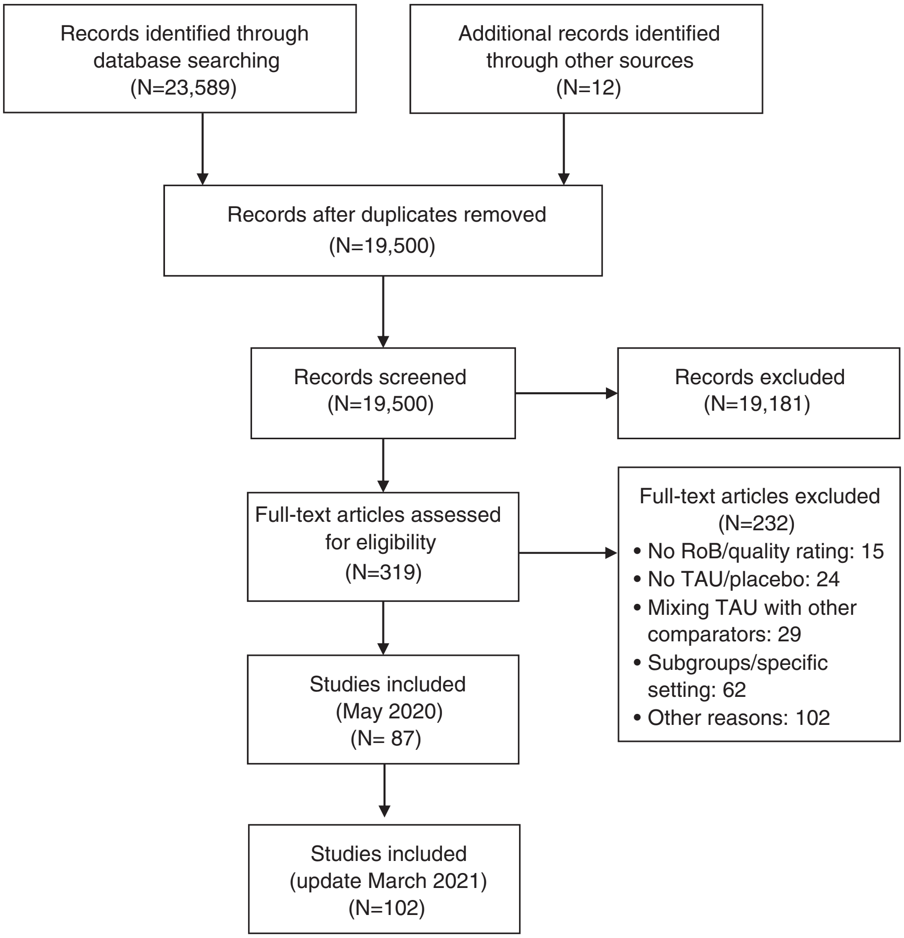
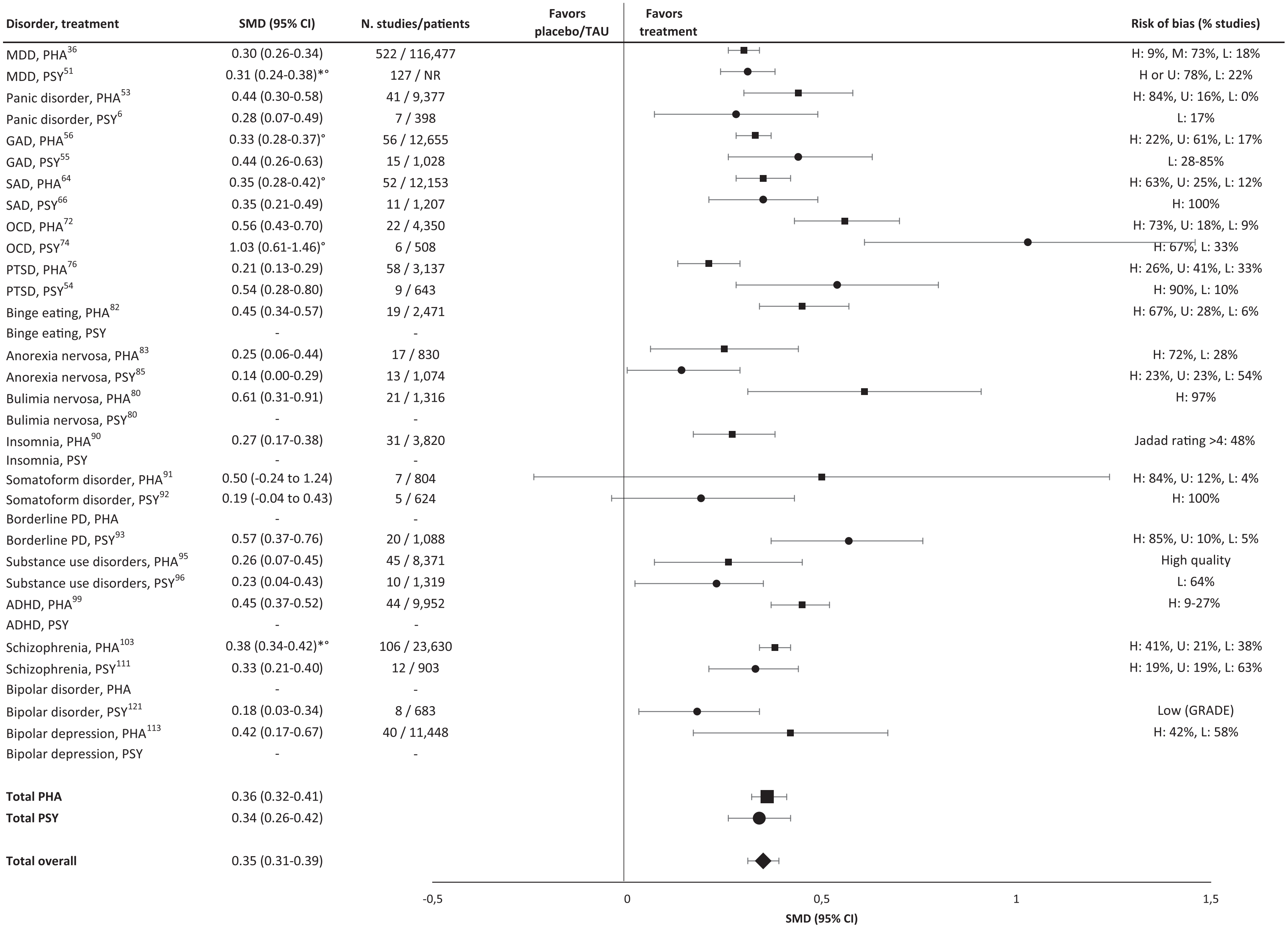


Figure 1 PRISMA flow chart. RoB – risk of bias, TAU – treatment as usual



Disorder, treatment	SMD (95% CI)	N. studies/patients	Risk of bias (% studies)
MDD, PHA[36]	0.30 (0.26-0.34)	522 / 116,477	H: 9%, M: 73%, L: 18%
MDD, PSY[51]	0.31 (0.24-0.38)*°	127 / NR	H or U: 78%, L: 22%
Panic disorder, PHA[53]	0.44 (0.30-0.58)	41 / 9,377	H: 84%, U: 16%, L: 0%
Panic disorder, PSY[6]	0.28 (0.07-0.49)	7 / 398	L: 17%
GAD, PHA[56]	0.33 (0.28-0.37)°	56 / 12,655	H: 22%, U: 61%, L: 17%
GAD, PSY[55]	0.44 (0.26-0.63)	15 / 1,028	L: 28-85%
SAD, PHA[64]	0.35 (0.28-0.42)°	52 / 12,153	H: 63%, U: 25%, L: 12%
SAD, PSY[66]	0.35 (0.21-0.49)	11 / 1,207	H: 100%
OCD, PHA[72]	0.56 (0.43-0.70)	22 / 4,350	H: 73%, U: 18%, L: 9%
OCD, PSY[74]	1.03 (0.61-1.46)°	6 / 508	H: 67%, L: 33%
PTSD, PHA[76]	0.21 (0.13-0.29)	58 / 3,137	H: 26%, U: 41%, L: 33%
PTSD, PSY[54]	0.54 (0.28-0.80)	9 / 643	H: 90%, L: 10%
Binge eating, PHA[82]	0.45 (0.34-0.57)	19 / 2,471	H: 67%, U: 28%, L: 6%
Binge eating, PSY	-	-	
Anorexia nervosa, PHA[83]	0.25 (0.06-0.44)	17 / 830	H: 72%, L: 28%
Anorexia nervosa, PSY[85]	0.14 (0.00-0.29)	13 / 1,074	H: 23%, U: 23%, L: 54%
Bulimia nervosa, PHA[80]	0.61 (0.31-0.91)	21 / 1,316	H: 97%
Bulimia nervosa, PSY[80]	-	-	
Insomnia, PHA[90]	0.27 (0.17-0.38)	31 / 3,820	Jadad rating >4: 48%
Insomnia, PSY	-	-	
Somatoform disorder, PHA[91]	0.50 (-0.24 to 1.24)	7 / 804	H: 84%, U: 12%, L: 4%
Somatoform disorder, PSY[92]	0.19 (-0.04 to 0.43)	5 / 624	H: 100%
Borderline PD, PHA	-	-	
Borderline PD, PSY[93]	0.57 (0.37-0.76)	20 / 1,088	H: 85%, U: 10%, L: 5%
Substance use disorders, PHA[95]	0.26 (0.07-0.45)	45 / 8,371	High quality
Substance use disorders, PSY[96]	0.23 (0.04-0.43)	10 / 1,319	L: 64%
ADHD, PHA[99]	0.45 (0.37-0.52)	44 / 9,952	H: 9-27%
ADHD, PSY	-	-	
Schizophrenia, PHA[103]	0.38 (0.34-0.42)*°	106 / 23,630	H: 41%, U: 21%, L: 38%
Schizophrenia, PSY[111]	0.33 (0.21-0.40)	12 / 903	H: 19%, U: 19%, L: 63%
Bipolar disorder, PHA	-	-	
Bipolar disorder, PSY[121]	0.18 (0.03-0.34)	8 / 683	Low (GRADE)
Bipolar depression, PHA[113]	0.42 (0.17-0.67)	40 / 11,448	H: 42%, L: 58%
Bipolar depression, PSY	-	-	
Total PHA	0.36 (0.32-0.41)		
Total PSY	0.34 (0.26-0.42)		
Total overall	0.35 (0.31-0.39)		

Figure 2 Effect sizes in the largest meta-analyses of pharmacotherapies (squares) and psychotherapies (circles) in comparison to placebo or treatment-as-usual (TAU). PHA – pharmacotherapy; PSY – psychotherapy, SMD – standardized mean difference, * – adjusted for risk of bias, ° – adjusted for small-study effects, MDD – major depressive disorder, GAD – generalized anxiety disorder, SAD – social anxiety disorder, OCD – obsessive-compulsive disorder, PTSD – post-traumatic stress disorder, PD – personality disorder, ADHD – attention-deficit/hyperactivity disorder, H – high, M – medium, L – low, U – uncertain, NR – not reported. Where SMD is not provided, this means that no valid meta-analysis reporting this value was available.

For psychotherapies and pharmacotherapies, second-order random effects meta-analyses in comparison to placebo or TAU yielded statistically significant but small SMDs of 0.34 (95% CI: 0.26-0.42, I^2=66.33%) and 0.36 (95% CI: 0.32-0.41, I^2=70.61%), respectively, across disorders (see Figure 2). For the aggregated data of psychotherapies and pharmacotherapies, the SMD was 0.35 (95 CI: 0.31-0.39, I^2=68.23%).

Depressive disorders

For psychotherapies of depressive disorders, the largest meta-analysis reported a small SMD of 0.31, adjusted for biases, in comparison to TAU[51] (see Figure 2). Taking all included meta-analyses into account, psychotherapy achieved effect sizes (SMDs) between 0.11 and 0.61 in comparison to placebo or TAU[6,12,37,50,51,52], except for one outlying meta-analysis reporting a large SMD post-therapy (1.11), reduced to 0.27 at 3 to 12 month follow-up and associated with a high risk of bias[52]. The majority of effect sizes were small (<0.50).

Only between 1% and 17% of studies of psychotherapy for depression were found to show a low risk of bias. When meta-analyses took risk of bias into account, they consistently found a decrease in effect sizes (see supplementary information).

Across all forms of psychotherapy, remission from major depressive disorder (Hamilton Depression Rating Scale, HAM-D <7) was achieved in 43% of patients, with no significant differences between the various psychotherapies[5]. Response (50% reduction of HAM-D score) was achieved in 54% of patients[5]. TAU was superior to no treatment with regard to remission (33% vs. 23%), but inferior to psychotherapy (33% vs. 43%)[135].

The largest meta-analysis of pharmacotherapy for depressive disorders reported a SMD of 0.30[36] (see Figure 2). All effect sizes (SMD) achieved by pharmacotherapy in comparison to placebo were below 0.50, ranging from 0.19 to 0.41. The exception was ketamine, which achieved large short-term effects (0.83, 0.88) 24 hours and 3-4 days after treatment, dropping to 0.31 after 7 days[13,34-39,41-49]. Most effect sizes in terms of RRs were small as well (≤1.22).

The mean response rate for selective serotonin reuptake inhibitors (SSRIs) was 51% vs. 39% for placebo[35], corresponding to a small effect size[27].

Many trials of pharmacotherapy in depression showed a high risk of bias[13,35,36,42] (see supplementary information).

Anxiety disorders

In the largest meta-analyses of anxiety disorders, psychotherapies achieved SMDs between 0.28 and 0.44[6,55,66] (see Figure 2). Overall, psychotherapies of anxiety disorders achieved SMDs compared to TAU or placebo between 0.01 and 0.72[6,54,55,59,65,66,71], except for two outlying effect sizes in generalized anxiety disorder (1.44, 1.32), each based on three studies only[6,55]. Two effect sizes of psychotherapy (CBT) in social anxiety disorder were medium (0.72, 0.56)[66], but most effect sizes were small (see supplementary information).

Overall, only 17% of psychotherapy studies in anxiety disorders were found to show a low risk of bias[6].

In the largest meta-analyses for anxiety disorders, pharmacotherapies achieved SMDs in comparison to placebo between 0.33 and 0.45[53,56,64] (see Figure 2). Overall, effect sizes for pharmacotherapy were between 0.01 and 0.56, with the majority of effect sizes being small[53,55-64,66,67,69,70] (see supplementary information). RR ranged between 1.20 and 4.03, with most values being small, one medium (monoamine oxidase inhibitors), and one large (benzodiazepines, RR=4.03)[69].

For social anxiety disorder and generalized anxiety disorder, pharmacotherapy yielded response rates of 52% and 56%, respectively, versus 32% and 41% with placebo[59,69].

Obsessive-compulsive disorder

For psychotherapy (CBT) of OCD, the largest meta-analysis reported a large SMD (1.03)[74] (see Figure 2). Considering all meta-analyses, large SMDs in comparison to placebo were reported (0.91-1.46)[72,74]. At follow-up of on average of 15.1 months after the end of treatment, SMDs decreased from 0.57 to 0.06 for all comparators[74]. Follow-up results were not available for a comparison against placebo. Most psychotherapy trials included patients taking stable doses of antidepressants[72,74], possibly overestimating effect sizes in favour of psychotherapy[72].

For pharmacotherapy of OCD, the largest meta-analysis reported a medium effect size (SMD=0.56)[72] (see Figure 2). Considering all meta-analyses, small to medium SMDs were reported (0.45-0.66).

For most studies of psychotherapy and pharmacotherapy, the risk of bias was high (see Figure 2 and supplementary information).

Post-traumatic stress disorder

For psychotherapy (CBT) of PTSD, the largest meta-analysis reported a medium effect size compared to TAU (SMD=0.54)[54] (see Figure 2), which was stable at follow-ups of up to 12 months after end of therapy[54]. For PTSD related to childhood maltreatment, a SMD of 0.50 in comparison to TAU/placebo was found, which was reduced to 0.21 after adjusting for small sample size[79].

For pharmacotherapy of PTSD, the largest meta-analysis reported a small SMD in comparison to placebo (0.21)[76] (see Figure 2). Considering all meta-analyses, effect sizes achieved by pharmacotherapy in comparison to placebo were heterogeneous (SMDs: –0.10 to 0.97)[75-78]. Risk of bias was often high[77,78]. A large SMD was obtained with phenelzine (0.97), a medium one with mirtazapine (0.79), desipramine (0.52) and olanzapine (0.51), all based on only one RCT except for olanzapine[75]. For SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs), a medium SMD was reported (0.50)[77]. For all other drugs, SMDs were <0.50 (from –0.10 to 0.47).

Personality disorders

For psychotherapy of personality disorders, only a meta-analysis of borderline personality disorder was available, which reported a medium SMD in comparison to TAU (0.57), with a high risk of bias in most studies (see Figure 2)[93].

An update for developing a Cochrane report of pharmacotherapy in borderline personality disorder did not provide meta-analytic results since the authors did not find robust evidence[136].

Somatoform disorders

For psychotherapy of somatoform disorders, the largest meta-analysis reported a small SMD (0.19, see Figure 2) in comparison to enhanced care, with high risk of bias due to lack of blinding[92]. For pharmacotherapy of somatoform disorders, the largest meta-analysis reported a medium SMD (0.50, see Figure 2) in comparison with placebo[91].

Considering all meta-analyses, heterogeneous SMDs (from 0.13 to 0.91) were reported for pharmacotherapy, based on two or three RCTs, with a high risk of bias for most RCTs[91].

Eating disorders

For psychotherapy of bulimia nervosa, no recent meta-analysis fulfilled the inclusion criteria. For pharmacotherapy, the largest meta-analysis reported a medium SMD in comparison with placebo (0.61, see Figure 2)[80]. Considering all meta-analyses, considerable heterogeneity among classes of drugs were found (SMDs: 0.10-1.00)[80].

For psychotherapy of binge eating disorder, no meta-analysis fulfilled the inclusion criteria. For pharmacotherapy, the largest meta-analysis reported a small to medium SMD in comparison with placebo (0.45, see Figure 2)[82]. Considering all meta-analyses, a small to medium effect size compared to placebo was found for pharmacotherapy (SMD=0.45, RR: 1.67, 2.61)[81,82]. One of these meta-analyses reported a high[82], the other a medium to low risk of bias[81].

For psychotherapy of anorexia nervosa, the largest meta-analysis reported a small SMD in comparison with TAU (0.14, see Figure 2)[85]. Overall, the effect sizes in comparison to TAU or placebo were small (SMD=0.10-0.31, RR: 0.97, 1.28)[84-86]. For pharmacotherapy, the largest meta-analysis reported a small effect size (SMD=0.25)[83].

Substance use disorders

For both psychotherapy and pharmacotherapy of substance use disorders, the largest meta-analysis reported small SMDs in comparison with TAU or placebo (0.23 and 0.26, respectively, see Figure 2)[95,96]. For psychotherapy, the effect size decreased at follow-ups ≥8 months after end of treatment (SMD=0.05)[96]. Considering all meta-analyses, small effect sizes were found for pharmacotherapy (SMDs: 0.07 to 0.35, RR: 0.32-1.39)[94,95].

Insomnia

For psychotherapy, no recent meta-analysis fulfilled the inclusion criteria. The quality of studies was found to be low[137]. For pharmacotherapy, the largest meta-analysis reported a small SMD in comparison with placebo (0.27, see Figure 2)[90]. Overall, for pharmacotherapy of insomnia, small to medium SMDs were reported (0.07 to 0.58)[88-90]. One meta-analysis provided effect sizes only for one of eight outcome measures, with large SMDs (0.88-1.38), suggesting selective reporting[87].

Attention-deficit/hyperactivity disorder (ADHD)

For psychotherapy of ADHD in adults, no meta-analysis could be included[134]. For pharmacotherapy, the largest meta-analysis reported a small to medium SMD in comparison with placebo (0.45, see Figure 2)[99]. Considering all meta-analyses, the effects of pharmacotherapy were heterogeneous (from 0.16 to 0.97)[98-102]. Large SMDs were found for amphetamines[98,100,102], small to medium SMDs for methylphenidate[100,101]. Risk of bias was often high or unclear, and level of evidence was low to very low[98,100].

Schizophrenia spectrum disorders

Results of psychotherapy in schizophrenia spectrum disorders were evaluated in the context of pharmacotherapy (i.e., patients usually received concomitant medication). The largest meta-analysis reported a small SMD in comparison with TAU (0.33, see Figure 2)[111]. Considering all meta-analyses, small effect sizes compared to nonspecific controls were found for overall symptoms, positive and negative symptoms (SMDs: 0.32, 0.24 and 0.08, respectively)[138]. In comparison to TAU, psychotherapy achieved small to medium SMDs for negative symptoms (0.15-0.58)[110,112].

For psychotherapy, a response rate of 13% for overall symptoms and 25% for positive symptoms was found[139] (a reduction of symptoms of at least 50% was required). The response rate decreased considerably if researcher allegiance (authors evaluated the therapy that they developed) was taken into account (from 13% to 4.9%)[139].

For acute pharmacological treatment of schizophrenia, the largest meta-analysis reported an overall SMD of 0.45 for target symptoms, reduced to 0.38 after adjusting for publication bias (Figure 2)[103]. These results are consistent with meta-analyses on specific drugs, such as quetiapine (SMD=0.33), cariprazine (SMD: 0.32-0.37), lurasidone (SMD: 0.34-0.47), and aripiprazole and brexpiprazole (RR=1.1)[104,107-109]. A large effect size was reported for clozapine (SMD=0.89)[103]. Large and medium SMDs were achieved by long-acting injectable antipsychotics in the maintenance treatment of non-affective psychoses (RR: 1.75-3.70)[107].

For the acute treatment of schizophrenia with pharmacotherapy, differences in response rates in comparison with placebo were small (23% vs. 14%)[14].

Bipolar disorder

For psychotherapy of bipolar disorder, the largest meta-analysis reported a small effect size in comparison to TAU (SMD=0.18, see Figure 2)[121], with small effect sizes for both depression and mania symptoms (SMDs: 0.23 and 0.05, respectively) and for relapse prevention post-therapy (RR: 1.52)[121]. At follow-up 26 to 78 weeks post-therapy, SMDs were 0.21 and 0.38; RR for relapse was 1.35[121]. Psychotherapy was given in the context of concomitant pharmacotherapy.

For the acute treatment of mania, the results for pharmacotherapy are heterogeneous. One meta-analysis reported medium SMDs for cariprazine (0.51-0.52)[119], and another reported a small effect size for aripiprazole (SMD=0.16)[115]. These two meta-analyses included only three RCTs. A third meta-analysis reported a very large SMD (1.51) for tamoxifen[120], based on two RCTs with small samples (16 and 66 cases, respectively), making the results questionable. This study represents a clear outlier.

For the acute treatment of bipolar depression, the largest meta-analysis of pharmacotherapy reported heterogeneous results, with effect sizes (SMDs) between 1.41 and –1.84[113]. Large effect sizes were achieved by fluoxetine (1.41), divalproex (1.25), lurasidone (1.15), moclobemide (1.09), cariprazine (0.85) and imipramine (0.86)[113], all of them based, however, on only 0-3 direct comparisons. Some drugs achieved medium effect sizes (olanzapine, phenelzine, tranylcypromine). The effect sizes of all other drugs were small[113]. Quetiapine achieved an almost medium effect size (SMD=0.48) based on 11 direct comparisons[113].

For the prevention of manic/hypomanic/mixed episodes, effect sizes of lithium were almost medium (RR=1.85)[114]. Medium effect sizes were reported for olanzapine (RR=2.88) and risperidone (RR=2.88); large effect sizes for aripiprazole (once monthly) and asenapine (RR: 3.31, 4.81)[114]. The results for asenapine are based on only one RCT[116]. For all other drugs, effect sizes were small[114].

For the prevention of any mood episode relapse, a large effect size was found for asenapine (RR=3.82), with the caveat mentioned above[114]. Medium effect sizes were reported for quetiapine and olanzapine[114,116,118]. Small effect sizes for the prevention of any mood episode were achieved by lithium (RR: 1.60, 1.61) and several other drugs[114,118]. Earlier meta-analyses reported heterogeneous results for the prevention of any relapse by lithium (SMD: 1.12, 0.47)[140].

For the prevention of depressive episodes, quetiapine and asenapine achieved medium effect sizes (RR: 2.08, 2.60). For all other drugs, including lithium (RR=1.26), effect sizes were small[114]. Small effect sizes were found for antidepressants (RR=1.56)[117].

Psychotherapies vs. pharmacotherapies

Head-to-head comparisons of psychotherapies vs. pharmacotherapies yielded small effect sizes for all disorders examined, i.e., depressive disorders, anxiety disorders, PTSD and OCD (SMDs: 0.00-0.24, see Figure 3)[37,66,74,126]. A second-order random effects meta-analysis across the effect sizes of the largest meta-analyses (Figure 3) yielded a non-significant SMD of 0.11 (95% CI: –0.05 to 0.26, I^2=61.99).

Considering all included meta-analyses, no substantial differences in short-term efficacy between psychotherapies and pharmacotherapies in depressive disorders, anxiety disorders and PTSD were found[12,37,66,122-126], with only a few exceptions. In OCD, psychotherapy achieved medium to large SMDs (0.61-0.95) in comparison to SSRIs[72], but most psychotherapy trials included patients taking stable doses of antidepressants, affecting results in favour of psychotherapy. Most studies of psychotherapy and pharmacotherapy in OCD had a high risk of bias[72]. With regard to long-term efficacy, psychotherapy achieved a large SMD compared to pharmacotherapy in PTSD (0.83)[126]. For other disorders, no head-to-head comparisons fulfilled the inclusion criteria.

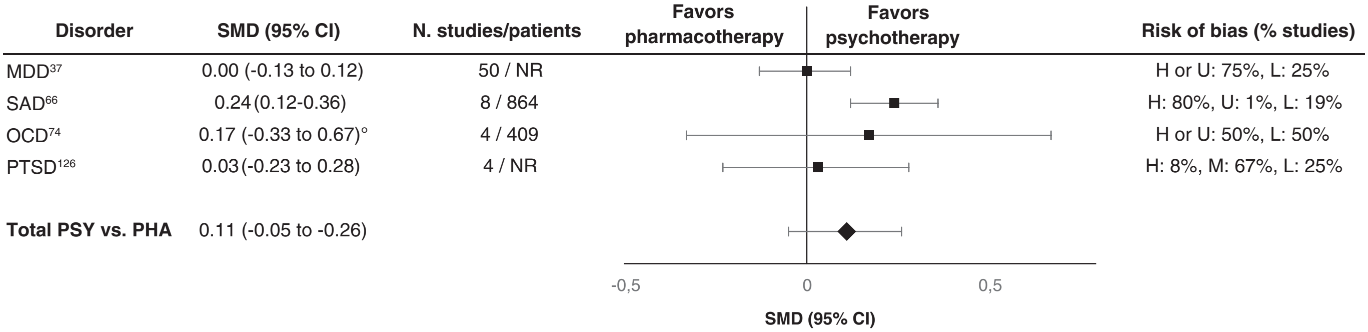
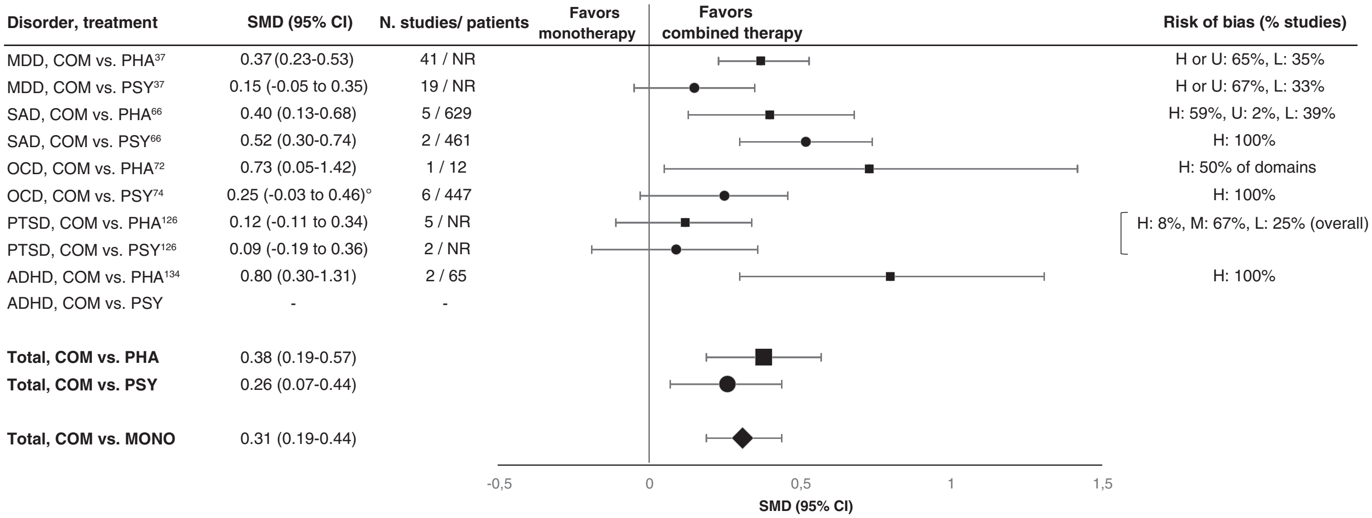


Figure 3 Effect sizes in the largest meta-analyses for head-to-head comparisons of psychotherapies (PSY) vs. pharmacotherapies (PHA). SMD – standardized mean difference, ° – adjusted for small-study effects, MDD – major depressive disorder, SAD – social anxiety disorder, OCD – obsessive-compulsive disorder, PTSD – post-traumatic stress disorder, H – high, M – medium, L – low, U – uncertain, NR – not reported



Disorder, treatment	SMD (95% CI)	N. studies/ patients	Risk of bias (% studies)
MDD, COM vs. PHA[37]	0.37 (0.23-0.53)	41 / NR	H or U: 65%, L: 35%
MDD, COM vs. PSY[37]	0.15 (-0.05 to 0.35)	19 / NR	H or U: 67%, L: 33%
SAD, COM vs. PHA[66]	0.40 (0.13-0.68)	5 / 629	H: 59%, U: 2%, L: 39%
SAD, COM vs. PSY[66]	0.52 (0.30-0.74)	2 / 461	H: 100%
OCD, COM vs. PHA[72]	0.73 (0.05-1.42)	1 / 12	H: 50% of domains
OCD, COM vs. PSY[74]	0.25 (-0.03 to 0.46)°	6 / 447	H: 100%
PTSD, COM vs. PHA[126]	0.12 (-0.11 to 0.34)	5 / NR	H: 8%, M: 67%, L: 25% (overall)
PTSD, COM vs. PSY[126]	0.09 (-0.19 to 0.36)	2 / NR	
ADHD, COM vs. PHA[134]	0.80 (0.30-1.31)	2 / 65	H: 100%
ADHD, COM vs. PSY	-	-	
Total, COM vs. PHA	0.38 (0.19-0.57)		
Total, COM vs. PSY	0.26 (0.07-0.44)		
Total, COM vs. MONO	0.31 (0.19-0.44)		

Figure 4 Effect sizes in the largest meta-analyses for combined therapy vs. pharmacological (squares) or psychological (circles) monotherapy. SMD – standardized mean difference, ° – adjusted for small-study effects, COM – combined therapy, PHA – pharmacotherapy, PSY – psychotherapy, MONO – monotherapy, MDD – major depressive disorder, SAD – social anxiety disorder, OCD – obsessive-compulsive disorder, PTSD – post-traumatic stress disorder, ADHD – attention-deficit/hyperactivity disorder, H – high, M – medium, L – low, U – uncertain, NR – not reported

Combining psychotherapy and pharmacotherapy

In the largest meta-analyses (Figure 4), effect sizes (SMDs) in favour of the combined treatment were small for most disorders, that is depressive disorders (0.37, 0.15)[37], social anxiety disorder (combined vs. pharmacotherapy: 0.40)[66], OCD (combined vs. psychotherapy: 0.25) and PTSD (0.09, 0.12)[126]. Effect sizes (SMDs) were medium in favour of the combined treatment vs. psychotherapy in social anxiety disorder (0.52)[66] and for the combined treatment vs. pharmacotherapy (SSRIs) in OCD (0.73), based on a network meta-analysis including only one direct comparison with very small samples[72]. A large effect size was found only for the combined treatment vs. pharmacotherapy in ADHD (0.80)[134], based on only two RCTs showing a high risk of bias in at least one domain.

A second-order random effects meta-analysis across the effect sizes of the largest meta-analyses yielded a statistically significant but small SMD of 0.31 (95% CI: 0.19-0.44, I^2=53.02) in favour of the combined treatment (Figure 4).

Considering all included meta-analyses, most effect sizes (SMDs) achieved by the combined treatment compared to either monotherapy in depressive disorders, anxiety disorders, PTSD, OCD and ADHD were small (0.09-0.48) when risk of bias was taken into account[12,37,66,72,74,126,128,129,131,132,134]. Exceptions were the superiority of the combined treatment in long-term outcome of PTSD over pharmacotherapy (SMD=0.96, based on only two direct comparisons)[126], and the superiority of the combined treatment over psychodynamic therapy in social anxiety disorder (SMD=0.68), based on a network meta-analysis including zero direct comparisons for the condition[66], making a study of inconsistencies impossible[141].

In several of these meta-analyses, risk of bias was high in several domains, or results were based on only a few or small studies[66,72,126,134].

DISCUSSION

In this field-wide assessment of psychotherapies and pharmacotherapies for mental disorders in adults, we included evidence from 102 meta-analyses with 3,782 RCTs and 650,514 patients. We found small benefits overall for both types of interventions, with an average SMD of 0.35 and moderate heterogeneity across conditions[142]. This finding challenges the result of the previous most comprehensive review, which reported an overall medium effect size (SMD=0.50) across psychotherapies and pharmacotherapies, based on 61 meta-analyses with 852 RCTs and 137,126 patients[8]. This latter estimate seems to be due to including waiting list comparators and averaging effect sizes without performing a random effects meta-analytic evaluation.

According to the results of this umbrella review and second-order meta-analyses, there is an additional gain of psychotherapy and pharmacotherapy in the treatment of mental disorders in adults, but this is small in terms of effect sizes[26]. Conditions for which very extensive evidence was available (e.g., depression) almost always had such modest effect sizes when only studies with low risk of bias were considered, or efforts were made to correct for bias. Medium or large effect sizes were found only for few conditions, and most of the effects sizes ≥0.50 were associated with a high risk of bias and/or limited evidence. Nevertheless, the argument still holds that, although there are some medications for general medical conditions with clearly higher effect sizes, psychotropic agents or psychotherapies are not generally less efficacious than those medications[140].

Some limitations and features of this umbrella review should be discussed as they affect the interpretation of overall evidence.

First, several meta-analytic comparisons included only a few studies, affecting statistical power and external validity of results.

Second, the results of network meta-analyses need some extra caution[141,143]. It has been argued that these meta-analyses can only provide observational evidence, since the comparisons between treatments are both direct and indirect, and the latter are not randomized[144]. As a related issue, transitivity (similar distribution of effect modifiers) can be controlled statistically only for known modifiers, in contrast to controlling all modifiers by randomization. Some of the network meta-analyses included in this review encompassed only a few or even no direct comparisons of specific treatments[66,72,75]. Statistical power may be low if only a few studies with small samples and large heterogeneity are included[141,145]. Thus, some inconsistencies between direct and indirect comparisons may not have been detected[145], possibly affecting effect size estimates.

Third, we followed Cohen's convention of small, medium and large effect sizes[26]. However, the clinical relevance of these estimates is not clear. The clinical benefit of an intervention needs to be determined by comparison with a benchmark such as the minimal clinically important difference (MCID)[146]. For the HAM-D, for example, a minimal clinically relevant improvement has been claimed by some authors to correspond to a 7-point difference[147] or to an SMD of 0.88[148]. If this is correct, in psychotherapies or pharmacotherapies for depression, effect sizes of 0.30, 0.40 or even 0.50 correspond to a difference on the HAM-D of 2 or 4 points (i.e. <7) which cannot be detected by clinicians and can therefore hardly be regarded as clinically significant. In schizophrenia, a SMD of 0.73 is required for a minimal clinical improvement of 15 points on the Positive and Negative Syndrome Scale (PANSS)[149], implying that SMDs below 0.73 are not detectable by clinicians and may not be clinically significant.

For a better judgment, the CIs of the effect size estimates may be compared with the proposed MCID values[150]. It has been argued that, if the upper limit of the 95% CIs is smaller than the MCID, effect sizes can be regarded as "definitely clinically not important"[150]. For the vast majority of meta-analyses on depression and schizophrenia, this would be the case if SMDs of 0.88 and 0.73 are used as MCID. However, even if the summary effect sizes are substantially smaller than the MCID, there is heterogeneity in treatment responses across patients. Therefore, a minority of patients may still achieve large benefits from treatment.

Fourth, identical effect sizes may have different clinical importance in different patient populations (e.g., according to disorders, gender or age) and for different outcomes (e.g., mortality)[151]. For outcomes including vital events (e.g., rates of suicide) small differences in success rates may be clinically important, whereas for continuous measures of (often transient) depression, anxiety or other symptoms, small differences of a few scale points may not[152]. Of the meta-analyses on the treatment of depression, for example, only a few examined hard outcomes such as suicidal behaviour[41,42,44]. In the meta-analyses on schizophrenia and bipolar disorder, data on suicidal behaviour were not reported, except for one meta-analysis[118]. Future studies and meta-analyses should include such important hard outcomes.

Fifth, TAU as a comparator was found to be superior to no treatment in depression (with regard to remission, 33% vs. 23%)[135]. However, TAU is a heterogeneous condition, and effect sizes achieved depend on the type of treatment actually delivered. Larger effect sizes may be achieved in comparison to weaker forms of TAU[23,153]. This applies to psychological placebo as well[154].

Sixth, the results of RCTs may not necessarily represent real-world effectiveness[155]. In clinical practice, patients often suffer from multiple mental disorders, and treatments are usually tailored to the individual patients´ needs. This applies, for example, to treatment duration. Most of the treatments included in this review were short-term[6]. Data on longer-term treatments are widely missing from RCT research.

In summary, a systematic re-assessment of recent evidence across multiple meta-analyses on key mental disorders provided an overarching picture of limited additional gain for both psychotherapies and pharmacotherapies over placebo or TAU. A ceiling seems to have been reached with response rates ≤50% and most SMDs not exceeding 0.30-0.40. Thus, after more than half a century of research, thousands of RCTs and millions of invested funds, the "trillion-dollar brain drain"[2] associated with mental disorders is presently not sufficiently addressed by the available treatments. This should not be seen as a nihilistic or dismissive conclusion, since undoubtedly some patients do benefit from the available treatments. However, realistically facing the situation is a prerequisite for improvement. Pretending that everything is fine will not move the field forward[156], nor will conforming and producing more similar findings[157].

A paradigm shift in research seems to be required to achieve further progress. Suggestions for such a shift have recently been made[11], for example, for improving methodological quality and replicability (e.g., open science[158,159]), improving available treatments – e.g., by personalized management[160-162], defining specific targets and outcomes[163], considering response to previous treatments (staging)[164,165], switching or augmentation strategies[166] – or developing new treatments (e.g., exploration of out-of-the box ideas and accidental discoveries[167]). A focus on prevention (e.g., in educational or occupational settings)[168,169] may improve the situation as well.

Improving treatment strategies for mental disorders can be regarded as a central health challenge of the 21st century.

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Assessing the impact of environmental factors on the adolescent brain: the importance of regional analyses and genetic controls

There is substantial brain development during adolescence, which continues up to the early 20s. One of the earliest questions in neuroscience has been the role of experiences, or environmental factors, in that development. As pointed out by Turkheimer[1], "development is fundamentally nonlinear, interactive, and difficult to control experimentally". But, in the last two decades, there has been an enormous progress in brain measurements, cognitive testing, and sample sizes.

Perhaps the most well-studied environmental factor in cognitive development is socioeconomic status (SES). This index is a combination of multiple factors that can impact the cognition of a child, such as the influence of parental education (e.g., the types of books in the household and the intellectual stimulation at the dining table); the influence of income in the quality of the school and the number of extra-curricular activities; the influence of the neighborhood in the type of peers and services available. Children born and raised to parents with low SES have on average a worse development in a wide range of areas: they tend to have lower cognitive abilities and worse academic performance, and to suffer more frequently from mental disorders[2,3].

It is not surprising then that functional magnetic resonance imaging (fMRI) studies show that the brain systems whose activity is affected by SES are frontal and parietal regions related to reasoning and executive functions, temporal language areas, as well as the hippocampus and the medial temporal lobe, which are related to long-term memory[4].

The neurological impact of SES goes even beyond task-specific brain activity at the moment of scanning (as measured by fMRI). SES is one of the few environmental variables that we know can impact the very macrostructure of the brain (as measured by structural MRI), such as cortical surface area, which is typically stable over months and even years of life. A large study imaging the brains of 1,099 individuals between the ages of 3 and 20 years found that the total cortical surface area was related to both parental income and parental educational level[5]. There were regional associations in most parts of the cortex, but in particular in regions supporting language, reading, executive functions, and spatial skills. Other studies have supported these findings, but some show that the frontal cortex is especially targeted, while others show no single region that is specifically connected to SES[4].

There are, however, some caveats that should be kept in mind when interpreting MRI results in this field. First, studies typically suffer from a methodological "blind spot", because global differences in the structural measures, for example in cortical surface area, are often not taken into account. It is therefore unclear if regional findings mean that low SES selectively impacts only specific brain areas or if the impact is better described as broad and global, with minor local variability. Second, SES is likely not to be an entirely environmental factor, but to have a substantial genetic component. For example, it has been reported[6] that a set of genetic markers explained as much as half of SES contributions to school achievement in 16-year-olds.

In a recent study[7], we used a sample of 551 typically developing adolescents, studied at ages 14 and 19, to try to tackle the problem of the entanglement between genetic and environmental effects in the developing brain. In order to estimate genetic effects, we used a combined measure, called polygenic score (PGS), from several thousand DNA markers that were selected and given a weight to optimize prediction of educational attainment (henceforth called EduYears-PGS). As expected, EduYears-PGS and SES were moderately correlated. But, even when controlling for this overlap, SES still had independent effects on cognitive ability at age 14. Interestingly, the SES effect was about twice as strong as that from EduYears-PGS. When analyzing the change in cortical surface area from age 14 to 19, there was an effect of SES, but not EduYears-PGS. This indicated that SES continued to affect brain maturation throughout adolescence.

One limitation of the study was that, although the EduYears-PGS measure is the most powerful genetic predictor available for educational attainment, it does not capture all the genetic variance associated with SES, as suggested by twin studies. Another limitation is that the EduYears-PGS was optimized to predict educational outcome, rather than SES. However, our *post-hoc* analysis suggested that the SES associations that we found were driven almost exclusively by differences in parental education and, as a control for that, the EduYears-PGS we used is optimal.

Regarding the methodological "blind spot" problem mentioned above, we also obtained structural MRI from the adolescents. Initially, we found that both EduYears-PGS and SES were positively correlated with total cortical surface area. However, after controlling for the global effects, there were no additional regional associations of SES to cortical surface area. This means that there were no signs of any particular structure or neural system being selectively affected above and beyond the broad effects of SES. The EduYears-PGS, on the other hand, had an additional regional association with cortical surface area in the right parietal lobe.

The association of SES to global cortical surface area means that the behavioral and psychological consequences of low SES are likely wide-ranging. What could be the environmental factors behind such a broad effect in the developing adolescent brain? Low SES is associated with a range of environmental factors that could impact cognition and brain development. These include toxins, infections and stress during gestation, inferior nutrition, chronic stress, and lack of cognitive stimulation during childhood and adolescence[8,9].

Because research typically shows that the impact of SES continues throughout adolescence, one could expect that the environmental factors during this period play an especially important role, such as chronic stress or lack of intellectual stimulation, rather than gestational factors. Furthermore, if these broad brain impacts (as suggested by regional analyses controlling for global measure) are indeed true, this has negative implications for societies. It makes it less likely that any particular intervention, such as language training, could compensate for the cognitive and behavioral problems. An unfortunate implication of poverty.

However, it is possible that the global neural effect of low SES is the result of a combination of a multitude of environmental effects, and that each of these can be identified and targeted. Future research might thus highlight the role of specific environmental factors in affecting cognitive development, which could help inform policy decisions.

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The evolving epidemiology and differential etiopathogenesis of eating disorders: implications for prevention and treatment

Profound changes in the classification of eating disorders have occurred over the past decades. The expanded diagnostic spectrum of feeding and eating disorders now ranges from conditions characterized by food restriction (anorexia nervosa and avoidant/restrictive food intake disorder, ARFID) through to those typified by food craving and overeating (bulimia nervosa and binge eating disorder).

Since the advent of the DSM-5 in 2013, amenorrhea is no longer required to diagnose anorexia nervosa, and binge eating disorder is a fully recognized diagnostic entity. Most previous differences between the ICD and DSM have now been eliminated: the ICD-11 is broadly similar to the DSM-5, the only important difference being that subjective binges are accepted for an ICD-11 diagnosis of binge eating disorder.

About 1.4% of women and 0.2% of men experience anorexia nervosa during their lifetime; 1.9% of women and 0.6% of men are affected by bulimia nervosa, while 2.8% of women and 1.0% of men develop binge eating disorder. So, binge eating disorder is the most prevalent eating disorder[1].

To judge time trends in the occurrence of new cases, only longitudinal incidence studies on large population-representative samples can provide clarity. Incidence studies count new cases of eating disorders in dynamic populations, meaning that individuals can enter or leave the underlying population by, for example, immigrating to a country or dying. Therefore, each individual in the population is followed up for a different time period. These individual follow-up durations are summed to the total follow-up time expressed in person-years. New cases per person-year are measured by incidence rates.

Although diagnostic specifiers have evolved over time, the incidence of anorexia nervosa and bulimia nervosa presenting to primary care, in countries (such as the UK and the Netherlands) where this is an entry point for secondary care, has been relatively stable over the last six decades[2]. On the other hand, admissions for inpatient treatment for anorexia nervosa have rapidly increased in several European countries, despite most guidelines recommending this as a tertiary form of management. The explanation for this discrepancy in service use is uncertain. One possibility is that a reduced mortality rate has allowed those with a severe form of illness to survive for longer. Another possibility is that environmental protective factors may have decreased whilst perpetuating factors have increased.

There are many contrasts in the clinical features and underlying etiopathogenesis between anorexia nervosa and binge eating disorder. Anorexia nervosa has an earlier onset in the peripubertal period. In binge eating disorder, the female:male ratio is lower, the risk in ethnic minorities is higher, and a developmental and/or family history of higher weight is commonly present. As binge eating disorder is such a recent diagnosis, incidence studies with sufficient follow-up time have not yet been performed[2].

There are no genome-wide association studies on bulimia nervosa or binge eating disorder, but emerging work suggests that the genetic risk profile differs from that of anorexia nervosa. For example, a study using the UK Biobank cohort found that adults who engage in binge eating carry a polygenic liability to higher body mass index (BMI) and attention-deficit/hyperactivity disorder (ADHD)[3]. This contrasts to the negative genetic association with BMI and variables related to the metabolic syndrome in anorexia nervosa[4].

Over the past 70 years, the food environment has changed rapidly. Food technology has increased access to cheap, highly palatable foods (combining salt, sweet and fatty elements), refined for rapid absorption. This has contributed to changes in eating behaviour, such as the reduction in social eating and increase in fast food consumption. These changes in the food environment are likely to have contributed to an increased prevalence of binge eating.

Another key social determinant is weight stigma (social rejection, teasing, bullying and devaluation because of a bigger body), particularly if the body shaming induced is internalized. Weight stigma may be compounded by other forms of trauma, alienation and discrimination that may occur in marginalized groups.

The source of this intolerance is widespread, ranging from family, peers, friends, the online community, the medical profession and policy makers. For example, public health interventions targeting obesity may harm through weight stigmatization and increasing body dissatisfaction[5]. Indeed, data from three ongoing birth cohorts in the UK suggest that weight control behaviours have increased in adolescents of both genders (almost 50% report dieting), which may produce a steep increase in eating disorders within the next decade[6].

The implications drawn from the epidemiology of disordered eating and the emerging genetic associations suggest that complex interactions between the environment and somatic and psychological factors are causally involved in the development of eating disorders. A wide range of variables can moderate the expression of these vulnerabilities. A broader approach to the prevention of both eating disorders and obesity is needed, with a central focus on reducing weight stigma and increasing healthy forms of eating and exercise behaviours rather than promoting unhealthy patterns of food restriction. Eating disorders affect individuals of all body weights, shapes and sizes, and it is of concern that heavier patients may not be considered "ill enough" either by themselves or by the gatekeepers of financially constrained eating disorder services, thus missing the opportunity for early intervention.

At the other end of the care pathway, new approaches are being developed for people with eating disorders who have failed to respond to standard treatment. Advances in the management of binge eating disorder include treatments targeting psychological processes believed to precede and perpetuate the disorder, such as reward sensitivity, inhibitory control, ADHD tendencies and interoceptive awareness. One example is represented by strategies that focus on increasing inhibitory effortful control[7].

In severe anorexia nervosa, there are intriguing case reports describing the use of metreleptin, a recombinant human leptin analogue often used to treat excess appetite in people with lipodystrophies. The seemingly counterintuitive rationale for this is based on experimental work derived from activity-based animal models of anorexia nervosa[8]. Metreleptin led to an immediate reduction in depression, and a later resolution in eating disorder behaviours[9]. A similar profile of change has been seen following neuromodulatory techniques.

Thinking forward, advances in our understanding of the evolving epidemiology and differential etiopathogenetic factors associated with eating disorders can improve prevention and treatment, and hopefully reduce the incidence of these conditions.

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Mental health of children and parents after very preterm birth

Having a baby at less than 32 weeks gestation is a highly stressful and potentially traumatizing experience for parents. For almost all parents, there is heightened anxiety about their baby's health and well-being. In some cases, the birth itself may be traumatic, and women may require an intensive care admission and/or longer stay in hospital. Parents may be separated from their baby for extended periods of time unless there is provision for them to stay alongside their baby in the neonatal intensive care unit.

As well as the immediate risks to their baby's health, parents are faced with uncertainty about their baby's longer-term health and development. There is increasing recognition that children born very preterm (<32 weeks gestation) are vulnerable to mental health difficulties in childhood and adolescence[1]. In the preschool period, they are more likely to experience internalizing and dysregulation difficulties compared with term-born peers[2]. There is also evidence of an increased risk for symptoms and diagnoses of attention-deficit/hyperactivity disorder (ADHD) in the preschool period for children born extremely preterm (<28 weeks gestation)[1]. By school age, compared with term-born children, children born very preterm have three times higher odds of meeting criteria for any psychiatric disorder[3].

The pattern of mental health difficulties and psychiatric diagnoses in children born very preterm appears to be clustered around the key areas of attention, social and emotional difficulties. This is reflected in increased rates of autism spectrum disorder (ASD) and ADHD diagnoses by school age for those born very or extremely preterm[1,3]. This pattern continues into early adolescence, with the most prevalent diagnostic categories for those born preterm being ADHD, ASD and anxiety disorders[4]. Over time, the risk for psychiatric disorder associated with preterm birth appears to decrease, although some studies report ongoing differences in mental health outcomes[5], with implications for quality of life and functioning.

Mothers and fathers of infants born very preterm experience elevated levels of depressive, anxiety and post-traumatic stress symptoms compared with parents of term-born babies. One study found that approximately 40% of mothers and fathers experienced depressive symptoms and almost 50% reported anxiety symptoms soon after the birth[6]. Another showed that approximately one third of mothers and fathers experienced post-traumatic stress symptoms in the early months after very preterm birth, with almost one fifth of parents continuing to report post-traumatic stress symptoms two years after the birth[7]. Symptoms of depression and anxiety in parents of babies born preterm also appear to remain higher across childhood and adolescence compared with parents of term-born babies.

For those born very preterm, early social-emotional difficulties have been associated with later mental health symptoms and diagnoses[1,3]. Factors such as higher socioeconomic risk early in life and severe neonatal brain abnormalities have also been associated with increased risk for later mental health difficulties in these children[3].

Currently, less is known about factors that increase the risk for parental mental health problems after preterm birth. Some studies suggest that social disadvantage increases the risk for poor maternal mental health, while others have not shown an association. Parental history of mental health difficulties may be an important factor to consider, but has rarely been studied in this population.

Given the complexity of predicting which babies and which parents might be at greatest risk for mental health difficulties after very preterm birth, it is important to remember that experiencing preterm birth is in itself a risk factor for mental health difficulties. Knowing this, we need a systematic and integrated response to promote well-being, monitor mental health, and facilitate access to evidence-based early intervention for *all* families who experience very preterm birth. Parents and babies are often in the hospital for several months, meaning that there are opportunities to implement screening and support programs within the hospital, and connect families with external services which can continue to provide monitoring and intervention where needed across early childhood and into adolescence for both children and parents. In development of such systems, it is important to keep in mind that rates of mental health difficulties after preterm birth are similar in mothers and fathers[6,7].

Intervention after preterm birth should be responsive, individualized and multi-layered, and include direct psychological support for parents and broader early intervention programs to enhance infant development and the parent-child relationship. For example, individualized parent trauma-informed psychological interventions in the neonatal intensive care unit, and broad early intervention programs for families after preterm birth have been associated with better parental mental health[8]. There is also evidence that early intervention for families after preterm birth can improve child emotional regulation and behaviour[9]. Longer-term effects of early intervention on school-age and adolescent mental health are unknown, and support should be guided by current evidence-based practice in child and adolescent mental health intervention.

Health professionals working with children and parents after preterm birth should be aware of the increased rates of depression, anxiety and post-traumatic stress symptoms in parents, and the elevated risk for ADHD, ASD and anxiety symptoms and disorders in children and adolescents. In the early years after preterm birth, medical and allied health professionals who see families for routine post-discharge assessment or are working with families in early intervention services are well-placed to continue or initiate conversations around mental health and well-being with parents and provide information and referrals to mental health professionals when needed.

For mental health professionals working with paediatric clients, asking parents about whether the child was born preterm and subsequent history of physical and mental health and development would not only provide important information about the child, but also potentially open discussion around the experience of the parents. Mental health professionals working with parents after preterm birth should be mindful of its potential long-term impact on parental mental health and the risk for ongoing post-traumatic stress symptoms, that may present in both mothers and fathers.

Overall, the available evidence suggests that the individual as well as the couple and/or family experience of very preterm birth is an important under-recognized issue.

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How clinicians can support women in making decisions about psychopharmacological treatments in pregnancy

Ensuring that women can make fully informed decisions about all aspects of their care in pregnancy is not only required by law in many jurisdictions, but is integral to the provision of respectful and contemporary person-centred health care.

Many health systems acknowledge now the importance of mental health in pregnancy through the common practice of universal screening for depression, as well as the increased awareness and health promotion campaigns around maternal mental health. However, when it comes to delivering a clear message that supports women to prioritize their mental health, ambivalence emerges, particularly if staying well involves psychopharmacological treatments.

A common misperception is that not treating a mental health disorder with medication is a risk free option. Also, undertreating with medication is common and perceived as a lower risk option, although it may result in exposure both to the agent and to the illness. For women with moderate to severe mental disorders, such as major depression, schizophrenia and bipolar disorder, it is not a risk free pathway to undertreat or not treat, as both these options may have significant implications and impacts for maternal health, for pregnancy outcomes, as well as for the longer-term outcomes in the child.

The overarching principles of informed consent for psychopharmacological treatment in pregnancy involve understanding and communicating risks associated with treatment. These include the nature, magnitude and probability of risks associated with a treatment and any alternative options, including no treatment[1].

Adapting information, checking on shared understandings, and providing information in a number of formats and, where appropriate, involving partners, family or carers, can be important tools. Moreover, many women are motivated by wanting the best outcomes for their unborn child. Going through the risks of a specific treatment on the one hand, but, on the other, the risk of significant relapse in the early postpartum, potentially impacting the woman's ability to care for her newborn, is recommended practice. It is important to deliver a clear message that caring for one's own mental health is also the start to parenting and caring for the unborn child.

An essential principle, when supporting informed decision making for mental health treatments in pregnancy, is indeed to not only focus on the risks/benefits for a woman's health, but also understand the implications for her fetus/infant and for the evolving relationship between the two. These three elements of focus – maternal mental health, fetal/infant well-being, and the quality of the mother-infant relationship – should be core to all perinatal mental health care[2]. To do this requires a clinician to support decision making that encompasses information across all these three aspects of risk/benefit from treatment options.

First of all, clinicians should be skilled in understanding and interpreting the latest research findings and also be able to place them in the complex interplay of multiple factors that occur in pregnancy[3]. Unfortunately, our research base for psychopharmacological treatments in pregnancy requires navigating a web of conflicting and often confusing findings, including associations without adjustment for relevant confounders or with other obvious methodological flaws. Clinical guidelines can provide some direction, but evidence-based practice also requires consideration of broader expertise, individual patient characteristics and, importantly, patient preference.

Secondly, clinicians must distil research findings for key outcomes into information that can be adapted during a clinical discussion. It is not comparing outcomes to the general population, but comparing outcomes for those treated compared to untreated. Equally important is communicating if a risk is unlikely to be clinically significant[4]. The overall aim is to provide clear and respectful communication that fosters a women's sense of empowerment, choice and control. Getting this right not only improves informed decision making, but also leads to a positive therapeutic relationship. What each woman wants may vary from copies of scientific papers to a brief summary of risks and benefits. Ensuring that clinicians adapt information appropriately is part of woman-centred care.

Thirdly, the discussion of viable alternative treatments is critical to ensuring that informed decisions can be authentically made. However, viable means available, acceptable and appropriate to the clinical presentation. Evidence base for psychosocial interventions usually relies on training and fidelity to a specific intervention, not a grab bag of techniques[5]. Ensuring that an evidence-based alternative is offered is essential. However, informed decision making is not served by a discussion of options that are not truly viable or clinically appropriate.

Finally, the clinician needs to be clear about his/her own recommendation while respecting the women's right to choose the best option for her, whether this aligns or not with the clinician's own choice.

Putting all this into practice is challenging. For women with long-standing mental disorders, such as schizophrenia or bipolar disorder, the ideal time to discuss options is pre-conception. For women in the childbearing years, caution should be exercised with some agents, such as valproate. In many jurisdictions, there are now limitations on prescription of valproate to women, due to the risks to fetal well-being and the high rate of unplanned pregnancies. Changing a woman from medications contraindicated in pregnancy should be well in advance of trying to conceive.

For those women on medications such as lithium, lamotrigine or antipsychotics, ensuring effective treatment leading into a pregnancy is recommended, as well as consideration of areas such as folate supplementation, assessing vitamin D levels and a focus on overall general health. While it may not be advisable to change a medication, it is possible to minimize harmful impacts through careful monitoring and dose adjustment, since both hepatic metabolism and renal clearance accelerate in later pregnancy.

There are clinical aids that can be adapted to support this within services[6]. An example of monitoring and dose adjustment is with lithium: this includes ensuring early screening for risk of a cardiac malformation, then careful and close blood monitoring of levels throughout third trimester, prior to delivery and into the postpartum[7]. For antipsychotics, especially those with metabolic risks, another example is early screening for gestational diabetes at 16-18 weeks, rather than waiting until the usual routine screening at 28 weeks, to detect and manage any emerging diabetes early and prevent harm from prolonged hyperglycaemia to the woman and the baby[8].

For some women taking antidepressants, there is a concern that their baby may be born addicted and this comes from the misunderstanding of poor neonatal adaptation symptoms associated with antidepressants in pregnancy. Explaining that this may be neither a withdrawal or toxicity response, is likely self-limiting and mostly mild is important to place this in context of managing mental health[9].

The choice between uncertain options is not easy for women or for treating clinicians. Any change in the foreseeable future will require a concerted effort by clinicians, researchers, funders and women, to shift the current research agenda and ensure there is investment in studies able to provide clarity for risks and benefits from psychopharmacological treatments during pregnancy. Ultimately, it will be this investment, together with delivery of person-centred care, that will support the evolution of truly informed decision making for mental health treatments, including pharmacological ones, in pregnant women.

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Clinical response to SSRIs relative to cognitive behavioral therapy in depression: a symptom-specific approach

Both antidepressant medication and cognitive behavioral therapy (CBT) have been found efficacious in reducing overall depression severity[1,2]. A patient-level meta-analysis[3] showed that medication was slightly more efficacious than CBT and that this was independent of pre-treatment depression severity. A crucial step in improving clinical practice would be to identify factors that do play a role in the clinical response to treatment and, thus, can be used in decision support tools guiding the personalization of treatment[4].

In a previous paper published in this journal[5], we reported that individual symptoms differ in their response to antidepressant medication relative to CBT. In general, medication was more efficacious than CBT in reducing affective symptoms (i.e., depressed mood and psychic anxiety) and cognitive symptoms (e.g., feelings of guilt and suicidal thoughts), whereas their efficacy was comparable for most symptoms related to, for example, sleep, arousal and bodily functions. We also applied network estimation techniques to reveal the complex patterns in which changes in individual symptoms were related and could, consequently, detect those symptoms that were directly affected by medication (i.e., direct treatment effects) or only indirectly affected through impact on other symptoms (i.e., indirect treatment effects).

As the neurobiological actions and consequent clinical profiles of antidepressant classes differ, it is important to study one medication class at the time. While we previously had lumped together data regarding different classes of antidepressants[5], the current analysis focused on only one group, selective serotonin reuptake inhibitors (SSRIs), as these are the most commonly prescribed antidepressant drugs. From our previous sample[3,5], we hence selected patients with a DSM-based primary diagnosis of a depressive disorder (major depressive disorder or dysthymia) participating in trials comparing an SSRI with CBT. The 599 patients (68.4% women; mean age: 42.7 years) of six trials with complete pre- and post-treatment symptom data comprised the sample of the current study. Of these patients, 391 (65.3%) received an SSRI and 208 (34.7%) CBT.

Statistical software R (version 4.0.5) was used to estimate a network including treatment condition (SSRI relative to CBT) and changes in individual depressive symptoms during treatment. As this combines a binary variable (treatment condition) with continuous variables (change scores), the network was estimated with package *mgm*[6] using a mixed graphical model and visualized with package *qgraph*[7].

Changes in individual depression symptoms were assessed using the 17 separate items of the Hamilton Depression Rating Scale (HDRS)[8], both before and after treatment (8-16 weeks after the pre-treatment assessment). To improve the interpretation, we divided the 17 symptoms into five categories: two affective symptoms (i.e., depressed mood and psychic anxiety), four cognitive symptoms (i.e., feelings of guilt, suicidal thoughts, loss of interest in work/activities, and retardation – including concentration difficulties), seven arousal/somatic symptoms (i.e., agitation, somatic anxiety, general somatic symptoms – including lack of energy, genital symptoms, hypochondriasis, and gastrointestinal symptoms), three related to sleep (i.e., early night, middle night, and early morning insomnia), and one concerning lack of disease insight. Items were scored from either 0 to 4 (all affective and cognitive symptoms, arousal/somatic symptoms of anxiety, and hypochondriasis) or 0 to 2 (most arousal/somatic symptoms, all sleep symptoms, and lack of insight).

In the resulting network, the only direct beneficial effects of SSRIs relative to CBT were found for the two affective symptoms, i.e., depressed mood and psychic anxiety (both connection strengths = –.05). Changes in depressed mood were mainly related to changes in psychic anxiety (connection strength = .17), all four cognitive symptoms (connection strengths ranging from .08 for feelings of guilt to .24 for loss of interest in work and activities) and, although less strongly, specific arousal/somatic symptoms (e.g., connection strengths of .11 for gastrointestinal problems and .08 for general somatic symptoms including lack of energy). Changes in psychic anxiety were mainly related to changes in depressed mood (connection strength = .17) and most arousal/somatic symptoms (e.g., connection strengths of .20 for somatic anxiety and .08 for agitation).

Interestingly, we also found two detrimental effects of SSRIs relative to CBT, both on arousal-related symptoms, i.e., somatic anxiety (connection strength = .09) and agitation (connection strength = .03). Changes in somatic anxiety were related to changes in specific other symptoms (connection strength of .20 for psychic anxiety), whereas changes in agitation were not or only very weakly related to changes in other symptoms.

Our findings show that, relative to CBT, SSRIs are more efficacious in improving depressed mood and psychic anxiety, whereas they are less efficacious in improving somatic anxiety and agitation. This suggests that patients suffering more from the former two symptoms and less from the latter two may benefit the most from SSRIs, and vice versa.

To explore this, we distinguished groups of patients (quartiles, Q1 to Q4) based on a pre-treatment severity measure in which these four symptoms were summed and weighted by their connection strengths as derived from the network. As expected, the overall efficacy of SSRIs over CBT increased in groups scoring higher on this severity indicator (i.e., Cohen's d=.10 in Q1, .01 in Q2, –.05 in Q3, and –.16 in Q4).

In conclusion, our study is the first distinguishing the direct and indirect symptom-specific effects of SSRIs relative to CBT (and vice versa) and can, consequently, provide important insights into the potential mechanisms of clinical change during the different treatments. SSRIs mainly have direct beneficial effects on the two affective symptoms, which is in line with an individual patient meta-analysis comparing SSRIs to a placebo control condition[9]. The most important indirect effects of SSRIs are found for all cognitive symptoms, including highly clinically relevant symptoms such as suicidal thoughts and loss of interest, and specific arousal/somatic symptoms. SSRIs have detrimental effects on two specific arousal symptoms (i.e., somatic anxiety and agitation), which are common side effects of SSRIs that can be captured by the HDRS.

We also found that information from these networks could help in improving the identification of patients who were the most likely to benefit from one treatment relative to the other. That is, patients who suffered more from depressed mood and psychic anxiety and less from somatic anxiety and agitation were the most likely to benefit from SSRIs, whereas the opposite was true for CBT. It is, however, important to note that effect sizes were small (Cohen's d ranging from .10 in Q1 to –.16 in Q4), somewhat limiting the relevance of findings for clinical practice.

A symptom-specific approach is valuable, but also challenging, as more research is needed on the reliability and validity of assessing individual symptoms with individual (HDRS) items. In addition, the current categorization of symptoms – just like any categorization – may be overly simplistic, as, for example, affective symptoms may also comprise a cognitive component and cognitive symptoms an affective component. However, we do want to emphasize that a symptom-specific approach is highly promising in capturing the complex clinical response to depression treatments and in guiding the personalization of treatments.

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COVID-19 vaccination uptake in people with severe mental illness: a UK-based cohort study

The COVID-19 pandemic has exacerbated pre-existing health inequalities between people with severe mental illness (SMI) and the general population. These inequalities are rightly regarded as a human rights issue[1]. Rapidly accumulating evidence indicates that people with SMI are disproportionately affected by COVID-19 infection, showing increased risks of hospitalization and mortality[2].

Attention has recently turned to equitable COVID-19 vaccine allocation. Drawing on ethical frameworks, there have been calls – the first one appearing in this journal[3] – to prioritize people with SMI for vaccination. Having been severely affected by the pandemic, the UK has been among the fastest countries worldwide to deploy its vaccination plan and one of the few countries to explicitly prioritize persons with SMI[4]. Evidence on vaccine uptake among population subgroups in the UK is emerging[5]. However, more fine-grained evidence of uptake among people with different psychiatric diagnoses is necessary to evaluate delivery of vaccination plans and inform mental health practitioners.

We are investigating COVID-19 outcomes using de-identified electronic health record data from the Greater Manchester Care Record (GMCR), a shared care record for 2.8 million people, comprising real-time information from primary care, hospital admissions and mental health records. Using the GMCR, we compared vaccination rates in a sample of 1,152,831 adults with and without SMI. Individuals were followed up until June 30, 2021, ahead of the UK's relaxation of COVID-19 restrictions on July 19, 2021. Approval was granted by GMCR's secondary uses and research governance process.

All patients who were registered with a general practitioner in Greater Manchester on January 31, 2020, aged 18 years or over, and with a lifetime diagnosis of SMI recorded in their primary care record, were eligible for inclusion in the SMI sample. This sample was divided into three hierarchically defined, mutually exclusive groups of individuals with schizophrenia or related psychotic disorders (N=46,859), bipolar disorder (N=3,461), and recurrent major depressive disorder (N=134,661). Alongside this, we also obtained a 10% sample of individuals with diagnoses of other depressive disorders, excluding all previously mentioned diagnoses (N=45,586). For comparison purposes, we obtained records for 922,264 age and gender-matched controls with no evidence of SMI or depressive disorders, sampled at a 4:1 ratio against cases.

Our outcome measure was the proportion of individuals who received at least one dose of COVID-19 vaccine by June 30, 2021, as recorded in their primary care records. We also sought to examine the proportions of individuals recorded as having declined vaccination. Conditional logistic regression models were used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs). Analyses controlled for sociodemographic covariates, including age, gender, ethnicity and Index of Multiple Deprivation (IMD) decile. Imputation was used for missing ethnicity (N=105,407; 9.1%), IMD (N=1,734; 0.2%) and gender (N=121; <0.1%) data. All statistical analyses were performed in R version 4.0.0.

Compared to matched controls, vaccination rates were highest among people with recurrent major depression (77.1%; aOR=1.22, 95% CI: 1.21-1.23), followed by bipolar disorder (75.7%; aOR=1.19, 95% CI: 1.14-1.23), other depressive disorders (75.1%; aOR=1.19, 95% CI: 1.18-1.20), and psychotic disorders (69.6%; aOR=1.03, 95% CI: 1.01-1.04). The prevalence of vaccination among all controls was 68.4%.

The proportion of individuals recorded as having declined vaccination by June 30, 2021 among all controls was 2.0%. Rates of having been recorded as declining vaccination were significantly higher across all mental disorders examined, with psychotic disorder diagnoses highest (5.0%; aOR=2.32, 95% CI: 2.22-2.42), followed by bipolar disorder (3.8%; aOR=1.91, 95% CI: 1.60-2.27), recurrent major depression (2.9%; aOR=1.43, 95% CI: 1.38-1.48) and other depressive disorders (2.8%; aOR=1.40, 95% CI: 1.32-1.48).

This is one of the few research studies internationally to report on COVID-19 vaccination uptake among people with mental disorders[5,6]. Our results show that people with SMI, particularly those with mood disorders, were significantly more likely to be vaccinated against COVID-19 than people without SMI. Despite this, however, individuals with psychiatric diagnoses, and particularly those with schizophrenia or related psychotic disorders, were significantly more likely to have a record of having declined vaccination for COVID-19.

A prior UK study reported that vaccination rates among people with SMI were significantly lower than people without SMI[5], but this analysis was restricted up until March 2021 among people aged 80 years and over. A study from Israel[6] – a country which also acted proactively regarding COVID-19 vaccination – also reported lower odds of vaccination among people with schizophrenia. Whilst it is encouraging that we did not see this gap in the UK, it seems that a significant proportion of people with SMI, and people with psychotic disorders in particular, remained unvaccinated as of June 30, 2021. This is concerning, given the higher rates of comorbid physical diseases observed in these groups, which may increase their risk of COVID-19 hospitalization and mortality[2], particularly as new variants arise and social distancing restrictions subside.

The higher odds of having declined a vaccine among people with SMI, and psychotic disorders in particular, warrant further attention. Taken at face value, this could indicate heightened vaccine hesitancy among people with SMI. Alternatively, this could merely be an artefact of vaccine deployment processes, reflecting that health care professionals may have more actively offered, discussed and/or recorded attempts to promote vaccination with people with SMI, thus resulting in the higher rates of recording declined vaccination offers.

While our results are limited to Greater Manchester, this constitutes a sizeable and important population in Northern England, a region known to have been disproportionately impacted by COVID-19[7]. Subtly different choices in data sources, regional boundaries and population denominators may have resulted in differences between our prevalence estimates and those recorded by central government. Furthermore, controls were matched using age and gender, but not comorbidities; thus, controls were likely to be physically healthier.

The notably higher odds of declining vaccination recorded among people with SMI, and particularly those with psychotic disorders, indicates that more targeted efforts may be required to support informed decision-making and encourage vaccine uptake among these vulnerable populations, while respecting personal autonomy.

Addressing the range of individual and systemic level barriers to vaccination that may apply among people with SMI warrants urgent investigation[8]. Alongside this, future research should explore the extent to which clinical and psychological predictors explain vaccination uptake and refusal among people with SMI.

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CopeNYP: a brief remote psychological intervention reduces health care workers' depression and anxiety symptoms during COVID-19 pandemic

The COVID-19 pandemic has significantly impacted the psychological well-being of health care workers globally[1]. Meta-analyses indicate that approximately 20-30% of health care workers experience depression, anxiety or symptoms of post-traumatic stress disorder[2,3]. There are few data about the efficacy of tailored interventions[4].

We designed and implemented CopeNYP, an in-house, four-session, telehealth-delivered intervention. Our model incorporated brief skills-focused techniques from evidence-based psychotherapies (e.g., problem-solving therapy, behavioral activation, and supportive therapy), tailored to health care workers' specific needs and circumstances.

The first session focused on assessment of mental health needs and available social support, formulation of short-term treatment goals, de-stigmatization of mental health difficulties, and psychoeducation about symptoms of anxiety and depression and exposure to trauma and stress. In each subsequent session, clinicians focused on behavioral activation and stress reduction (i.e., engagement in pleasurable activities, relaxation, mindfulness skills), validation of emotional responses, and problem-solving techniques (i.e., resolving interpersonal conflicts, reducing social isolation, coping with loss and grief). The last session included reinforcement of skills, relapse prevention, and follow-up plans if needed.

CopeNYP was developed and launched at Weill Cornell Medicine's Psychiatry Department. We assessed the program's efficacy in reducing depression and anxiety symptoms among health care workers.

Interventions were delivered by 67 clinicians (including 41 clinical psychologists, three social workers or pastoral counselors, four psychiatrists, four psychology pre-doctoral interns, and 15 psychology post-doctoral fellows). Clinicians underwent brief training on manualized assessment, triage and skills-based therapeutic techniques and received weekly peer group supervision and on-call supervisory consults from senior clinicians.

CopeNYP was introduced to employees in hospital COVID-19 updates and internal communications. All employees were invited if they were experiencing distress and/or wished to speak with a psychotherapist. No exclusion criteria were implemented. Employees contacted administrators for scheduling via email or phone. The study was approved by Weill Cornell's institutional review board.

Anxiety and depression were assessed during the first and last sessions using the Patient Health Questionnaire-9 (PHQ-9)[5] and the Generalized Anxiety Disorder-7 (GAD-7)[6]. Suicidality was evaluated at intake using the Columbia-Suicide Severity Rating Scale (C-SSRS)[7], repeated if needed. The PHQ-4[8] was administered in sessions 2 and 3 for symptom monitoring.

Employees with severe symptom presentations were referred to longer-term clinical care or emergency services if at imminent risk of harm. If pharmacotherapy was indicated, employees were referred to a psychiatrist for evaluation/treatment and continued to receive CopeNYP sessions until psychiatric treatment started. Employees were referred for additional psychotherapy after the last session as needed.

PHQ-9 and GAD-7 scores were converted to PHQ-4 scores to estimate slopes over all time points using linear mixed-effects regression to account for within-subject correlations (random effects: subject slope and intercept; fixed effect: time). Analyses were conducted with a modified intent-to-treat sample (i.e., patients with at least one visit). Partial eta squared effect size was calculated for the fixed effect of time. We evaluated clinical response rates (i.e., 50% reduction in PHQ-9 or GAD-7) among employees who received four sessions of CopeNYP.

A total of 534 health care workers participated in the program. The institutional review board did not allow reporting their demographic data. The sample included 35.2% nursing staff (N=188), 24.3% patient support staff (N=130), 22.8% administrative support staff (N=122); 13.8% physicians/doctoral level faculty and trainees (N=74), 2.4% maintenance workers (N=13), and 1.3% employees' family members (seen at the request of an employee receiving services; N=7). Overall, 70% of employees were frontline, employed in-person; 19% worked remotely; 11% did not indicate.

A total of 1,423 sessions were delivered between March 27, 2020 and April 16, 2021, with an average of 25.41±13.31 sessions per week and an average of 2.66±1.28 sessions per employee (141 participants completed just one session; 106 two sessions; 103 three sessions; 166 four sessions; 18 over four sessions). At intake, 45% of employees reported at least moderate anxiety (GAD-7 score: ≥10); 42% reported at least moderate depression (PHQ-9 score: ≥10) and 10% reported suicidal ideation (PHQ-9 item 9 score: ≥1).

The linear mixed effects regression showed significant reduction in symptoms during the intervention for the entire sample (PHQ-4 mean score: 5.65±2.95 at intake, 3.32±2.46 at last session; $F_{3,823}$=109.23, p<0.001, eta squared = 0.27). Treatment effects were larger among workers who reported clinically significant symptoms at intake (PHQ-4: ≥6), with an average reduction on the PHQ-4 from 8.09±1.78 to 4.36±2.63 ($F_{3,462}$=139.99, p<0.001, eta squared = 0.46).

These effect sizes remained significant when we controlled for number of hospitalizations and employment format (frontline in person or remote) to account for potential effects of the pandemic on symptoms beyond the intervention (main effects and interaction with time were non-significant). Among participants with both intake and last session rating, 42% exhibited greater than 50% reduction on the GAD-7 (mean change: –4.45, SD=4.22), and 43% showed greater than 50% reduction on the PHQ-9 (mean change: –3.97, SD=4.42).

Thus, we found that a brief, in-house, telehealth-delivered, psychotherapy skills-based intervention significantly reduced symptoms of anxiety and depression among health care workers, the majority of whom were frontline workers, likely exposed to acute and chronic stress due to COVID-19. This is among the first reports of efficacy for such a brief, on-demand psychological intervention tailored to health care workers during the pandemic.

While direct comparison is difficult, the percentage of treatment responders was similar to that observed in brief evidence-based psychotherapies, and greater than reported effects in psychotherapy control conditions[9]. Limitations of the study include the lack of a control group and the brief follow-up. Nonetheless, our findings suggest that accessible, high-quality, brief interventions can reduce psychological distress among health care workers and may provide a template for other health systems.

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Sustainable Technology for Adolescents and youth to Reduce Stress (STARS): a WHO transdiagnostic chatbot for distressed youth

Up to half of mental disorders start by age 14, often with long-lasting and serious consequences for health and productivity throughout life. Among young people aged 10-24 years globally, self-harm, depression and anxiety are now respectively the third, fourth and sixth leading causes of disability-adjusted life years (DALYs) lost[1]. Adolescence provides a critical opportunity to support mental health. Evidence for the effectiveness of psychological interventions for adolescents is growing, but difficulties remain in accessing them.

To expand access to evidence-based psychological interventions, the World Health Organization (WHO) is developing and testing the effectiveness of brief transdiagnostic, scalable psychological interventions for youth and other populations affected by adversity[2-5]. This work is including digital interventions.

Digital mental health interventions have shown promise for reducing symptoms of depression and anxiety in adolescents[6]. However, high drop-rates are reported[7], possibly because adolescents are accustomed to digital tools with higher levels of interactivity and attractiveness than those commonly found in digital mental health interventions[8].

Using human centered design (HCD) methods to create digital interventions may help improve user engagement[8] by forming an understanding of user needs and the setting where the product will be used, and applying this to the product design process. HCD has been used in the development of a range of user-friendly health interventions, for example to support the implementation of evidence-based psychotherapies in low-resource communities[9].

The WHO Sustainable Technology for Adolescents and youth to Reduce Stress (STARS) project is aiming to develop and test an evidence-based digital psychological intervention for youth experiencing high levels of psychological distress. The development process was guided by HCD methods and thus far has focused on adolescents aged 15-18 years, incorporating feedback on prototypes from adolescents, expert input, and literature reviews. The end product was not pre-determined, but evolved through the design process, resulting in a chatbot (an online application that engages the user through a messaging conversation) that delivers transdiagnostic cognitive behavioural therapy (CBT) content.

The first step in the design process was to develop an understanding of adolescents' context and the settings where the intervention would be used. To do this, a team from WHO (two psychologists and an HCD expert) collaborated with partners in South Africa, Pakistan, Jamaica, Nepal and occupied Palestinian territories to conduct interviews and observations to understand the mental health needs, technology use and daily lives of adolescents. Concurrently, narrative literature reviews (e.g., technology use; effective psychological interventions for adolescents) and interviews with experts (e.g., community leaders, adolescent mental health researchers) were completed. The outputs of this stage included fictional characters called "personas", commonly used in HCD methods, which broadly represented the context, needs and motivations of the adolescents interviewed.

The second step focused on creating ideas for "how" and "what" psychological content would be delivered. Ideas for how to deliver content were developed through creative workshops with adolescents and experts; reviews of related products that adolescents already used (e.g., mobile apps); and feedback from adolescents on pre-existing digital interventions. Findings from the literature reviews and expert interviews were also used. Outputs of this stage included ideas on how to deliver psychological content (e.g., through videos, radio messages, apps) and the types of evidence-based content that could be delivered (e.g., problem management techniques, mindfulness techniques).

Basic prototypes were developed based on these ideas and tested with adolescents in the five settings to understand use. Prototypes were updated based on feedback and further tested. This iterative cycle (idea creation, prototype development and feedback) continued with the intervention being progressively written and developed until a fully functioning, user friendly, version emerged.

The resulting STARS intervention uses a decision-tree logic chatbot to deliver content over ten chat sessions. Chat sessions are approximately 10 min long each and use conversational text with a friendly tone, videos, emojis and stories to communicate core psychological content. The user can respond to the chatbot through pre-defined button responses and sometimes typing. Quizzes, content reminders and options to complete shorter "recap" versions of previous modules are used to support learning. Elements of personalization are included to increase engagement, such as choice over notifications and content delivered by the chatbot (e.g., which emotion regulation activity to complete, which story to follow).

The psychological content delivered by the chatbot follows a CBT framework, as supported by the narrative review, prototype test results, and consultations with experts. To address the broad mental health needs reported by adolescents, a transdiagnostic approach is used. The ten sessions are: 1. Introduction (intervention overview, privacy and confidentiality); 2. Emotions (psychoeducation about emotions); 3. Relax (emotion regulation techniques, such as slow breathing); 4. and 5. What we do (behavioural activation); 6. and 7. Managing problems (problem management techniques); 8. and 9. Self-talk (thought challenging); and 10. What next (consolidating learnings and planning for the future).

STARS has been designed for adaptation across multiple settings, including low- and middle-income countries. It can be delivered through existing chatbot systems using different technologies (e.g., apps, websites, messaging platforms) which require relatively low amounts of data and may support scaling of STARS once released. The conversational scripts, and the use of pictures, videos and stories have been designed to aid translation and adaptation. Human review of messages can be added to the chatbot to allow for use with or without human guidance.

STARS has been piloted in South Africa. Additional formative work is underway in other countries, and a randomized controlled trial is scheduled to begin in Jordan. If results from at least two randomized controlled trials demonstrate effectiveness, the intervention will be released open access, allowing older adolescents and young adults to access this highly scalable intervention.

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Mental health services on the roof of the world

In the past decade, mental health services have developed rapidly in China[1]. The number of psychiatric hospitals increased from 583 in 2002 to 1,026 in 2016 nationwide. The numbers of licensed psychiatrists and psychiatric registrars in psychiatric hospitals increased from 1.27 per 100,000 in 2002 to 2.15 per 100,000 in 2016[2].

However, due to historical, sociocultural and economic reasons, mental health resources are mostly located in cities, but often less accessible or even lacking in economically underdeveloped areas, such as in Qinghai-Tibetan Plateau, the "roof of the world".

Compared to other parts of China, very few studies examined the epidemiology of psychiatric disorders in Qinghai-Tibetan Plateau. An epidemiological survey using a multi-stage, random sampling method was conducted in Tibet Autonomous Region (part of the Qinghai-Tibetan Plateau) in 2003[3,4], and found that the lifetime prevalence of mood disorders, schizophrenia, and alcohol dependence was 0.56%, 0.37%, and 3.08%, respectively. The lifetime prevalence of severe psychiatric disorders was 1.14%.

There are around 10.24 million inhabitants in Qinghai-Tibetan Plateau. According to the above findings, this translates to approximately 116.7 thousand persons suffering from severe psychiatric disorders, and 315 thousand persons suffering from alcohol dependence.

Tibetans suffering from psychiatric disorders usually do not seek professional help. Due to the impact of Tibetan Buddhism, they commonly seek help from living Buddha in temples, rather than health professionals. In addition, sometimes they receive Tibetan medicine, although no solid evidence suggests that this is effective for psychiatric disorders[4].

Furthermore, mental health services are almost not available in Qinghai-Tibetan Plateau. For instance, the first and only psychiatric outpatient clinic in Lhasa (the capital city of the Tibet Autonomous Region) was established in 2004, with only one psychiatrist, and was closed in 2008 as the psychiatrist moved elsewhere[4,5].

In the past few years, the importance of mental health services has gained recognition in the Tibetan area. The Chinese Government has taken effective measures to provide regular mental health care. In 2017, the first and currently only available psychiatric hospital in the Tibetan area was established in Nangqian county, Qinghai province, with 32 psychiatrists and psychiatric nurses and 52 psychiatric beds[6].

Due to insufficient local mental health resources, medical training and continuing education in Qinghai-Tibetan Plateau, the Chinese government assigns senior psychiatrists and nursing staff from Beijing to this hospital on an annual basis and ensures training for this personnel. However, this hospital can only provide services for local patients and those in neighboring areas. Most Tibetans with psychiatric disorders in Qinghai-Tibetan Plateau still have no accessible mental health services.

In summary, the endeavors of the Chinese government and health authorities have improved access to mental health services, but further progress is still needed to address the major challenges facing mental health care in Qinghai-Tibetan Plateau.

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Alternatives to coercion in mental health care: WPA Position Statement and Call to Action

The WPA wishes to spur progress worldwide in implementing alternatives to coercion in mental health care. Agreement is widespread among psychiatrists, other health practitioners and people with lived experience and their families that coercive practices are over-used[1,2], and that implementing alternatives is essential to improving standards of mental health care.

In October 2020, the WPA General Assembly adopted a Position Statement and Call for Action to begin this work[3]. Action is needed in all countries, involving health services, communities, service users and their organizations, and governments, to ensure that people living with mental disorders and psychosocial disabilities have access to high-quality care and support that meet their needs and respect their rights.

These rights are set out in the United Nations Convention on the Rights of Persons with Disabilities[2,4]. They include rights to: equality and non-discrimination; equal recognition before the law; freedom from torture, inhuman or degrading treatment; respect for physical and mental integrity of the person; and respect for home and the family.

The term "coercion" describes forceful action, involuntary treatment, or threats undertaken in the course of providing treatment or addressing perceived harm that a person poses to his/her own self or others due to a mental health condition. Coercive practices include formal detention, treatment without consent (or "compulsory treatment"), seclusion and restraint, including the use of mechanical devices, person-to-person restraint, or psychotropic drugs for the primary purpose of controlling movement ("chemical restraint")[4].

The question of whether coercive interventions can ever be justified in psychiatric treatment and mental health care, to protect rights holders' own interests or on other grounds, is highly debated[5,6]. The WPA Position Statement recognizes the diversity of views and experiences among psychiatrists, other health practitioners, people with lived experience, and their families and carers. Developed in consultation with WPA Member Societies and service user advocates, the Statement sets a direction and gives a practical starting point for action, even while recognizing the importance of the seemingly intractable question of competing rights (sometimes referred to as the "Geneva impasse")[7,8].

The WPA Call for Action takes a pragmatic approach. There is a large and growing evidence base[4] on implementing effective alternatives to coercion in health settings across low-, middle- and high-income countries. Many of the changes promote the rights and recovery of service users and the transition towards recovery-oriented systems of care, for example: service user involvement, attention to early intervention, integrated and personalized care, continuity beyond clinical settings and support for full participation in community life[9-11].

Failing to make these changes exposes people with lived experience and their informal and professional carers to continued risk of harm, heightened when stigma and discrimination prompt fear and exclusion through sensationalized media coverage and politicization of efforts to stop coercive practices. Social, cultural and economic barriers of all types exist in countries. Patterns of practice and awareness of coercion, quality of training, attitudes toward care, service resources, the types of facilities, and the laws under which they operate can all act as facilitators or barriers[4].

Given the evidence that alternatives to coercion are achievable, improve care and avoid harm, the WPA calls on psychiatrists and all care providers, community groups and policy-makers to: a) consider the evidence base on alternatives to coercion (such as *Safewards*, *Six Core Strategies*, *Open Door Policies*, and the World Health Organization's *QualityRights Initiative*)[4], and learn from the experiences of those who have generated change; b) identify alternatives that are feasible to implement; and c) take active steps with partners to develop and implement evidence-based alternatives. Working with all stakeholders is exemplified by WPA's recommendations on working with service users and family carers[12], now incorporated in the WPA Code of Ethics[13].

The Call for Action encourages WPA Member Societies and partners to decide on priority actions for their own countries. They can choose from 15 recommendations across several arenas: treatment and care; policy and legislation; service culture and attitudes; and research programs. For example, psychiatrists can have a strong influence on attitudes, practice and training in health services. They often have significant roles in persuading policy-makers to give priority and resources to implement alternatives to coercion, to regard these changes as indicators of health service performance and to establish public databases relevant to measuring these. They can explain the need to intervene early in an episode of ill health to avoid situations in which coercion is perceived as necessary.

Psychiatrists are important in generating political will, developing evidence-informed policy, and sharing experiences with colleagues in other settings; and ensuring that service users and their families and carers are involved centrally in decisions about care, research, evaluation and policy-making. The testimony of persons who have experienced coercive practices and their families, and the advocacy of services users' and family movements are essential. The united voices are key to governments, researchers and funders giving priority to development and testing of alternatives to coercion in a wide range of settings, including those with vastly different access to resources[1,2].

The WPA plans to continue the work through engagement with its Member Societies and the other partners involved in developing the Position Statement as well as wider national and international communities. Translation of the Statement into several languages is in progress or planned. We can aim through a sustained effort that gathers pace and size over time to implement evidence-based alternatives to coercion, improve standards of mental health care, and promote lasting change fundamental to the lives and health of service users and their families and the practice of psychiatry everywhere.

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WPA Secretariat's work: reorganization almost completed

The COVID-19 pandemic has entered our life[1-4], and the largest psychiatric organization in the world, the WPA, which unites under its wing more than 250,000 specialists from 121 countries and represents 145 national societies of psychiatrists, was not excluded from this process. In these absolutely new conditions, to reorganize the work of the Secretariat based on today's reality and to optimize it became our highest priority. This included restructuring the entire communication process; defining development prospects, strategy and coordination of our media resources; and using new digital technologies, including the operational management of our website (www.wpanet.org).

The responsibilities of each of the members of the Geneva Secretariat have been more clearly defined; their working relationship with each individual member of the Executive Committee has been consolidated; the section of the Secretariat responsible for financial work has been functionally transformed, and new employees have been recruited who are now directly involved in this activity.

Concerning allocation of responsibilities and support to Executive Committee members, the agreed principle is that each member of the Committee should be supported by a designated staff member. As there are limited staff resources, each Committee member should also continue to use his/her own local support. It is important to emphasize that this optimization of work has taken place without increasing funding, only by regrouping the functions of employees. The process has been completed directly under the leadership of the President and with the active assistance of other members of the Executive Committee. We also used the services of external consultants specialized in the management of large international organizations. Based on their recommendations, the Secretariat is optimizing the workflow and accounting using modern digital technologies. This will allow to significantly improve the feedback of the WPA Secretariat to all components of the organization and, obviously, to all Member Societies.

Our communication with all the eighteen Zone Representatives has improved significantly. In addition to their mandatory annual meetings, the Representatives hold now – at our suggestion and with the help of the Secretariat – a number of informal consultation meetings, in which they discuss pressing problems and coordinate their actions. In order to speed up this process, a special chat has been created. The Secretary General is involved in all these processes. These arrangements are particularly helpful in the periods of preparation for WPA Congresses. Upon the initiative of this group, the idea of holding a number of Regional and Thematic Congresses, including the first one in Africa, is being discussed.

A new initiative which has been successfully promoted and organized in practice is the publication of a quarterly WPA e-Newsletter. In agreement with the Executive Committee and with the contribution of various WPA components, the first issue was released in July and the second in October 2021.

A lot of preparatory work was done for this activity; sources of funding for the project for the next year were secured; and a communications consultant was appointed, who performs technical and editorial functions. The publication of the e-Newsletter was entrusted to the Secretary General, but the general management and coordination of the project is carried out directly by the WPA President. The WPA Executive Committee approved the principles, plan and structure of each issue of the e-Newsletter proposed by us: 1. Message from the President; 2. Administration update (e.g., a reminder to send updated details if an Association's component has changed executive or contact details, forthcoming dues payments, option to send web details, other information), provided by the Secretary General and Chief Executive Officer; 3. Updates from other Executive Committee members – each Secretary can either provide an update on highlights from the past quarter or do a "spotlight" on an important project –

e.g., a particular Section's work, a forthcoming or past meeting, a new publication or a new addition to the educational portal, finance updates or fundraising efforts; 4. News related to the 2020-2023 Action Plan[5-7], including updates from Working Groups; 5. News from WPA components, including Member Societies, Scientific Sections, Board, Council, Committees, Collaborating Centres[8]; 6. Highlights from *World Psychiatry*; 7. Recommended reading – links to new articles/journals/publications, preferably related in some way to the Action Plan or the broader WPA mission; 8. Upcoming events – a list of forthcoming WPA meetings and co-sponsored meetings or courses; 9. Highlights on upcoming courses on the educational portal; 10. Questions and Answers – this is an opportunity to encourage a two-way engagement with the Association's components.

It is important to note that this is being a group effort, with the contribution not only of all the members of the Executive Committee, but also of all the components of the Association. It is essential that fresh content is developed for all categories to make the e-Newsletter interesting. In order for the initiative to be successful, it is planned that the WPA Executive Committee, Board and Council be engaged in obtaining and developing content with agreed upon deadlines. We are considering also to include articles in languages other than English to broaden appeal, some video links to promote the President's messages, and WPA history highlights.

Petr V. Morozov
WPA Secretary General

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WPA Volunteering Programme: a pilot project in Mexico

The WPA has a core mission of enhancing access to quality care in all countries around the world[1-3]. A key to this achievement is the provision of high-quality psychiatric education to mental health professionals, especially those working for underserved populations.

As part of the WPA Action Plan 2020-2023, a Workgroup on Volunteering has been set up[4], whose aim is to provide a platform for the delivery of high-quality psychiatric education through expert volunteering from Member Societies with better training resources to mental health professionals working in countries with relatively constrained training resources.

In view of the potential pitfalls and challenges in organizing and implementing a cross-national volunteering programme, especially in times of travel restrictions due to the COVID-19 pandemic, it was felt necessary to conduct pilot projects (including online volunteering) in designated sites to allow full evaluation and learning by the Workgroup before the full implementation of the programme[5].

A pilot project has been completed in April-June 2021. Colleagues in the city of Zapopan, Mexico, working at the San Juan de Dios Hospital, were linked with a training psychotherapist from the Netherlands, J. Van Hoof, who kindly prepared and delivered six modules of modern psychotherapeutic theory and practice in relationship to brain mechanisms.

Organizing the programme followed the process outlined on the WPA Volunteer webpage (https://www.wpanet.org/wg-on-volunteering). Prof. B. Ng, based in the city of Mexicali, worked with colleagues in various Mexican cities to ascertain what would work best, made the appropriate introductions and offered support. The potential sites first considered included Campeche, Monterrey and Zapopan, where the pilot project finally took place.

Ten trainees (40% early career psychiatrists and 60% psychiatry residents; 60% males; mean age 30.1±3.3) were selected on the basis of their interest in the subject covered in the material. Early career psychiatrists had up to 5 years of clinical experience in psychiatry.

Due to COVID-19 pandemic, the focus of the pilot programme was on online volunteering[5] and the methodology was interactive online lecturing, with a focus on what participants already knew and what they wanted to learn. So, in order to offer a suitable flexible programme tailored to their ideas, much time was put aside for questions and answers. The trainees participated in choosing the topics of each session.

One-hour sessions were delivered over three months and included the functions and activities of main brain structures, evolutionary psychiatry, attachment, object relations, neurotransmission, depression, trauma theory and therapy, as well as genetics and development.

The anonymous evaluation after the training revealed trainee satisfaction, with high scores for applicability and helpfulness of the knowledge gained in clinical practice (Likert scale score of 4.3±0.8 out of a maximum of 5 points) and overall satisfaction of 4.4±0.5 (out of a maximum of 5 points). There were no technical difficulties, and English was acceptable as the language used (despite both trainer and trainees having another first language).

All participants in the pilot project were satisfied with the size of the group during training, and 80% of the trainees were also satisfied with the duration of the training. Only 10% each would have preferred either a longer or a shorter training. Comments included the appreciation of the trainer's kindness and warmth, the human perspective of the course, the opportunity to hear about the experience of a professional from another country, and hearing about new treatments and neurobiological advances. There were several suggestions that sending a bibliography and a schedule ahead of online meetings would be helpful.

Feedback from the trainer was that the training was a most enjoyable experience and that the atmosphere was friendly from the beginning. The participants were motivated as they had already indicated which topics they were interested in. The trainer also stressed that it was important that he could access support at any time directly from the organizers in Mexico.

At the start of the training sessions, the participants and the trainer agreed that they would keep the content of the meetings confidential, in order to give everyone the freedom to communicate freely, especially in case somebody wanted to speak about patient matters.

Notwithstanding the great physical distance between Mexico and the Netherlands, there was a sense of closeness, similarity of experiences, and friendliness. Although the sessions were not videotaped, from anonymous evaluation after the pilot project it emerged that participants would agree that the online training be recorded in the future, so that other people who do not participate in the course can benefit from the recording.

The WPA Continuing Professional Development (CPD) certificate was offered to the attendees, all of whom completed each module of the course.

A second larger pilot exercise focused on child and adolescent mental health is now planned in Pakistan. The WPA Workgroup on Volunteering welcomes proposals from Member Societies for further training projects.

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[1]WPA Workgroup on Volunteering; [2]WPA Zone 2 Representative; [3]WPA Secretary for Education

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Update on WPA Scientific Meetings

The COVID-19 pandemic has changed the world and continuously disrupted the organization of medical conferences across the entire world. While facing these uncertain and unprecedented times, the WPA continues to closely monitor the global risk assessment regarding the pandemic and its impact on international travel to hold face-to-face meetings.

The Association has made significant adjustment and progress in the recent months and will continue to do so. During the past year, it has built a state-of-the-art platform designed to make the virtual experience easy, educational, convenient, interactive, and memorable. Scientific events continue to meet the needs of the global psychiatric community and provide cutting-edge information on recent advances in psychiatry.

For this time of limited in-person gathering, this virtual format meeting is a safe and excellent way to allow WPA Member Societies to network, continue to build bonds with each other and allow all to participate within their own safety. Virtual meetings have allowed us to create new opportunities together and make the events even more accessible to a worldwide audience.

The WPA is mindful that the global spread of the infection is increasing risk of developing mental disorders, relapse of existing mental disorders and poor mental health, in addition to impacting the work of mental health services. The Association aims to promote an increasing understanding of public mental health among professionals and the public, including collaboration with patient and family organizations. Sixteen working groups have been established to address the six priorities of the WPA Action Plan 2020-2023[1].

The key features of the Action Plan are to promote psychiatry as a medical specialty in clinical, academic and research areas, and to promote public mental health as a guiding principle; to highlight the specific role of psychiatrists in working with other professionals in health, public health, legal and social aspects of care; to ensure WPA's positive engagement with Member Societies, mental health professionals and general health care workers[2]. The six areas of the WPA Action Plan include: public mental health; capacity building; child, adolescent and youth mental health; addressing comorbidity in mental health; developing partnerships with other professional and non-governmental organizations; and continuation and completion of the previous WPA Action Plans.

Among the current priorities, public mental health continues getting particular attention[1,3].

As the COVID-19 pandemic has put tremendous burden on health care systems all over the world, mental health services have also been severely affected. The devastating global burden of mental disorders continues unabated and, in fact, has been significantly exacerbated by the pandemic. The true burden lies not only among identified patients, but also within the general population, where stress, burnout, depression, anxiety, and sleep disorders are often unrecognized, untreated, and seldomly prevented. Now, overwhelmingly, these conditions are compounded by the impact of the pandemic, including death of loved ones and associated grief. Most preventable ill-health conditions have major consequences not only for the individual well-being but also for every nation's economic prosperity[4-7].

The WPA Scientific Meetings are geared up to align with the WPA Action Plan and its six areas, and to address the above-mentioned priorities. The programme of these meetings has been in full swing. The following events have been held or are confirmed or proposed: the first-ever virtual World Congress of Psychiatry "Psychiatry in a Troubled World", Bangkok, Thailand, March 10-13, 2021, with a wonderful program of interactive sessions and world-class speakers that made it an engaging and fulfilling experience; the Regional Congress "Interdisciplinary Understanding of Co-morbidity in Psychiatry: from Science to Integrated Care", St. Petersburg, Russia, May 15-18, 2021; the Regional Congress "Psychopathology in Periods of Transition", Kyiv, Ukraine, July 7-9, 2021; the World Congress of Psychiatry "New World, New Challenges for Psychiatry and Mental Health", Cartagena, Colombia, October 18-21, 2021; the Thematic Congress, Cartagena, Colombia, February, 2022; the Thematic Congress "Public Mental Health", Lahore, Pakistan, March 11-13, 2022; the Thematic Congress, Moscow, Russia, June 2-3, 2022; the Thematic Congress "Early Intervention in Psychiatry Across the Life Span", Athens, Greece, June 23-25, 2022; the World Congress of Psychiatry, Bangkok, Thailand, August 3-6, 2022; the Intersectional Thematic Congress, Malta, November 10-12, 2022; the Regional Congress, Hammamet, Tunisia, December 15-17, 2022; the Thematic Congress "Mental Health in a New Era", Karachi, Pakistan, March 3-5, 2023; and the World Congress of Psychiatry, Vienna, Austria, September 2023.

At present, it is still uncertain when the pandemic will be mitigated and we will be able to travel safely and resume in-person meetings. We will closely monitor the future development of the pandemic and diligently make appropriate adjustments in planning for future meetings. In the meantime, we have continued to do our utmost to promote the mission of the WPA and to contribute to the achievements and success of the Association, working closely with the Executive Committee and the Secretariat to oversee and co-ordinate all official WPA meetings and manage applications for WPA co-sponsored meetings, and maintaining responsibility for the development of proposals to host the World Congresses of Psychiatry and other meetings, and assist in all aspects of their organization[8].

The WPA is confident that, by embracing these opportunities, taking global action and working closely together with international collaborations, we will overcome all the challenges. Together we shall move forward and define the future in psychiatry.

Edmond H. Pi
WPA Secretary for Scientific Meetings

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Internet-based field trials of the ICD-11 chapter on mental disorders

The ICD-11 chapter on mental, behavioural and neurodevelopmental disorders has been now finalized, and a substantial effort to train mental health professionals in the use of the relevant Clinical Descriptions and Diagnostic Guidelines (CDDG) is ongoing worldwide[1-5]. The many contentious issues that have been debated in the development of the chapter have been extensively dealt with in this journal[6-15].

The finalization of the chapter has been preceded by a vast programme of international field studies. These included Internet-based and clinic-based studies. The Internet-based field studies have been implemented through the World Health Organization (WHO) Global Clinical Practice Network (GCPN). This now includes more than 16,000 clinicians from 159 countries (51% psychiatrists, 30% psychologists; 40% from Europe, 25% from Western Pacific, 24% from the Americas, 5% from Southeast Asia, 3% from Eastern Mediterranean, and 3% from Africa; 63% from high-income countries, 37% from middle- and low-income countries. The clinic-based field studies have been conducted with the participation of WHO Collaborating Centres.

The Internet-based field studies have used the case vignette methodology to examine clinical decision-making in relationship to the proposed diagnostic categories and guidelines; while the clinic-based (or ecological implementation) field studies have assessed the reliability and clinical utility of the diagnostic guidelines with real patients.

Several papers reporting on the results of the Internet-based field studies have been published during the past two years, covering some of the main sections of the ICD-11 chapter on mental disorders[16].

In a paper comparing the diagnostic accuracy and clinical utility of ten mental disorders (schizophrenia, schizoaffective disorder, bipolar type II disorder, recurrent depressive disorder, moderate personality disorder, adjustment disorder, complex post-traumatic stress disorder, binge eating disorder, bodily distress disorder, and compulsive sexual behaviour disorder), it was reported that the ICD-11 CDDG had a significantly higher diagnostic accuracy (71.9% vs. 53.2%), higher ease of use, better goodness of fit, higher clarity, and lower time required for diagnosis compared to the ICD-10 CDDG. Diagnostic accuracy was consistent across WHO regions and independent of participants' clinical experience. There were no differences between medical doctors and psychologists in the diagnostic accuracy, but participants representing other health professions had more difficulty in identifying the correct diagnoses on the basis of the ICD-11 CDDG[16].

In an Internet-based field study conducted with the participation of 2,288 mental health professionals registered with the GCPN, the ICD-11 CDDG significantly improved the accuracy of the diagnosis of all feeding and eating disorders compared to the ICD-10 CDDG, and attained higher clinical utility ratings. Similar results were obtained across five languages (English, Chinese, French, Japanese and Spanish). The inclusion of binge eating disorder and avoidant-restrictive food intake disorder in the ICD-11 reduced the use of residual diagnoses[16].

A further Internet-based field study carried out with the participation of 1,357 members of the GCPN in four languages (English, Spanish, Japanese and Russian) found similar overall levels of accuracy in diagnosing mood disorders using ICD-11 and ICD-10 CDDG, but the use of the ICD-11 CDDG was associated with a greater accuracy in identifying depressive episodes in recurrent depressive disorder[16].

An Internet-based field study conducted with 1,840 mental health professionals registered with the GCPN found that clinicians were significantly more accurate in diagnosing generalized anxiety disorder, specific phobia and adult separation anxiety disorder when using ICD-11 vs. ICD-10 CDDG, and provided high clinical utility ratings for these disorders. The participants found the ICD-11 CDDG easy to use, clear, and with a good fit to patients they saw in their clinical practice, although having some difficulty in distinguishing the boundary between disorder and normality for subthreshold cases of anxiety[16].

An Internet-based field study with 1,717 mental health professionals who were members of the GCPN found that the use of the ICD-11 CDDG resulted in a more accurate differentiation of presentations of obsessive-compulsive and related disorders from one another compared with the use of the ICD-10 CDDG[16].

A small improvement was also found in accurately diagnosing vignettes depicting schizoaffective disorder using ICD-11 vs. ICD-10 CDDG in an Internet-based field trial involving 873 clinicians. However, the problem in identifying whether the presence of mood symptoms was more consistent with a diagnosis of schizoaffective disorder or a mood disorder was still observed[16].

Finally, an Internet-based field study carried out with 196 clinicians in three languages (English, Spanish and Japanese) found that the ICD-11 led to a more accurate identification of severe irritability, and a better differentiation from boundary presentations. Notably, participants using the DSM-5 mostly failed to apply the diagnosis of disruptive mood dysregulation disorder when it was appropriate[16].

These results, adding to those of the clinic-based field studies – showing that the interrater reliability for the main groups of mental disorders in the ICD-11 ranged from .45 to .88 and was generally superior to that obtained with the ICD-10, and that the ICD-11 CDDG were perceived as easy to use, clear and understandable, corresponding accurately to patients presentations, and providing useful guidance about distinguishing each disorder from normality and from other disorders[16] – are reassuring about the clinical utility of the ICD-11 chapter on mental, behavioural and neurodevelopmental disorders, at a time in which the implementation of the new diagnostic system is being planned worldwide.

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