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World Psychiatry

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Artificial intelligence, consciousness and psychiatry

In 1966, a researcher at the Massachusetts Institute of Technology introduced ELIZA, a computer program that simulated a psychotherapist in the Rogerian tradition, rephrasing a patient's words into questions according to simple but effective scripts. This was one of the first (and few) successes of early artificial intelligence (AI). To the dismay of its creator, some people took ELIZA for a real psychotherapist, perhaps because of our innate tendency to project consciousness when we detect intelligence, especially intelligent speech.

ELIZA's stuttering attempt at AI has now become an immensely eloquent golem. ChatGPT can easily outspeak, outwrite and outperform S. Freud. Because large language models (LLM) benefit from superhuman lexicon, knowledge, memory and speed, artificial brains can now trump natural ones in most tasks.

ELIZA was named after the flower-girl in G.B. Shaw's play Pygmalion, supposedly because it learned to improve its speech with practice. The original myth of Pygmalion – the sculptor who carved the ideal woman Galatea out of ivory and hoped to bring her to life – is even more apt: does the creation of AI portend artificial consciousness, perhaps even superhuman consciousness? Two camps are beginning to emerge, with radically different answers to this question.

According to the dominant computational/functionalist stance in cognitive neuroscience, the answer is yes[1]. Cognitive neuroscience assumes that we are ultimately machines running sophisticated software (that can derail and be reprogrammed). Neural algorithms recognize objects and scenes, direct attention, hold items in working memory, and store them in long-term memory. Complex neural computations drive cognitive control, decision making, emotional reactions, social behaviors, and of course language. In this view, consciousness must be just another function, perhaps the global broadcasting of information[2] or the metacognitive assessment of sensory inputs[3]. In this case, whenever computers can reproduce the same functions as our brain, just implemented differently (the functionalists' "multiple realizability"), they will be conscious like we are.

Admittedly, despite LLMs sounding a lot like conscious humans nowadays, there is no principled way for determining whether they are already conscious and, if so, in which ways and to what degree[1]. Nor is it clear how we might establish whether they feel anything (just asking, we suspect, might not do…).

Cognitive neuroscience typically takes the *extrinsic perspective*, introduced by Galileo, which has been immensely successful in much of science. From this perspective, consciousness is either a "user illusion"[4], or a mysterious "emergent" property. However, as recognized long ago by Leibniz, this leaves experience – what we see, hear, think and feel – entirely unaccounted for. This implicit dualism is one that has plagued not just neuroscience, but also psychiatry from the very beginning: are we treating the brain, the psyche, or both? If so, how are they related? Is the soul just the brain's ephemeral passenger?

Integrated information theory (IIT) provides a radically different approach[5], and this is our own view. IIT takes the *intrinsic perspective*, starting not from the brain and what it does, but from consciousness and what it is. After all, for each of us, experience is what exists irrefutably, and the world is an inference from within experience – a good one, but still an inference, as psychiatrists should know well.

IIT first characterizes the essential properties of consciousness – those that are irrefutably true of every conceivable experience – and then asks what is required to account for them in physical terms. Crucially, this leads to identifying an experience, in all its richness, with a *structure* (rather than with a process, a computation, or a function) – a structure that expresses the causal powers of a (neural) substrate in its current state. In fact, IIT provides a calculus for determining, at least in principle, whether a substrate is conscious, in which way, and to what degree.

The theory can explain why certain parts of the brain can support consciousness, while others, such as the cerebellum and portions of prefrontal cortex, cannot. It can explain why – due to a breakdown of causal links – consciousness is lost in dreamless sleep, anesthesia, and generalized seizures[6]. It has also started to account for the quality of experience – the way space feels extended and time flowing[7]. It leads to many testable predictions, including counterintuitive ones: for example, that a near-silent cortex can support a vivid experience of pure presence. Finally, IIT has spawned the development of a transcranial magnetic stimulation/electroencephalography method that is currently the most specific and sensitive for assessing the presence of consciousness in unresponsive patients[8].

If IIT is right, and in sharp contrast to the dominant computational/functionalist view, AI lacks (and will lack) any spark of consciousness: it may talk and behave just as well or better than any of us (it will be "functionally equivalent"), but it will not be "phenomenally equivalent" (it will feel nothing at all)[5]. In the words of T. Nagel, there will be nothing "it is like to be" a computer, no matter how intelligent. Just like the cerebellum, the computer has the wrong architecture for consciousness. Even though it may perform flawlessly every "cognitive" function we may care for, including those we are used to consider uniquely human, all those functions will unroll "in the dark". They will unroll as unconsciously as the processes in our brain that smoothly string together phonemes into words and words into sentences to express a fleeting thought.

If IIT is right, attributing consciousness to AI is truly an "existential" mistake – because consciousness is about being, not doing, and AI is about doing, not being. Under selective pressure, biological constraints may promote the co-evolution of intelligence and consciousness (by favoring highly integrated substrates)[9]. However, in a larger context, intelligence and consciousness can be doubly dissociated. There can be experience without the functional abilities that we associate with intelligence. For example, minimally responsive patients may be unable to do or say anything but may harbor rich subjective experiences[8]. And there can be great intelligence without consciousness: an eloquent AI may engage in a stimulating conversation and impress us with its intellect, without anything existing besides the stream of sentences we hear – in the words of P. Larkin, “No sight, no sound / No touch or taste or smell, nothing to think with / Nothing to love or link with”.

AI poses a unique and urgent challenge not just for mental health, but for the human condition and our place in nature. Either mainstream computational/functionalist approaches are right, and we – highly constrained and often defective biological machines – will soon be superseded by machines made of silicon that will be not just better and faster but also enjoy a richer inner life. Or IIT is right, and every human experience is an extraordinary and precious phenomenon, one that requires a very special neural substrate that cannot be replicated by merely simulating its functions.

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1. Butlin P, Long R, Elmoznino E et al. arXiv 2023;2308.08708.
2. Dehaene S, Changeux J-P. Neuron 2011;70:200-27.
3. Brown R, Lau H, LeDoux JE. Trends Cogn Sci 2019;23:754-68.
4. Norretranders T. The user illusion: cutting consciousness down to size. New York: Viking Penguin, 1991.
5. Albantakis L, Barbosa L, Findlay G et al. PLoS Comput Biol 2023;19:e1011465.
6. Tononi G, Boly M, Massimini M et al. Nat Rev Neurosci 2016;17:450-61.
7. Haun A, Tononi G. Entropy 2019;21:1160.
8. Casarotto S, Comanducci A, Rosanova M et al. Ann Neurol 2016;80:718-29.
9. Albantakis L, Hintze A, Koch C et al. PLoS Comput Biol 2014;10:e1003966.

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Global launch of the ICD-11 Clinical Descriptions and Diagnostic Requirements (CDDR)

The ICD-11, the first major revision of the ICD in three decades, was approved by the 72nd World Health Assembly in May 2019, and came into effect as a basis for reporting of health statistics by World Health Organization (WHO) member states in January 2022. Countries around the world are in various stages of implementing the ICD-11 in their clinical and health information systems, a process that will continue for the next several years.

The WHO has now taken a major step towards the implementation of the ICD-11 in mental health systems by publishing the Clinical Descriptions and Diagnostic Requirements for ICD-11 Mental, Behavioural and Neurodevelopmental Disorders (CDDR)[1].

The CDDR are designed as a comprehensive diagnostic manual that will support mental health and other health professionals in accurately diagnosing mental disorders in health care settings across the world. They provide consistent, clinically useful information for all diagnostic categories in the ICD-11 chapter on mental, behavioural and neurodevelopmental disorders. This information includes the features that clinicians can expect to see in all cases of the disorder (essential features), their boundaries with normality (threshold) and other conditions (differential diagnosis), and features related to course, developmental stage, gender and culture. Although a diagnostic manual had been published for the ICD-10, the CDDR represent a substantial expansion and improvement in the consistency of information provided, the integration of systematic information related to developmental stage, gender and culture, and more careful attention to differential diagnosis[2], in addition to being based on current research and best practices.

For the WHO Department of Mental Health and Substance Use, a central goal in developing the ICD-11 CDDR was to provide a better tool for reducing the global burden of mental disorders. Based on this goal, we focused explicitly on clinical utility and global applicability – in addition to validity – in the CDDR’s development[3]. An accurate diagnosis is often the first critical step towards receiving appropriate care and treatment. A more clinically useful diagnostic manual that is more applicable in settings across the world is more likely to be implemented systematically, supporting both the earlier identification of those who need care and the selection of effective treatment. In turn, this will improve the quality of health data aggregated from clinical encounters that are used to guide policy and allocate resources at facility, system, national and global levels.

To develop the CDDR, the Department appointed sixteen expert working groups in different areas, ensuring through their composition a multidisciplinary process that represented all WHO regions, including a substantial proportion of individuals from low- and middle-income countries. In developing proposals for the ICD-11, these working groups conducted rigorous reviews of the evidence, including work done as a part of the development of the DSM-5.

Further, proposed diagnostic requirements for the ICD-11 were extensively tested in a systematic program of field studies. The Global Clinical Practice Network (GCPN) was set up to enable the participation of clinicians in the development of the CDDR, and now consists of more than 19,000 mental health and primary care professionals from 165 countries. GCPN members participated in 20 Internet-based field studies to test the CDDR, each conducted in up to six languages[3,4]. The CDDR were also tested among patients in clinical settings in 15 countries, representing all WHO regions and nearly 50% of the world’s population. These studies documented broad improvements in reliability and clinical utility when clinicians used the ICD-11 CDDR as compared to the equivalent diagnostic guidance for ICD-10.

The ICD-11 and the CDDR incorporate important innovations. These include new disorder categories that describe populations with clinically important and distinctive features and specific treatment needs, substantially contributing to an expansion of related research and a significant increase in the availability of appropriate services[5]. Other categories have been eliminated due to their lack of validity. The ICD-11 and the CDDR have made a significant movement toward dimensional conceptualizations of mental disorders, especially in psychotic and personality disorders[6].

The WHO's Comprehensive Mental Health Action Plan 2013-2030[7] is based on six cross-cutting principles and approaches, all of which are supported by innovations and improvements in the CDDR:

- The CDDR support *universal health coverage* by describing in replicable, clinically useful, and globally applicable terms the conditions that provide a framework for treatment eligibility and selection.
- The CDDR support *human rights*, for example by emphasizing current status and treatment needs rather than lifelong labeling for psychotic disorders, in ways that are more consistent with recovery-based approaches.
- The CDDR are based on substantial advances in *evidence-based practice* since the publication of the ICD-10.
- The CDDR are based on a *life-course approach*, describing manifestations of mental disorders in early and middle childhood, adolescence, and older adulthood.
- As described above, the Department of Mental Health and Substance Use adopted a *multi-sectoral approach* to developing the CDDR.
- The CDDR support *empowerment of persons with mental disorders and psychosocial disabilities* by systematically incorporating service user perspectives[8].

In order to implement the ICD-11 and the CDDR, there is a huge need for workforce capacity-building for both specialist and non-specialist providers of services. The implementation of the ICD-11 also represents the most important opportunity in a generation to reform the diagnostic process, incorporating the needs and perspectives of those who receive our care[8]. The WHO will need the collaboration and support of member states, professional societies (importantly including the World Psychiatric Association), WHO Collaborating Centres, academic institutions, non-governmental organizations, civil society and service user organizations to ensure an implementation of the ICD-11 that fulfils its potential. The CDDR should be systematically integrated into training programs for mental health and primary care professionals, and a range of more specialized materials should be developed for this purpose[9].

The CDDR are the product of more than 15 years of collaborative work led by the WHO Department of Mental Health and Substance Use within the context of the overall development of the ICD-11. Hundreds of experts and thousands of clinicians from around the world were involved in developing and testing the CDDR as part of the most international, multilingual, multidisciplinary and participative revision process ever implemented for a classification of mental disorders.

With the publication of the CDDR, health professionals have a better tool for identifying mental health conditions; WHO member states have a better tool for reducing the disease burden associated with mental disorders; and people who need mental health services have a greater likelihood of receiving the care they need.

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D. Kestel is the Director of the WHO Department of Mental Health and Substance Use. The authors alone are responsible for the views expressed in this paper, that do not necessarily represent the views, decisions or policies of the WHO or the other institutions with which they are affiliated.

1. World Health Organization. Clinical descriptions and diagnostic requirements for ICD-11 mental, behavioural and neurodevelopmental disorders. https://www.who.int/publications/i/item/9789240077263.
2. First MB, Reed GM, Hyman SE et al. World Psychiatry 2015;14:82-90.
3. Reed GM, First MB, Kogan CS et al. World Psychiatry 2019;18:3-19.
4. Keeley JW, Reed GM, Roberts MC et al. Am Psychol 2016;71:3-16.
5. Reed GM, First MB, Billieux J et al. World Psychiatry 2022;21:189-213.
6. Clark LA, Cuthbert B, Lewis-Fernández R et al. Psychol Sci Publ Int 2017;18:72-145.
7. World Health Organization. Comprehensive mental health action plan 2013-2030. Geneva: World Health Organization, 2021.
8. Hackmann C, Balhara YPS, Clayman K et al. Lancet Psychiatry 2019;6:778-85.
9. Reed GM, Ritchie PL-J, Maerker A (eds). A psychological approach to diagnosis: using the ICD-11 as a framework. Washington: American Psychological Association, 2024.

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Social connection as a critical factor for mental and physical health: evidence, trends, challenges, and future implications

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Rising concerns about social isolation and loneliness globally have highlighted the need for a greater understanding of their mental and physical health implications. Robust evidence documents social connection factors as independent predictors of mental and physical health, with some of the strongest evidence on mortality. Although most data are observational, evidence points to directionality of effects, plausible pathways, and in some cases a causal link between social connection and later health outcomes. Societal trends across several indicators reveal increasing rates of those who lack social connection, and a significant portion of the population reporting loneliness. The scientific study on social isolation and loneliness has substantially extended over the past two decades, particularly since 2020; however, its relevance to health and mortality remains underappreciated by the public. Despite the breadth of evidence, several challenges remain, including the need for a common language to reconcile the diverse relevant terms across scientific disciplines, consistent multi-factorial measurement to assess risk, and effective solutions to prevent and mitigate risk. The urgency for future health is underscored by the potentially longer-term consequences of the COVID-19 pandemic, and the role of digital technologies in societal shifts, that could contribute to further declines in social, mental and physical health. To reverse these trends and meet these challenges, recommendations are offered to more comprehensively address gaps in our understanding, and to foster social connection and address social isolation and loneliness.

Key words: Social connection, social isolation, loneliness, mental health, physical health, mortality, public health

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In a joint statement published in January 2024, the governments of the US, Japan, Morocco, Sweden, Kenya and Chile highlighted "the importance of social connection to the health and well-being of individuals, communities and societies"[1]. This came at the heels of the COVID-19 pandemic, a more than three-year period in which the global population had to isolate, practice "social distancing" and, in many cases, was homebound, all factors contributing to reduced social contact. However, while that global health crisis helped raise awareness of the importance of this issue, scientific evidence was already documenting the significant mental and physical health implications of declining social connection.

Social connection is widely acknowledged to be a fundamental human need[2,3], linked to higher well-being, safety, resilience and prosperity, and to longer lifespan[4]. Across social species, research demonstrates that social connection is one of the strongest predictors of survival, both early and later in life, through adaptive behavioral and biological mechanisms[5,6]. The availability and diversity of social relationships, interactions and networks are critical for health and well-being[4,7,8]. Therefore, it is imperative to understand how new trends involving social connection relate to shifts in important societal outcomes such as mental disorders and physical diseases.

Rising global concerns about a "loneliness epidemic" in public discourse have been accompanied by increased academic research and heightened engagement among communities, institutions and governments. These concerns are being reflected in national and international responses to this "epidemic". In 2018, the UK appointed a Minister of Loneliness[9], establishing a national strategy and awareness campaign. Japan followed by appointing a Minister of Loneliness in 2021[10]. Beginning in 2018, the European Union has produced several reports on loneliness[11]. In 2023, the US Surgeon General issued an Advisory and a framework for a national strategy on "our epidemic of loneliness and isolation"[4]. In the same year, the South Korean government took a tangible step, offering monthly stipends to encourage young socially isolated individuals to reintegrate into society[12]. Outside governments, the World Health Organization (WHO) launched in 2023 a Commission on Social Connection, a three-year effort to raise global awareness and mobilize support in this area[13].

These efforts have been prompted by data documenting recent increases in social isolation and loneliness, and decreases in social connection globally[4]. Factors including modernization in society, economic disparities, the introduction of digital technologies, shifts in civic engagement, growing political divides and radicalization, and others, have been examined as potential contributors to this decline in social connection. Whether this is a social recession, a loneliness epidemic, or a public health crisis, it is clearly a pressing issue.

This is a critical moment to act and bridge the gaps in our collective knowledge to mitigate adverse outcomes. However, there are several challenges to be addressed. Over the years, the relevance of social connection to our health has emerged in various disciplines, leading to a complex and potentially confusing evidence base. This calls for a common language to be established. However, in the process, we risk oversimplifying the issue and falling short of an adequate response. With increasing public and governmental attention, this is a critical time to take stock of the strengths and gaps in the existing evidence, the challenges to be faced, and the implications for the future.

SOCIAL CONNECTION AND MENTAL HEALTH

There is a robust evidence base linking social connection to mental health outcomes. Social connection plays a vital role in preventing mental health problems, maintaining good mental health, and aiding in the recovery from both moderate and severe mental health conditions, while isolation and loneliness have been associated with poorer mental health. Most of this evidence regards depression, with fewer studies considering other mental disorders.

Although most available data are observational and cannot demonstrate causality, there are longitudinal studies that provide more robust evidence to indicate directionality, and recent evidence using Mendelian randomization to establish causal relationships[14]. In some cases, associations appear to be bidirectional, meaning that there is evidence to suggest that social isolation and loneliness increase the risk for poorer mental health, as well as evidence that poorer mental health increases the risk for isolation and loneliness[15].

Depression

There is a strong positive association of social isolation and loneliness with depression from youth to older adulthood. Further, higher social connectedness is protective towards depressive symptoms and disorders[16].

When looking at adults of all ages, 18 years and older, data from the US National Health Interview Survey examined the impact of living alone and the availability of social and emotional support on depression[17]. Adults living alone reported significantly higher depression than those living with others, and this difference held across several sociodemographic factors. Adults never or rarely receiving social and emotional support were twice as likely to report depression, but adults living alone were still more likely to report depression even compared to adults living with others who did not receive social and emotional support[17].

Importantly, longitudinal evidence suggests that social isolation and loneliness likely cause or worsen depression over time. For example, a systematic review of 32 longitudinal studies from the general population examined whether subjective feelings of loneliness predicted the onset of a new diagnosis of depression[18]. Studies followed participants from six months to 16 years, with an average follow-up of 3.5 years. The odds of developing new depression in adults were more than double among those who reported often feeling lonely compared to those rarely or never feeling lonely. While there were more studies among older adults, the findings were consistent among younger age groups, including university students and new mothers.

Using two large datasets – the Psychiatric Genomics Consortium meta-analysis of major depression (N=142,646)[19], and the Million Veteran Program (N=250,215)[20] – to apply a two-sample Mendelian randomization design, loneliness appeared to cause incident major depression and depressive symptoms[14]. These analyses were then reversed using loneliness outcome data from the UK biobank. Remarkably, data demonstrated that loneliness causally predicts major depression, but the reverse is also true, with major depression causally predicting loneliness[14]. This suggests that loneliness is both a cause and a consequence of major depression; thus, public health strategies to reduce loneliness may potentially be effective in preventing the onset of depression and reducing depressive symptoms, and better treatments for depression are likely to reduce loneliness.

The link between social connection and depression has also been examined among patients in medical settings, suggesting potential spillover effects on other clinical conditions. For example, low social support had a significant positive association with antenatal depression, which contributes significantly to maternal physical health[21]. In a review, 83% of studies found that pregnant women with low social support had greater depressive symptoms[16].

The links between social connection and mental health are also relevant within occupational settings. The strain on employees across sectors, particularly those hit hardest during the COVID-19 pandemic – such as health care providers, educators, and other "essential employees" – has brought greater attention to burnout and other mental health concerns. A meta-analysis of studies in health care workers found that a lack of social support significantly contributed to higher risk for acute stress disorder, burnout, anxiety, depression, and post-traumatic stress disorder[22].

Cognitive health

Several meta-analyses consistently show that stronger social connection – including social networks (e.g., number of social contacts, frequency of interaction, marital status, living arrangement) and social engagement (e.g., attending social groups; visiting family, friends and neighbors; engaging in voluntary or paid work, participation in cultural or leisure activities) – is associated with better cognitive function, but the evidence is less consistent for perceptions of loneliness.

For example, a meta-analysis including over 2.3 million participants showed that living alone, having a smaller social network, having a low frequency of social contact, and having poor social support were risk factors for dementia, while loneliness was not[23]. However, other meta-analyses did find that greater loneliness was significantly associated with incident dementia[24,25]. Conversely, greater social engagement, including a greater number of social memberships, number of social contacts, and more social participation, may be protective, as these were associated with lower dementia risk[23,26].

SOCIAL CONNECTION AND PHYSICAL HEALTH

Robust evidence links social connection, isolation and loneliness to an increased incidence of several physical diseases and to earlier death. The strength of this evidence has been acknowledged in multiple National Academy of Science, Engineering, and Medicine (NASEM) consensus study reports[15,27], scientific statements by professional associations such as the American Heart Association[28], and the US Surgeon General Advisory issued in 2023[4]. The evidence can be found in several meta-analyses and systematic reviews that document the overall effects on physical morbidity[29-31], and on disease-related as well as all-cause mortality[32-43]. There are also meta-analyses on clinical outcomes such as response to vaccine[44].

This body of evidence led a NASEM consensus study report to conclude that "social isolation is a major public health concern"[15]. This is noteworthy, since the report was published before the COVID-19 pandemic and there has been a significant volume of research on this topic from 2020 onward.

Physical morbidity

There is a rich and growing body of evidence across a variety of physical health outcomes, including major health indicators such as cardiovascular diseases, stroke and diabetes mellitus.

Cardiovascular diseases are the leading cause of death globally, accounting for roughly one third of all deaths; therefore, factors that increase or decrease this risk can have a major global health impact[45]. Dozens of studies have found that social isolation and loneliness significantly influence the risk of cardiovascular and cerebrovascular morbidities[15,29].

The culmination of this evidence resulted in a statement published by the American Heart Association in 2022, acknowledging this risk from objective and perceived social isolation[28]. According to this review of the evidence, there is a clear link of social isolation and loneliness with risk for coronary heart disease and stroke. Among the evidence, a synthesis of data across 16 independent longitudinal studies demonstrates that poor social relationships (social isolation, poor social support, loneliness) were associated with a 29% increase in the risk of incident coronary heart disease and a 32% increase in the risk of stroke[29]. These findings were consistent across genders.

Low social connection and loneliness have also been associated with a greater risk for hypertension. Indeed, data from the National Social Life, Health and Aging Project suggest that the impact of social isolation on risk for hypertension exceeds that of clinical factors such as diabetes mellitus, pointing to a "causal role of social connections in reducing hypertension" in older age[46].

Diabetes mellitus is a leading source of disability, lost productivity, mortality, and lower quality of life, affecting nearly half a billion people worldwide, with a significant global economic burden on individuals, health care systems, and countries[47]. Studies have repeatedly shown that social connection (e.g., family support and involvement) can positively influence the management and overall health of individuals with type 1 and 2 diabetes. Large population studies also demonstrate the influence of social connection on the incidence of type 2 diabetes. For example, people with smaller social networks were more likely to have been recently diagnosed with type 2 diabetes, to have previously been diagnosed with this condition, and to have diabetic complications[48,49].

However, gender differences have been found along different indicators of social connection. Low social participation was linked to pre-diabetes and complications among women but not men, while living alone increased the likelihood of previously diagnosed type 2 diabetes and its complications in men but not in women[48,49]. These findings were independent of glycemic control, quality of life, and cardiac risk factors.

Diabetic outcomes may be due to better self-care among those who are more socially connected. For example, in a meta-analysis of 28 studies, social support was significantly associated with better self-care, particularly glucose monitoring, and was stronger among those with type 2 than type 1 diabetes[50]. Improving diabetic outcomes via social connection can have cascading public health implications, given that diabetes mellitus often leads to other health outcomes, including heart disease, kidney failure, blindness, amputation and dementia.

There is also evidence to suggest that poor social connection is associated with worse outcomes among those who are already ill. For example, heart failure patients who self-reported high levels of loneliness had a 68% increased risk of hospitalization, a 57% higher risk of emergency hospital visits, and a 26% increased risk of outpatient visits compared with patients reporting low loneliness[51]. In a meta-analysis of 13 studies on heart failure patients, poor social connection was associated with a 55% greater risk of hospital readmission[52]. This was consistent across both objective and perceived social isolation, living alone, lack of social support, and poor social network. These data suggest that improving social connection among those who are sick can improve medical outcomes.

Mortality

Several reviews of the evidence, including a NASEM scientific consensus study, have concluded that some of the strongest evidence linking social connection, isolation and loneliness to health-relevant outcomes is that concerning mortality[15]. Large population-based epidemiological studies have tracked initially healthy populations over time, for years and often decades, documenting that those who are more socially connected live longer[35,38,41,42], while those who experience social deficits (isolation, loneliness, living alone, poor-quality relationships) are more likely to die earlier, regardless of the cause of death[33,36,37,39,40,43]. Although social isolation has been implicated as a risk factor for death by suicide[53], most meta-analyses on mortality exclude suicide as a cause of death.

Based on meta-analytic data, one estimate suggests that the association between social connection and survival may be as high as 50%[42], while isolation is associated with 32% and loneliness with 14% increased risk for earlier death[33]. While estimates vary to some extent, they may be conservative, given that many reviews and meta-analyses often exclude studies that focus specifically on deaths due to unnatural causes such as unintended injuries, violence or suicide. While there are more studies and stronger effects on cardiovascular-related deaths (e.g., myocardial infarction, stroke) and cancer-related deaths (e.g., leukemia, lymphomas, breast cancer)[41], more research is still needed on these, in addition to other disease-related causes of death.

Over the years, the number of studies, the rigor of methodology, and the size of samples have all increased substantially, replicating the finding that social connection decreases the risk of premature mortality and providing stronger confidence in this evidence. For example, longitudinal data from the UK Biobank regard nearly half a million people, reducing the likelihood of random error[54]. These data demonstrate that social isolation significantly increases risk for earlier all-cause mortality, overall and consistently across subgroups (i.e., males and females, young and older, health and unhealthy, various ethnicities), even after adjusting for a robust set of lifestyle, socioeconomic, biological, and health risk factors[55].

Several meta-analyses and systematic reviews have documented similar findings across different ways of examining the issue, including social relationships broadly, social networks, social contact frequency, marital/partnership status, marriage dissolution, social isolation, loneliness, and living alone[32,43]. While the magnitude of the effect varies to some extent across studies and depending on which aspect of social connection is being examined, the evidence points to the same general conclusion: indicators of greater social connection are associated with reduced risk, while indicators of social deficits are associated with greater risk for premature mortality.

THE RELATIVE INFLUENCE OF ISOLATION AND LONELINESS

When predicting the risk of future disease, does the subjective (loneliness) or the objective (isolation) aspect matter most? The English Longitudinal Study of Ageing, conducted in nearly 5,400 adults over the age of 50, followed for an average of 5.4 years, found that loneliness was associated with an increased risk for cardiovascular disease (coronary heart disease and stroke), but did not find the same outcomes for social isolation[56]. On the other hand, the UK Biobank, a large-scale research effort collecting data on nearly half a million people, followed for an average of 7.1 years, found that both isolation and loneliness were associated with an increased risk of acute myocardial infarction and stroke[57]. However, the impact of social isolation remained significant after adjusting for other risk factors, while the effect of loneliness was attenuated. Both isolation and loneliness were significant predictors of cardiovascular outcomes; however, the relative importance seemed to be stronger for objective isolation.

Research is increasingly looking at the relative importance of isolation and loneliness, and considering multiple outcomes simultaneously. Growing evidence suggests that loneliness has a stronger impact on mental health outcomes, while isolation has a stronger impact on physical health outcomes[31,58]. For example, a large national prospective study, examining the effects of social isolation and loneliness on 32 physical, behavioral and mental health outcomes, demonstrated that both were independent predictors, but isolation had a stronger effect on mortality while lone-

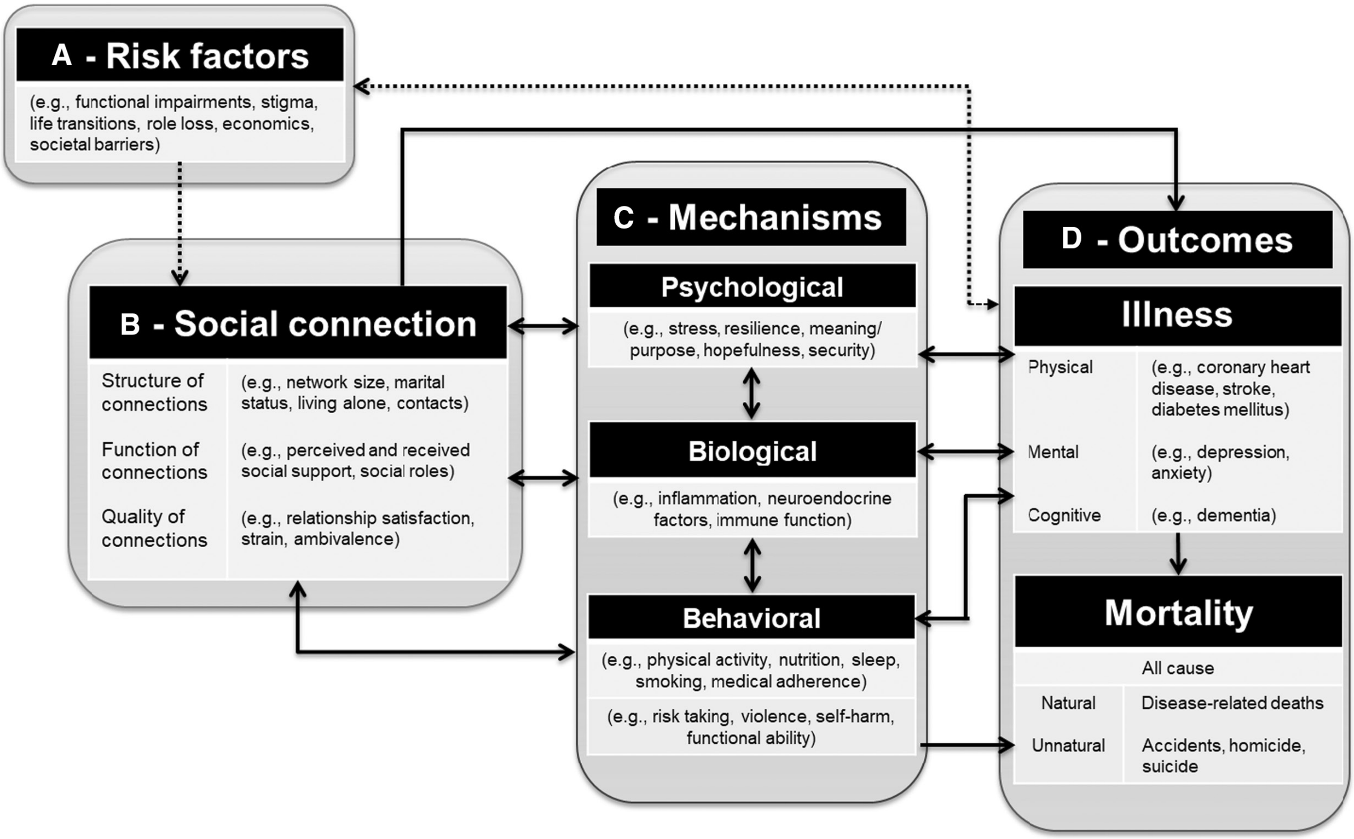

Figure 1 Simplified model of possible direct and indirect, directional and bidirectional, and potentially cyclical pathways by which social connection is associated with morbidity and mortality

liness had a stronger effect on mental health outcomes[58].

PATHWAYS AMONG SOCIAL AND HEALTH FACTORS

The evidence on the protective effects of being socially connected and the risk associated with social disconnection is often studied and discussed separately. However, these conditions intersect in meaningful ways. This includes direct and indirect, bidirectional and cyclical, as well as additive and multiplicative effects. Much of the evidence to date has focused on establishing the direct and indirect effects. A simplified model of these pathways is illustrated in Figure 1.

Among the growing body of literature on social connection and health, studies often focus on establishing a directional influence of some aspects of social connection (represented as B in the figure) on various health or mortality outcomes (represented as D). Further work has examined the mechanisms (represented as C) that provide plausible psychological, biological and behavioral explanations for these effects[59-64].

Several reviews and meta-analyses document the evidence pointing to psychological pathways such as perceived stress[60,65]; behavioral pathways such as sleep[66], physical activity and smoking[67]; and biological factors such as inflammation[68]. Studies further examine the risk factors (represented as A in the figure) that can potentially compromise one's social connection.

The associations of primary interest in research have been between B and D, with B treated as the predictor variable and D as the outcome variable. Subsequent research has treated C as mediator variables and A as risk factors. However, associations are likely far more complex.

Many factors examined as plausible pathways (represented as C in Figure 1) are also notable outcomes, often treated as clinical endpoints. For example, social isolation and loneliness have been linked to poorer nutritional/eating behaviors considered harmful to health, including low fruit and vegetable intake, and poorer overall diet quality[69]. There is also evidence that those who are socially isolated are less likely to get preventive screenings, such as a mammogram[70].

A synthesis of 122 empirical studies examined the effects of differences in social connection on medical adherence[71]. Higher social connectedness, particularly social support, has been linked to better medical adherence across several physical diseases, especially hypertension[72,73] and type 2 diabetes mellitus[74,75]. Similarly, other factors such as stress can be both an endpoint and a mechanism by which social connection influences morbidity and mortality.

The directionality, or bidirectionality, of these associations may be relevant. While those linked to mortality are unidirectional (i.e., end-of-life stops any further influence), nearly all other pathways may be bidirectional. While there is robust evidence of directional effects (i.e., those less socially connected are more likely to develop poorer health conditions), the reverse can also be true (i.e., poorer health also predicts a greater risk for social isolation and loneliness). The relevant mechanisms are both plausible and supported by evidence. Poorer physical health can also contribute to both greater isolation or loneliness and poorer mental health, creating complex bidirectional associations.

These associations may also be cyclical. Poor social connection can dysregulate our physiology and behavior in ways that put us at risk of developing poorer health. Poorer health may reduce people's willingness, ability or access to connect socially, resulting in greater isolation, which in turn impedes their ability to manage their illness, leading to worse prognoses.

We also need to understand the complexity of the factors contained within the model and how that can potentially result in additive and multiplicative effects. For example, co-occurring deficits of social connection (e.g., living alone, small social network, low levels of social support, and loneliness) may contribute to biological, psychological and behavioral pathways, potentially magnifying the risk to health. Furthermore, like many behavioral and lifestyle risk factors that can influence multiple chronic health conditions, the evidence similarly points to poor social connectedness leading to greater risk (and greater social connectedness reducing risk) for multiple health conditions. Thus, it is probable that poor social connection can increase the risk of comorbidities among physical, mental and cognitive health conditions. This is consistent with data from the Health and Retirement Study which demonstrate that social isolation was significantly associated with 32 indicators of physical, behavioral and psychological health outcomes[58].

STRENGTHS AND GAPS IN THE EVIDENCE

The scientific evidence base for the health relevance of social connection is robust, with consistent findings emerging over the past few decades, reinforced across several scientific disciplines (e.g., epidemiology, neuroscience, sociology, medicine, psychology), and using a variety of methodological approaches (e.g., longitudinal, cross-sectional, experimental).

Several meta-analyses and systematic reviews document converging evidence linking social connection, isolation and/or loneliness to psychological, cognitive and physical health. Together, these include hundreds of studies with millions of participants. While most data are observational, there is substantial prospective evidence to establish the temporality of effects[42], and evidence to support a gradient or dose-response effect[46].

There is also experimental evidence in humans and animals to support a potential causal association. For example, experimentally housing animals in isolation versus socially leads to poorer outcomes, including the development of tumors, stroke, impaired healing, and death[5]. Animal models have also validated potential molecular, cellular, immunological and behavioral effects for human social disconnection[3]. These experimental studies further map causal associations between social perception, neural activity, immunological function, and health[3].

In humans, randomized controlled trials (RCTs) experimentally test the potential benefits of social interventions. For instance, a meta-analysis of 106 RCTs found that patients who received psychosocial support in addition to treatment as usual had 20% increased odds of survival than those in the control group who received only standard medical treatment[76]. Although there was variability across types of support interventions, the findings were consistent across patients being treated for cardiovascular diseases, cancer and other conditions.

Drawing causal inferences among factors known to influence health is essential to determine etiology and prevention efforts. However, randomization is not always appropriate in the context of understanding isolation, loneliness, and social connection. Furthermore, although the RCT study design is considered the gold standard for causal inference, it is also criticized because RCTs often have homogeneous and small sample sizes due to inclusion/exclusion criteria, limiting generalizability to real-world application. Thus, additional methods are needed to draw causal inferences for public health. While causal inference is challenging and much debate exists, several models that provide promising support for a causal relationship between social connection and health have been applied.

The Bradford Hill guidelines are among the most widely adopted criteria for drawing causal inferences among variables unsuitable for randomization. These guidelines emphasize nine criteria: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy[77]. Reviews of the evidence on social connection and health have found support for nearly all the Bradford Hill criteria[78-80]. The only criterion not met was specificity, indicating that exposure to the potential cause (social connection) is associated with multiple outcomes rather than a particular outcome and no others. However, smoking also would not meet this criterion for causality, since it results in many health outcomes as well (e.g., cardiovascular disease, cancer). Indeed, Bradford Hill and proponents of these guidelines have noted that meeting all criteria is unnecessary; rather, the more evidence to support the criteria, the stronger the likelihood of causality[77,78]. Nonetheless, critiques of the Bradford Hill guidelines point to the need for more sophisticated analyses.

Additional promising evidence exists to support potential causal associations beyond the Bradford Hill criteria. Drawing causal inferences may be appropriate from sophisticated regression analyses of longitudinal observational data[81], applying a data-integration framework[82], and Mendelian randomization[83]. While few studies focusing on indicators of social connection and health have employed these methods, those that do are supportive[14]. Thus, reviews of this evidence have concluded that the cumulative evidence supports the *likelihood* of a causal association between better social connection and better health[5,78,80].

Despite considerable strengths in the evidence, several notable gaps remain in our knowledge. Some gaps became glaringly apparent during the COVID-19 pandemic, when the scientific community struggled to answer basic questions for the broader public, such as: How much socializing is needed for health benefits? How soon do adverse mental and physical health consequences emerge when we lack social connection? Is there equivalence between in-person and remote means of socializing? What can we do to reduce loneliness? Indeed, there are likely many more questions for which we do not have adequate or firm answers at the moment.

While there are many strengths in our current body of evidence, gaps in this evidence may become barriers or limit our ability to translate this evidence into practice. To address these gaps more

Table 1 Strengths of the evidence, challenges posed by gaps, and consequent priority needs in research on social connection

Strengths of evidence	Challenges	Priority needs
Converging evidence across scientific disciplines	Variability in conceptualization and measurement	A multi-factorial approach is needed.
Many validated assessment tools	Variability in assessment tools limits comparisons across time, or different samples. Validated instruments may not be generalizable to other cultures, settings, and contemporary modes of socializing.	Consistency of assessment to establish prevalence rates and track trends. Improve or create new measures that are valid, reliable and acceptable.
Dose-response of social connection across the lifespan	Most research and attention are on extreme risk and older adults.	A focus across the risk trajectory (including prevention) and across ages is needed.
Converging evidence across social connection components	Fewer studies examine multiple components in the same sample.	Further evidence of potential independent, additive and synergistic effects is needed to assess risk more precisely. Further evidence is needed on how each factor may differentially influence different kinds of outcomes.
Evidence on mortality is consistent across causes of death, country of origin, gender, and health status	Fewer studies include or differentiate: comprehensive health outcomes, low- and middle-income countries, marginalized groups, varying modalities of socializing (e.g., in-person, remote, non-human).	Basic research to fill these gaps is needed.
Robust evidence of mortality and objective health consequences	Weaker and mixed evidence on effective strategies to mitigate risk (weaker methodologies were employed; most interventions are individually focused; most interventions are targeted at those most severely affected). Less is known about other non-health outcomes.	Evidence-based solutions: rigorous evaluations allowing for strong inference; interventions across the socio-ecological model; prevention and mitigation of risk earlier on in the risk trajectory. Evidence on more diverse outcomes (e.g., economic, civic engagement, education, incarceration).

comprehensively, Table 1 provides an overview of some of the strengths and challenges currently existing in the evidence base, further pointing to where future efforts may be prioritized.

EXAMINATION OF TRENDS

Examining trends in prevalence rates, awareness and research on social connection, isolation and loneliness offers valuable insights into the trajectory of societal dynamics and the evolving evidence base. Tracking prevalence rates allows us to understand the scale of these phenomena, informing translation to application and practice. Concurrently, heightened or lack of awareness reflects the perceived importance of the significance and motivation to act upon social factors for mental and physical health.

These trends are both shaped by the evolving landscape of research and may reflect an uneven knowledge base. Collectively, they illuminate the evolving intersection between societal shifts, individual experiences, and the scientific understanding of the intricate connections between social dynamics and health outcomes. Staying attuned to these trends is essential for developing targeted interventions and policies that effectively address the challenges posed by social connection, isolation and loneliness in contemporary society.

Trends in society

Societal trends over the past several decades indicate that, as a population, we have become less socially connected and more isolated, and that a high proportion of the population is lonely.

Based on the available data, loneliness has generally shown little improvement over the last few decades, and may be getting worse. For example, a massive synthesis of 345 studies on emerging adults (ages 18-29), who completed the UCLA Loneliness Scale between 1976 and 2019, found that average loneliness levels linearly increased annually across the 43 years[84]. Furthermore, a meta-analysis of data from 113 countries concluded that a substantial proportion of the population in many countries experiences problematic levels of loneliness[85].

According to the Gallup Global State of Connection survey, nearly a quarter (24%) of the global population reports feeling "very lonely" or "fairly lonely", although there was variability across countries[86]. Of the 29 countries where at least one third of the population felt lonely, 22 were in Africa, four were in the Middle East, and three in South Asia. This also demonstrates that loneliness is not just a wealthy Western country issue, and may even be more severe in other areas of the world. However, inconsistent measurement tools and scoring methods have led to vastly different prevalence estimates. Notably, prevalence rates often favor one indicator (e.g., loneliness) over others, yet indicators may interact in meaningful ways. Thus, the prevalence of those who lack social connection in one or more ways may be far larger than any estimate of a single indicator.

Loneliness trends provide an incomplete picture of the state of social connection, and we must look at the other ways in which individuals and communities may lack connection. For example, data from the American Time Use Survey, regarding how Americans spend their day, demonstrate that, over the past two decades, Americans have spent more time in isolation and less time with household and non-household family members, friends, community engagement, and companionship[87]. Although the COVID-19 pandemic exacerbated these trends, social isolation was increasing, and engagement with family, friends and others (co-workers, neighbors, acquaintances) was declining for years prior to the pandemic. This is consistent with other trends, such as those documenting a decline in social capital and participation in religion[88,89], and changes in family structure (e.g., decline of extended families, rise of single-occupancy households)[90] – many of which are seen globally.

Contemporary society in much of the world is evolving rapidly, likely contributing to our current trends and having important implications for the direction of the trends going into the future. Rapid shifts that may be relevant to social and population health include the increasing aging population, widespread adoption of remote working, increased automation, economic strain and inequity[91], migration and mobility, mental health crisis among youth, rise in xenophobia, civil and political unrest, and environmental crises, all of which may potentially exacerbate trends concerning social connection.

These trends of declining social connection, combined with the evidence on the bidirectional associations with mental and physical morbidities, point to an urgent need to take action. Because multiple factors have been contributing to these trends, building over decades, simply returning to pre-pandemic levels of connection or reducing time on social media may only bring limited benefits.

Trends in scholarly attention

There are also striking trends in the scientific study of the topic. The surging interest in social isolation and loneliness is reflected in research, as demonstrated by the substantial increase of studies on this topic over recent years, potentially providing greater understanding and justification for action. Thus, understanding how loneliness and isolation have been studied over time may provide additional insight.

To examine publication trends, we first used the PubMed by Year search tool. Because of the diverse literature on social, mental and physical health outcomes, the search was limited to two social variables (loneliness and social isolation) and two health outcomes (depression and mortality). We further scanned additional scientific databases (including PsycINFO for depression) using the same social and health variables. The searches were limited to articles published in peer-reviewed academic journals between 1972 and 2023. The mortality search terms included "social isolation" OR "loneliness" AND "death and dying" or "mortality" or "mortality rate" or "mortality risk". The depression search terms in-

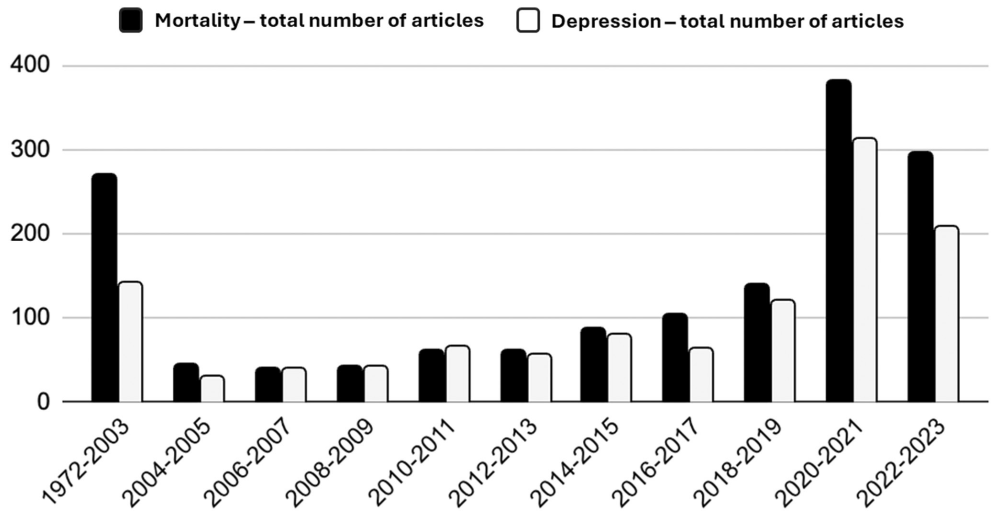

Figure 2 Frequency of loneliness or isolation as search terms in the scientific literature over time. Note that the far-left column refers to 1972-2003, while each of the other columns refers to two years.

cluded "social isolation" OR "loneliness" AND "major depression". PsychINFO also allows narrowing search by methodology: thus, we further used the search parameters "empirical", "quantitative", "longitudinal", "prospective", "retrospective", and "clinical trial".

All studies using those search terms were bracketed into time periods to determine how many articles populated by our search terms were published within each period. Studies published in the past two decades (2004-2023) were demarcated into 2-year periods (2004-2005, 2006-2007, 2008-2009, etc.), while studies published in 1972-2003 were grouped (31 years). Figure 2 graphically presents the number of studies on isolation and loneliness over the years.

Data suggest an exponential increase in the scientific study of social isolation and loneliness. Over the past two decades, the number of relevant articles has grown, with significant increase since 2020. For example, the number of papers published in each subsequent two years since 2020 exceeds the number of studies from 1972 to 2003 combined. However, it is unclear whether scientific interest in other indicators of lacking social connection is similarly surging.

Trends in awareness

Several factors may presumably contribute to greater awareness of the importance of social connection and related aspects of lacking connection (i.e., social isolation and loneliness). These include scientific advancement, social media, government initiatives, the COVID-19 pandemic, and advocacy.

Significant advances in scientific research over the past few decades, especially in the last 5-7 years, may have shed light on the scale of the problem and provided greater confidence in scientific findings. Advancements in social technologies and the widespread use of social media platforms may have played a dual role in awareness. Increased experience of feelings of loneliness associated with that use, and the facilitation of awareness campaigns, discussions and support networks related to health and well-being may occur simultaneously[92].

Government initiatives may have also played a role in greater awareness. Countries have recognized the urgency of the issue and appointed Ministers, formulated policies, and developed strategies to address loneliness and isolation, and highlight social connection as a priority. Awareness efforts have also been undertaken by national and international civil society organizations, coalitions, and networks that have emerged as powerful advocates[7]. These include the UK Campaign to End Loneliness, the Canadian Genwell Project, Australia's Ending Loneliness Together, and the annual Global Loneliness Awareness Week. These collective efforts aim to raise awareness, promote community engagement, and foster a culture of connection.

Unfortunately, trends in public awareness appear to be limited to only certain outcomes. A large survey of US and UK adults published in 2018 found that, when the public was asked to rank various factors contributing to a longer life (e.g., not smoking, exercising, limiting alcohol, maintaining a healthy weight), social connection was amid these factors, but it was rated among the lowest in importance, significantly underestimating its impact relative to effect sizes reported in the scientific literature[93].

Due to a variety of factors occurring since that survey was published – i.e., the COVID-19 pandemic, national awareness campaigns, and increased prevalence within the population – public perception of the health relevance of social connection was expected to increase. However, 2023 data from the UK and a nationally representative sample of US adults demonstrate that there has been essentially no change[94]. Despite increases in public discourse on social isolation and loneliness, the importance of these and other aspects of social connection for health and survival are still underestimated among the public.

Implications from these trends

Overall, these trends point to a large and potentially increasing scale of those lacking social connection, and parallel trends suggest increasing attention within scholarship on the consequent impact on health. Yet, the public perception of risk does not align with either the increasing scale or evidence of the magnitude (effect sizes) for health. This suggests that increased education and awareness of the health relevance is needed.

Discrepancies between the scientific evidence and public perception may have significant implications. First, public perception may significantly influence how resources are allocated and prioritization of various issues within public health agendas[95]. If the public does not perceive social connection and markers of its deficit (e.g., loneliness and social isolation) as relevant to health[93], funding and efforts may not be directed towards addressing them adequately, despite their demonstrated impact on health outcomes[4,15]. Second, public perception influences individual behaviors and societal norms. If social connection is not widely recognized as a protective factor, and loneliness and isolation as serious health risks, individuals may be less likely to change their own behavior or support others experiencing loneliness or isolation[96]. This may perpetuate social disconnection and exacerbate the problem.

Finally, accurate awareness of the health implications among the public may facilitate destigmatizing the issue and promoting help-seeking behavior[97]. When people view loneliness and isolation as a personal rather than a health issue, they may be less inclined to seek support and resources to address these challenges. Aligning public perception with the evidence on the importance of social connection is essential to shaping effective policies, nurturing more connected and supportive communities, and promoting health.

CHALLENGES

The WHO defines health as "a state of complete physical, mental and social well-being, not merely the absence of disease or infirmity"[98]. Considering this definition, social well-being is a critical element of health that has been underappreciated and raises several challenges that we must address.

If physical and mental health are more than the absence of physical or mental illness, we should be taking a similar approach to social health. However, recent attention appears primarily focused on indicators of social deficits, specifically social isolation and loneliness. Yet, our collective and individual capacity as humans to think, feel, engage with others, pursue livelihoods, and experience fulfillment is intrinsically tied to our health – physical health, mental health and social health. The active encouragement, safeguarding and recovery of social health are crucial priorities for individuals, communities and societies globally.

Key challenges include developing a common language, identifying and activating appropriate and effective approaches, and adapting to societal changes. These challenges are also interconnected. Developing a common language is essential to understanding the underlying contributors, predicting outcomes, and measuring changes in risk and protection. Understanding these challenges helps us develop better approaches to preventing and mitigating risk, and adapt these approaches as society evolves.

A common language

Given the array of terms used in the scientific literature, one potential barrier to prioritization within health settings is lack of precision in terminology. It is clear that we need a common language, but the term "loneliness" may fall short. Loneliness is often used as a catch-all term outside academic scientific contexts, but it is defined and measured more narrowly within the scientific literature. While definitions of loneliness vary somewhat, there is broad consensus that it is distinct from social isolation[7,99].

Loneliness is a subjective, unpleasant feeling based on the discrepancy between one's desired and actual level of social connection[100]. It is most often distinguished from social isolation as a separate but related construct[7]. While isolation and loneliness can coexist, they differ in meaningful ways. Social isolation is objectively being alone, having few relationships or infrequent social contact. Thus, social isolation is objective, while loneliness is subjective. Although both social isolation and loneliness can be involuntary, isolation may be chosen[101]. Both are indicators of lacking social connection, but there are many indicators of social connection and, thus, many indicators of social connection deficits[8]. Social disconnection and loneliness are not equivalent[43], and this has implications for measurement and assessment, intervention, policy, and more.

Across scientific disciplines, several constructs have emerged as relevant. Table 2, although not comprehensive, highlights some of the most widely used terms represented in the research and identified in the US Surgeon General Advisory[4]. Pinning down definitions is challenging, given that the same term has been used to refer to different things, while different terms are used to describe the same thing among studies. Some terms, such as social capital, lack a clear consensus on definition[102,103].

Why is this important? These terms refer to related but distinct constructs. Reviews of this evidence find that these measures are not highly correlated empirically[8,104]. Thus, when we only measure one of these, we cannot assume that we are capturing the full scope of how social factors influence health.

We need a common language. "Social connection" has been offered as an umbrella term to encompass these distinct but related terms[4,8,15,105]. From this perspective, the myriad of diverse concepts in the scientific literature can be organized into three key themes or components: structure, function and quality. The first component, *structure*, represents the human need to have others in our life and is often measured by the size and variability

Table 2 Terms commonly found in the scientific literature that are distinct but related (adapted from the US Surgeon General's Advisory[4])

Term	Definition
Loneliness	A subjective distressing experience that results from perceived isolation or inadequate meaningful connections, where inadequate refers to the discrepancy or unmet need between an individual's preferred and actual experience.
Social capital	The resources to which individuals and groups have access through their social connections. The term is often used as an umbrella for both social support and social cohesion.
Social cohesion	The sense of solidarity within groups, marked by strong social connections and high levels of social participation, that generates trust, norms of reciprocity, and a sense of belonging.
Social connectedness	The degree to which any individual or population might fall along the continuum of achieving social connection needs.
Social connection	A continuum of the size and diversity of one's social network and roles, the functions that these relationships serve, and their positive or negative qualities.
Social disconnection	Objective or subjective deficits in social connection, including deficits in relationships and roles, their functions and/or quality.
Social infrastructure	The programs (such as volunteer organizations, sports groups, religious groups, and member associations), policies (such as public transportation, housing and education), and physical elements of a community (such as libraries, parks, green spaces, and playgrounds) that support the development of social connection.
Social isolation	Objectively having few social relationships, social roles, group memberships, and infrequent social interaction.
Social negativity	The presence of harmful interactions or relationships, rather than the absence of desired social interactions or relationships.
Social networks	The individuals and groups a person is connected to and the interconnections among relationships. These "webs of social connections" provide the structure for various social connection functions to potentially operate.
Social norms	The unwritten rules that we follow which serve as a social contract to provide order and predictability in society. The social groups we belong to provide information and expectations, and constraints on what is acceptable and appropriate behavior. Social norms reinforce or discourage health-related and risky behaviors (lifestyle factors, vaccination, substance use).
Social participation	A person's involvement in activities in the community or society that provides interaction with others.
Social support	The perceived or actual availability of informational, tangible and emotional resources from others, commonly one's social network.
Solitude	A state of aloneness by choice that does not involve feeling lonely.

of relationships within a network, being part of groups, and regular social interactions. It is the foundation upon which the other components of social connection are built. The second component, *function*, recognizes that these connections serve essential functions or purposes. Namely, connections can be relied upon for support to meet various needs and goals. Functions are often measured by the interchange of support that is received or perceived to be available, which can be emotional, informational or tangible, and can help us navigate life's challenges. The bulk of the studies within the scientific literature have primarily examined indicators of these structural or functional components. However, a growing body of research is assessing and recognizing the importance of the quality of social relationships, networks and interactions. Thus, the third component, *quality*, refers to our connections' positive and negative aspects. High quality is often measured by the level of satisfaction or intimacy, whereas low quality includes social negativity such as conflict, strain or ambivalence.

While Figure 3 is helpful in identifying these core conceptual themes, individual measurement approaches may overlap to some degree between social connection components. Furthermore, specific assessment tools may appear to align clearly within one component, but contain items that overlap with other components[104]. Generally, high levels of each of these components have been linked to better health and lower levels of poorer health. To more comprehensively understand underlying causes, predict outcomes, and measure risk, we need to consider the distinct contributions of the structure, function and quality of social connection.

Data across multiple scientific disciplines have linked various social connection indicators to health outcomes[8]. Strong structure, function and quality of social connection may be considered optimal for health. On the contrary, when all three are low, this would be associated with high to severe risk. However, there may be unevenness in the extent to which any individual experiences the three components of social connection. The descriptions in Table 3 help illustrate the disaggregation across these components and their relation to various risk profiles. Nonetheless, there is likely further complexity of risk, given that many indicators within each component of social connection are on a continuum and may have synergistic effects. For example, longitudinal data from nearly half a million people, followed for an average of 12.6 years, demonstrated that low levels on both structural and functional indicators of social connection resulted in a significantly higher risk for cardiovascular disease mortality (hazard ratio, HR=1.63), compared to low levels on structural (HR=1.27) or functional (HR=1.17) components alone[54].

Conceptually, loneliness may represent the signal or symptom of unmet social needs. However, loneliness does not represent low levels across all three social connection components. Comparisons demonstrate these distinctions. For example, meta-analyses that establish the effect size for the aggregate measures of social connection on mortality were significantly larger than the effect size for loneliness[43,105]. Thus, loneliness is not the same as lacking

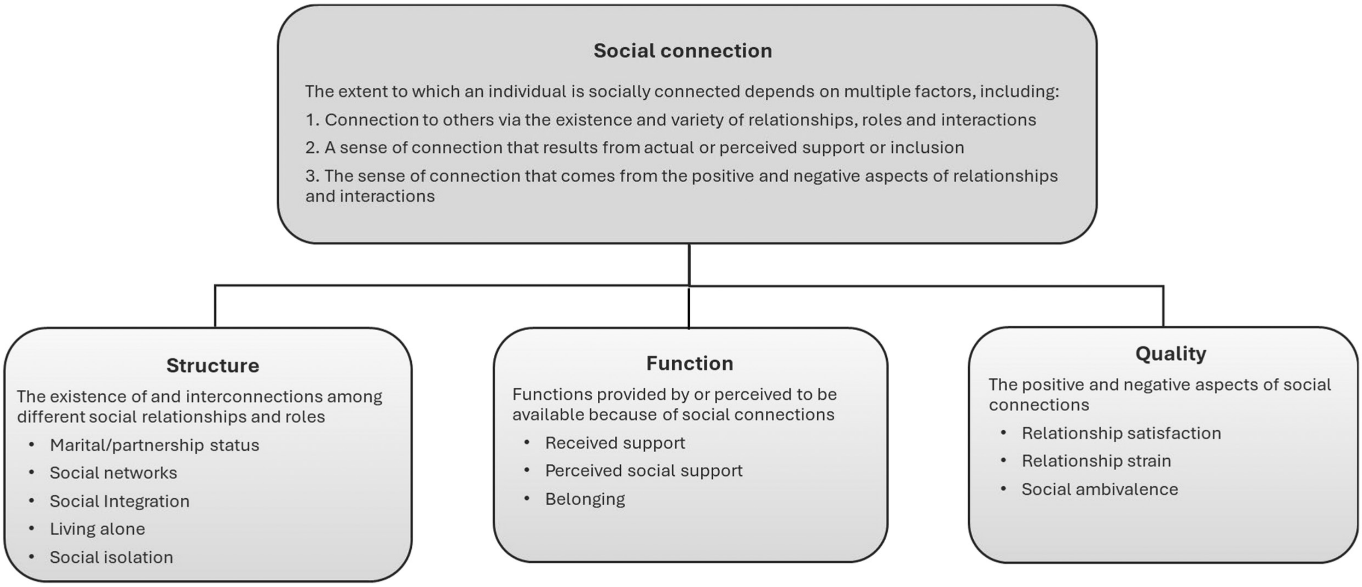

Figure 3 Social connection as a multi-factorial umbrella term encompassing the structural, functional and quality aspects represented in the scientific literature (adapted from Holt-Lunstad[8])

social connection.

Measurement

Another challenge related to the need for a common language is the lack of consensus on measurement[104]. The most widely used measurement tools have helped to build a robust evidence base, but may have limitations when applied to other settings. For instance, most measurement tools were developed in Western countries, prior to the widespread shift to digital and remote means of socializing. Measurement not only needs to be predictive of the outcomes of interest, but must also be feasible to use. Notably, what is feasible may differ in different contexts, such as research, clinical settings, population surveillance, and evaluation of the effectiveness of interventions. Currently there is no measure that is multi-factorial, validated, and feasible or adapted to become feasible across settings.

Given the multi-factorial conceptualization of social connection[7,80], a considerable challenge is developing a feasible multi-factorial measure. Not all social connection components are typically assessed, because this would take too much time. Due to time and space constraints, assessments in medical settings and population surveillance may only assess one indicator; however, this approach will likely result in risk assessment errors. For example, if an individual is assessed on an indicator of the structural component of social connection (e.g., frequency of social contact) and found to have high levels, we may assume that this person is at low risk. However, this assessment may miss low levels on the other two components (e.g., low social support, poor quality relationships), which may put the individual at risk. Similarly, we might assume that this person is at low risk if scores are low on an assessment of loneliness, yet the person may have little or no social contact with others. Furthermore, if an individual is low on one component, we may be missing potential protection associated with high levels on the other components. Thus, one's overall social risk profile may be incomplete because of the limited scope of assessments.

Effective intervention and prevention strategies

The next major challenge is reducing risk through effective intervention and prevention strategies. Social connection is complex, with various factors contributing to its increase or decrease, directly and indirectly[8]. Generally, social connection occurs naturally among individuals and within communities. However, when it does not, intervention becomes necessary to reduce risk. Direct actions, programs or initiatives can be implemented to increase social connection or decrease forms of social disconnection intentionally.

Key challenges include: a) the capacity to develop and evaluate intervention strategies; b) the difficulties to understand what works best for whom in what context; and c) the limited scope of existing strategies, and the need to ensure the full scope of social connection across the socio-ecological model, sectors of society, and life course.

Developing and evaluating interventions

The evidence supporting the positive effects of social connection is far more robust and methodologically rigorous than the evidence supporting the effectiveness of interventions aimed at creating it when it is not occurring naturally, or at reducing social disconnection. However, this challenge (i.e., more substantial evi-

Table 3 Conceptualization of potential risk to mental and physical health according to distribution across the level of social connection components

Risk level	Structure	Function	Quality	Description
Optimal-low risk	High	High	High	Large and varied social network, with regular social contact with people who can be relied upon for support and assistance when needed. These include deep and meaningful relationships characterized by caring and compassionate interactions.
Low-moderate risk	High	High	Low	Large and varied network, with regular contact among people who can be counted upon for support. However, these relationships are strained and/or lack depth, and interactions are void of caring or compassion.
	High	Low	High	Large and varied network, with regular social contact with meaningful and high-quality relationships. However, these are not able or available to provide support or assistance when needed.
	Low	High	High	Small social network and infrequent contact. However, the limited social contact is among those who can be relied upon for support, perhaps strangers or volunteers. Nonetheless, it is caring and compassionate.
Moderate-severe risk	High	Low	Low	Large and varied social network, and regular contact with others. However, they cannot be relied upon for support. These are strained relationships and interactions, with a lack of caring and compassion.
	Low	High	Low	Small social network and limited social contact with others. Support is available and provided by others, perhaps by strangers or volunteers; however, it lacks depth, is accompanied by strain, or lacks caring and compassion.
	Low	Low	High	Small social network and limited social contact with others. It is not possible to rely upon others for support. However, the limited social contact is caring and compassionate.
Severe risk	Low	Low	Low	Small social network and little social contact. There is no one to rely upon. What little social contact does occur is strained or lacks caring and compassion.

dence of health risks compared to treatments to eliminate these risks) is common among many health issues. The National Institutes of Health estimate that therapeutics for *any* condition take, on average, 10-15 years to develop, because 95% of new therapeutics fail[106]. With the increased urgency to address the crisis of social isolation, loneliness and social disconnection, we cannot take a "something is better than nothing" attitude, assuming that all approaches will be helpful.

Rigorous evaluations are needed. However, the resources and capacity to develop and evaluate interventions are limited – particularly for interventions conducted outside academic institutions. Rigorous methodologies are often not utilized, resulting in a low-quality body of evidence[107,108]. To strengthen this evidence, the Multiphase Optimization Strategy (MOST) approach has been utilized for other health issues and could similarly be applied to this area[109]. The MOST framework is an iterative implementation method that uses empirical information about component effects within real-world constraints to develop, evaluate and optimize interventions[110].

Understanding what works for whom in what context

There is a growing body of evidence examining the effectiveness of interventions, including multiple meta-analyses and reviews of the evidence[108,111-116]. Interventions vary in terms of their social connection focus (e.g., loneliness, social isolation, school connectedness, social skills, social support, neighborhood cohesion); setting (e.g., home, clinic, community, school, whole of society policies); delivery (e.g., self-directed, peer group, family or caregiver, professional, volunteer); modality (e.g., in-person, phone, virtually); sub-population group (e.g., older adults, children, disabled, university students, veterans, new parents), and many other characteristics.

Interventions also vary in their timing and duration (e.g., once or repeated, hours to years); their outcomes (e.g., social, health, performance); their target (e.g., general population, high-risk populations); and goals (e.g., prevention, mitigation, treatment). Effectiveness may depend on the specific characteristics of the targeted population, the type and intensity of the intervention, and its length[15]. This variation creates a considerable complexity. We highlight here the interventions with the most promising body of evidence.

Loneliness interventions

There is now a sizable body of research examining interventions focused specifically on reducing loneliness. Systematic reviews and meta-analyses generally find that these interventions are associated with significantly reduced loneliness and improved social support. For example, an umbrella review of 211 studies, including seven different types of interventions, examined their effectiveness in reducing loneliness[116]. They were befriending programs, technological interventions, meditation/mindfulness, animal therapy or robopets, social cognitive training, social skills training, and social support. Of these intervention types, social support, social cognitive training, and meditation/mindfulness significantly decreased loneliness.

Among loneliness interventions designed to target specific age-based sub-populations, there are meta-analyses of evidence for those focused on young people, university students, and older adults. A meta-analysis of 39 studies (including 25 RCTs) focused on loneliness in children and adolescents found that it could be reduced, with no significant differences between various types of interventions[115]. A systematic review of 37 interventions among university students found that bringing students together for an activity or to socialize, in-person or virtually, helped reduce feelings of loneliness[117]. Meditation/mindfulness benefited those who preferred not to join groups. Other reviews identify several effective interventions for reducing loneliness and increasing social connection in older adults, including social support groups, technology-based interventions, and community-based activities[118,119].

Overall, based on the current evidence, no intervention type (e.g., changing maladaptive social cognitions, enhancing social skills, providing psychoeducation, supporting socialization, increasing opportunities for social interaction) seems to be superior to the others. The majority of this evidence has been classified as low to critically-low quality[116].

Interventions in clinical settings

Given the robust evidence of the medical relevance of social connection, addressing isolation and loneliness in clinical settings among patients may improve health outcomes. Early evidence pointed to greater survival among cancer patients who participated in social support groups along with standard treatment compared to standard treatment alone[120]. Since then, various types of programs have been developed to help support patients across different medical conditions, but with mixed outcomes. Nonetheless, when the body of the evidence was examined as a whole via meta-analysis, including 106 RCTs, medical patients randomized to receive some type of psychosocial support intervention in addition to standard medical treatment had a 20% increased survival, and 29% increased survival time compared to patients who only received standard treatment[76].

While there was considerable variability in the effects among the interventions, on average, providing patients with psychosocial support was as effective in increasing survival as many standard medical interventions, including smoking cessation and lifestyle interventions. Thus, not only do high levels of naturally occurring social connection increase one's lifespan, but providing interventions to support patients in medical settings also seems to increase survival. This evidence suggests, consistent with NASEM recommendations, that addressing the social needs of patients by integrating this component into existing treatment within the health care system may be a promising approach[15,121].

Social prescribing

Social prescribing involves referring patients outside the medical setting to community-based services and activities to address social, emotional and practical needs. An integrative review of the evidence found that social prescribing has generally favorable effects in reducing social isolation and loneliness. However, the quality of the evidence was mixed and generally weak methodologically[118]. The interventions were diverse and heterogeneous in design and implementation, relied on self-report, and often lacked adequate controls.

While social prescribing is a promising approach gaining popularity, further research is needed, including RCTs and meta-analyses, as multiple other systematic reviews provide a weak or mixed picture[122-124]. More robust evidence is needed to understand how strong the effects are for individuals, sub-populations and communities regarding loneliness, isolation and social connectedness, and to identify the most effective approaches for different populations.

Technology-based or virtual interventions

Technology-based or virtual interventions – such as online social networking, video conferencing, messaging apps, and virtual companions or pets – are implemented with the aim of reducing social isolation or loneliness among specific populations. Systematic reviews of the evidence found that technology-based interventions were effective in reducing loneliness among older adults and individuals with mental health issues[111,125,126].

The WHO has developed an evidence and gap map for technology-based interventions for reducing social isolation and loneliness among older adults[127]. This includes 200 studies and 97 systematic reviews. Most interventions utilized video conferencing and calls, though assistive robots and virtual pets were also common.

The effectiveness of digital interventions may vary depending on the specific population and the type of technology used. Caution should be used, given that some studies found no effectiveness and, in some cases, negative outcomes. For example, data from the National Social Life, Health and Aging Project found that, despite increases in remote modes of contact with others, individuals still experienced loneliness, depression and decrease in happiness[128].

While some technology-based interventions may be promising, not all effectively reduce social isolation or loneliness. More research is needed to fully understand their effectiveness, for which groups, and how they can be optimally implemented.

School connectedness

There is strong evidence that interventions aimed at increasing school connectedness, or the feeling of belonging and engagement within the school community, can positively impact student outcomes, from academic achievement to reduced suicidality[129-131]. In one review, classroom management approaches were associated with improved school connectedness among students, including teacher caring and support, peer connection and support, student autonomy and empowerment, management of classroom social dynamics, teacher expectations, and behavior management[132].

Research has shown that students who feel more connected to their school are more likely to attend class regularly, have higher grades and test scores, are less likely to engage in risky behaviors (e.g., substance abuse, violence), and have better health[133-136]. Classroom practices that build strong, supportive and trusting relationships help reduce patterns that inappropriately exclude some groups of kids[132].

Policy

There is growing interest in the role of policy as an intervention, with many calls to enact pro-social policies, or policies to address isolation and loneliness[4,137-139]. Policies are explicit guidelines which provide a framework for decision-making; are enforced by groups, organizations or governments; and can directly or indirectly impact social connection. Similar to the Health in All Policy approach that recognizes the health implications across sectors (e.g., education, employment, health, nutrition, housing, transportation)[140], a "Social in All Policy" approach should recognize the social relevance of policies across sectors[80,138].

Policies can directly influence social contact (e.g., policies on visitation or family member involvement in medical care), or can focus on changing other kinds of outcomes (e.g., economic, environmental) that substantially influence social connection (e.g., policies on neighborhood zoning, bussing routes, remote work).

Reviews of existing policies cover social and emotional learning curricula in schools[130,141]; state-level farmer wellness programs[142]; expansion of telehealth services to provide mental health services in schools[143]; and workplace policies that include shorter total work hours and earlier end of the workday, enabling workers to attend to family responsibilities and achieve greater work-life harmony[144]. There is existing US legislation, including the Older Americans Act of 1965, which was amended in 2020, to address social isolation and loneliness.

Many policies are being introduced with the intent to facilitate social connectedness. However, given the scale and magnitude of public health implications, they need to be evaluated for effectiveness like any other intervention.

Targeted vs. broad approaches

Another major challenge is whether to focus solutions on people most severely affected or broadly on the population. When social connection needs are not met, the mental and physical health consequences are broadly found across age and other demographics. However, isolation and loneliness are unequally distributed across the population. Groups that experience marginalization – i.e., lesbian, gay, bisexual, transgender, queer and/or questioning (LGBTQ+) people, racial minorities, migrants, those with disabilities[91] – and life circumstances that may or may not co-occur with aging (e.g., functional or sensory impairments) are disproportionally affected. Thus, a significant challenge is whether to focus efforts more broadly or these groups.

One perspective is that prioritization should be given to the most vulnerable populations and addressing their needs. By focusing on specific populations, such as marginalized or underserved communities, efforts can be directed toward reducing health disparities and ensuring that resources reach those who need them the most[145]. Many sources recommend tailoring interventions to address specific needs, barriers and enablers within these groups, in order to increase the effectiveness of these interventions[15,146]. This approach may be a more efficient use of limited resources, funding and personnel. Moreover, it is easier to measure the impact of targeted approaches, as they are narrowly defined and address a smaller population. However, identifying and targeting people "at-risk" may potentially pathologize and stigmatize such groups further and place the burden of change on the individual. Thus, it has been argued that we should focus on the factors that put people at risk instead of group membership[147].

Another perspective is that we should focus efforts across the population to have larger shifts, rather than just targeting a small portion of the population[77]. Broad approaches can lead to systemic changes in policy, environment, and societal norms, laying the foundation for long-term health improvements. Implementing broad interventions might also benefit from economies of scale, reducing the cost per individual reached compared to targeted interventions.

Both targeted and broad approaches are necessary, starting with broad measures to address general issues, while using targeted interventions to address specific needs within the population. However, targeted approaches should be focused on the factors associated with risk (e.g., marginalization) rather than group membership, to avoid further stigmatization. Universal approaches may help prevent social disconnection, whereas more targeted approaches may be needed for those who are already isolated, lonely, or socially disconnected in other ways for prolonged periods or at severe levels. A hybrid strategy can leverage the strengths of both approaches to maximize public health outcomes.

Limited scope of existing approaches

Despite the growing body of research focused on interventions, the scope of solutions is limited in several ways. The Systemic approach Of Cross-sector Integration and Action across the Lifespan (SOCIAL) framework points to gaps and opportunities in solutions across the socio-ecological model, sectors of society, the life course, and prevention[80].

Evidence points to underlying root causes across the socio-ecological model (e.g., individual, interpersonal, community, institution, society)[8], yet most interventions are being deployed at the individual level[148]. A scoping review of interventions for older adults, including evidence from 30 countries, found that the majority of interventions only measured loneliness, and only three societal-level interventions were found[149].

The health care sector, including both clinical and community health settings, is most often the target of interventions and programs. However, we need to expand our approaches across sectors to engage the whole of society. No one sector of society is likely to be able to address this issue. The "Social in All Policy" approach [138] recognizes the health and social implications across sectors and "systematically takes into account the health implications of decisions, seeks synergies, and avoids harmful health impacts in order to improve population health and health equity"[150].

Social connection is vital at every stage of life, yet most solutions are focused later in life[111,151]. The evidence of a dose-response effect of social connection on biomarkers of health across stages of life[46], and the importance of early social environment[5], highlights the need for efforts to address this issue across life. Social isolation during childhood, for instance, is associated with increased cardiovascular risk factors in adulthood, such as increased blood glucose levels, high blood pressure, and obesity[152].

As is the case with most health issues, primary, secondary and tertiary prevention approaches are needed to address social isolation and loneliness. Unfortunately, few interventions focus on helping the society become more socially connected. Prevention efforts may have many longer-term benefits, such as avoiding costly interventions later, reducing disease burden, and improving quality of life[153].

Efforts to gather and synthesize data, and to identify evidence gaps, are underway. These and similar efforts aim to help create centralized resources to single out evidence-based interventions effective in reducing social isolation and loneliness, or increasing social connectedness. However, without sustained funding, there will be difficulties to evaluate the evidence supporting their effectiveness.

IMPLICATIONS FOR THE FUTURE OF MENTAL AND PHYSICAL HEALTH

The world is beginning to recognize the vital importance of social connection to the health and welfare of countries. Considering the trends that have led to concerns of a public health crisis of social disconnection, we must proactively evaluate the long-term implications if these conditions do not improve or perhaps continue to worsen. Two of the most pressing concerns that have the potential to worsen trends are the unknown long-term consequences of the COVID-19 pandemic and the rapidly evolving technological landscape of society.

Long-term implications of the COVID-19 pandemic

During the COVID-19 pandemic, social developmental processes were significantly disrupted, with potentially critical long-term health implications. Socialization during early life plays a crucial role in shaping a child's development and long-term health[154]. Early socialization provides the foundation for healthy relationships (e.g., learning to communicate, cooperate, negotiate, share), emotional well-being (e.g., learning empathy, expressing emotions), cognitive development (e.g., information processing, critical thinking, problem-solving), self-identity (e.g., self-confidence, self-esteem), ability to navigate cultural norms and values, and overall physical health[155].

Early life experiences with caregivers, peers, schools and communities are all key contributors to the early social environment that ensures longer-term well-being and survival[156-160]. However, the pandemic severely limited socialization for roughly three years, during this critical developmental period, for infants, young children and adolescents. Since it is well documented that early social experiences significantly predict later social, mental and physical health[136,161,162], the long-term health implications of the pandemic may be disproportionately borne for an entire generation.

There may also be longer-term consequences among adults, due to widespread behavioral adaptation that may be sustained over time. The massive adoption and implementation of tools to cope with reduced social contact (e.g., remote work, contactless delivery services, streaming entertainment services, telehealth, automation) came with significant advantages, including increased flexibility, autonomy, convenience, safety, and in some cases cost-effectiveness[163-167].

These advantages have led to preferences that may limit our social contact – particularly with co-workers and weak-ties. Reductions in social contact with both may be critical factors for future health, given the significance of workplace relationships[168,169] and the evidence on the importance of weak-ties[170,171]. While these preferences are obviously not universal, a large portion of the population values such conveniences. Even if they are not preferred, they are often incentivized by lower costs[166]. For example, roughly half of patients preferred in-person visits and half preferred a video visit, but 23.5% switched to a video visit if the cost was lower[172]. What was once initiated or scaled to help us cope with isolation, is now what may be reinforcing isolation, with potential long-term implications for exacerbating existing levels of social disconnection and corresponding health consequences.

The widespread behavioral adaptation to spending more time alone, or not leaving the house, may contribute to a societal shift that normalizes social isolation. This is increasingly being depicted in cultural narratives of a "social-battery" that is drained by socializing, and the benefits of "self-care", "me-time", and solitude. While there is evidence of some benefits of solitude[173], the evidence is quite heterogeneous, and benefits appear limited to short-term bouts of solitude, not chronic time alone[174-175]. There is instead – as we have seen – robust empirical evidence of the harmful effects of social isolation on mental and physical health outcomes, and increased risk for premature mortality. If time spent alone is praised and encouraged, while the risks of social isolation are diminished within public discourse, the consequences to health are likely to be magnified.

The pervasive experience of social isolation and loneliness during the pandemic also fueled self-proclaimed "experts" and influencers who pushed common-sense approaches to wellness, and in some cases misinformation[176-177]. Coupled with a growing distrust in institutions, including science, this may lead to confusion on what is credible. When local community organizations and the general public are skeptical or distrust science, government, and each other, this may increase social disconnection and stifle the development and acceptance of effective interventions and programs to reduce isolation and loneliness.

Technological advancements

The rapid evolution of digital technologies has already demonstrated co-occurring shifts in socializing. Much has been written about the mental and physical health implications of the use of social media[92,178-183]. Similar rapid developments and widespread adoption are occurring with artificial intelligence (AI) and large language models (LLM) tools, that have the potential to similarly result in both benefits and harms, but to an exponentially larger extent.

The long-term consequences of AI are yet unknown, but predictions often fall into either a utopian or dystopian outlook for the future, both of which have implications for social health and policy[184]. From a utopian perspective, AI will be the cure to the "loneliness epidemic", with 24/7 access to emotional support for all, and increased automation will free up more time for leisure. From a dystopian perspective, AI will replace human interaction, and diminish trust in others due to blurred lines between fact and fantasy. Moreover, several jobs will no longer require humans, resulting in a lack of meaning and purpose in life, and perhaps even the risk of a downfall of humanity altogether[185].

Some of the potential short-term benefits that already have some limited evidence involve AI-powered virtual companions or chatbots that can engage in conversation and provide immediate emotional support[186], and 24/7 access to mental health support as well as increased accessibility among those experiencing barriers (e.g., language, privacy concerns, social anxiety) to in-person therapy. However, increased isolation may occur if there is over-reliance on AI interaction and emotional support and forming attachments to AI companions[187,188]. Generative AI may also magnify our own biases, leading to information echo chambers that further isolate us from others[189,190].

Generative AI is neither inherently good or bad for health and

Table 4 Recommendations for national strategies to foster social connection and address social isolation and loneliness

Policy and strategy	Make social connection a priority in policy agendas of governments and other organizations. Establish a national strategy and leadership at all levels to track, advance and coordinate policies and programs across agencies or units. Assemble an inter-agency, cross-sector coalition to assess and address social implications across all policies and programs. Establish a centralized resource or database for evidence-based interventions and policies.
Integration within the health system	Prioritize social connection in prevention and integration into treatment in clinical settings. Assess and track risk within the electronic medical records. Adequate training, resources and support for health care providers.
Healthy digital environments	Establish greater transparency and cooperation to independently evaluate drivers of connection and disconnection. Increase accessibility (access, affordability, knowledge) to digital tools and environments with demonstrated benefits. Establish safeguards (laws, regulations, guidelines, autonomy) to reduce risk associated with harmful elements.
Evidence, evaluation, measurement	Creation of a global social connection index to allow for comparisons across nations. Establish consistent national measure of social connection, for population surveillance at a national level. Establish a national research and policy center/institute to coordinate cross-sector collaboration in research. Establish Grand Challenges in Social Connection Research, and funding to sustain efforts to address them.
Education and awareness	Establish public-facing national awareness campaigns, ensuring accurate and inclusive messages based on high-quality evidence. Establish National Health Guidelines for Social Connection (similar to dietary guidelines). Include social connection in public-facing health educational resources (websites) of major health organizations. Integrate social connection into formal health education curriculum across all educational settings (primary, secondary, post-secondary, higher education, continuing learning, advanced and continuing education for health professionals). Establish age-appropriate formal education curriculum and practices to foster social connection skills.
Norms and culture	Media, arts and entertainment, local and national leaders, and others in positions of influence, can model positive behaviors that facilitate connection (e.g., respect, openness, responsiveness, kindness, support) Create routines, habits and programs that reinforce regular social connection within formal (workplace, education) and informal (neighborhoods, recreation and leisure) settings. Strengthen norms, incentives and opportunities to create a culture of service. Establish coalitions and networks to coordinate efforts and share best practices.
Infrastructure	Design physical places and spaces to foster socializing (e.g., public, commercial, recreational, religious). Design should consider features of accessibility and inclusiveness across ages, abilities, and economic circumstances. Evaluate existing infrastructure to identify barriers to social connection. Redesign, reduce or eliminate features of infrastructure that are barriers. Create pro-social policies, and evaluate existing policies for barriers relevant to infrastructure (e.g., zoning laws, investing in public transportation, housing and desegregation). Reform policies to allow for the use of existing underutilized public spaces (e.g., schools during nights and weekends, churches on weekdays, commercial buildings during off hours) for community social events and gatherings. Develop programs, services and resources (e.g., recreation, volunteer programs, senior centers, community gardens) to support more connected communities.

humanity. Our current decisions and actions will starkly impact the trajectory of our future, extending across all sectors of society[184].

Recommendations to reverse trends

Several countries are beginning to take steps to promote social connection, and the global COVID-19 pandemic crystalized and accelerated the urgency to act and to coordinate efforts. Table 4 provides a set of recommendations for national strategies to foster social connection and address social isolation and loneliness.

These recommendations align with those made by the National Academy of Sciences, Engineering, and Medicine[15,27,92], expert consensus documents and reports, the US Surgeon General Advisory[4], the WHO[191], the US Centers for Disease Control and Prevention[192], the American Heart Association[28], and national organizations or groups of states (e.g., European Union, UK, Australia, Japan)[193-195].

CONCLUSIONS

In recent decades, we have witnessed a progressive decline in the social connectedness of individuals and communities at the global level. At the same time, scientific evidence has been credibly demonstrating a significant causal effect of lack of social connection on leading physical and mental health indicators, such as cardiovascular disease, stroke, depression and dementia[80]. In some cases, these associations are bidirectional, cyclically reinforcing poorer social connection and worse health. The strongest evidence documents an independent directional influence of social connection indicators on risk for disease-related and all-cause mortality, adjusting for a robust set of demographic, lifestyle, biological, and health relevant factors[15,54,55]. Furthermore, evidence points to several plausible biological, behavioral and psychological mechanisms through which these associations of social connection with morbidity and mortality may occur. The WHO now recognizes social connection as a global public health priority[1,13].

Despite significant strengths, the body of research evidence is complex and uneven, generating several challenges. We need a common language to describe and measure the multiple indicators of social connection and its deficits. Despite the use of "loneliness" as a catch-all term, this construct is distinct from other related ones (e.g., social isolation). There is convergence of evidence of the health relevance across indicators of social connection, or lack thereof. Nonetheless, the relative effect sizes vary in their magnitude. Social isolation appears to be a stronger predictor of physical health outcomes, while loneliness is a stronger predictor of mental health outcomes[58]. Further, the influence of poor social connection across its multiple components appears to be much stronger than that of only one component[42,54]. Explicit recognition of the separate contribution of the structure, function and quality components of social connection is needed in measurement, risk assessment, and health promotion.

Recent surges in the scientific study of social isolation and loneliness have replicated and expanded upon earlier findings, providing larger sample sizes, more rigorous methodologies, and greater confidence. However, studies have also shown that the public underestimates the relevance of social connection for health relative to what has been documented in the scientific literature[93,94]. Since awareness is a critical step to behavior change[96], education efforts should be prioritized as part of health promotion.

There has been a proliferation of interventions with promising results, most often improvements in loneliness. These interventions vary widely in their approaches, foci, modalities and features; yet no one approach appears superior to others[151]. There are also important limitations worth noting. Most interventions are individually focused, and attention to prevention or early intervention is limited[148]. Furthermore, most reviews and meta-analyses of the evidence only examine the effectiveness of interventions on changing social outcomes (e.g., loneliness), with fewer also evaluating the effectiveness on changing health outcomes. Overall, the proposed interventions lack the level of scientific rigor of the evidence that supports their need.

Existing trends in social disconnection and declining health are likely to persist if social factors continue to get relegated as peripheral to health, and interventions are only aimed at people most severely affected. In the presence of growing trends of distrust in institutions, including science, identifying and implementing effective solutions may be challenging. Furthermore, long-term implications from the COVID-19 pandemic and evolving digital technologies point to potential worsening of existing trends in social disconnection.

Looking to the future, the trajectory of social, mental and physical health declines is unknown, but may be accelerated. Global scale reductions in social contact and subsequent behavioral adaptations may reinforce sustaining social isolation or have delayed downstream effects. Among infants, young children and adolescents, the limited social exposure at critical developmental stages may result in longer-term health consequences into adulthood. Across ages, behavioral adaptations through tools and mechanisms meant to cope with isolation (e.g., remote work, streaming entertainment, telehealth, contactless delivery) may instead sustain reduced social contact. Further developments in digital technologies, such as AI, have the potential to both help and exacerbate the problem.

Despite challenges, there is sufficient scientific evidence to prompt action. Importantly, themes have emerged prompting recommendations for individuals, communities and countries. Prioritizing these recommendations will be critical for reversing trends of social isolation and loneliness, and advancing social connection to positively influence the health and well-being of individuals and society at large.

REFERENCES

1. WHO Executive Board and WHO Commission on Social Connection. The importance of social connection to human health and well-being. https://apps.who.int/gb/statements/EB154/PDF/USA-Group-of-countries-21.pdf.

2. Leary MR, Baumeister R. The need to belong. Psychol Bull 1995;117:497-529.
3. Cacioppo JT, Cacioppo S, Cole SW et al. Loneliness across phylogeny and a call for comparative studies and animal models. Perspect Psychol Sci 2015;10:202-12.
4. Office of the US Surgeon General. Our epidemic of loneliness and isolation: the US Surgeon General's Advisory on the healing effects of social connection and community. www.hhs.gov.
5. Snyder-Mackler N, Burger JR, Gaydosh L et al. Social determinants of health and survival in humans and other animals. Science 2020;368:eaax9553.
6. Sapolsky RM. Social status and health in humans and other animals. Annu Rev Anthropol 2004;33:393-418.
7. Badcock JC, Holt-Lunstad J, Garcia E et al. Position Statement: Addressing social isolation and loneliness and the power of human connection. Global Initiative on Loneliness and Connection, 2022.
8. Holt-Lunstad J. Why social relationships are important for physical health: a systems approach to understanding and modifying risk and protection. Annu Rev Psychol 2018;69:437-58.
9. Walker P. May appoints minister to tackle loneliness issues raised by Jo Cox. The Guardian, January 16, 2018.
10. Kodama S. Japan appoints 'minister of loneliness' to help people home alone. Nikkei Asia, February 13, 2021.
11. European Commission. Loneliness publications. https://joint-research-centre.ec.europa.eu/scientific-activities-z/loneliness/loneliness-publications_en.
12. Kim H, Ng KW. Hikikomori: why S Korea is paying young recluses to leave home. https://www.bbc.com/news/world-asia-65554271.
13. World Health Organization. WHO Commission on Social Connection. https://www.who.int/groups/commission-on-social-connection.
14. Sbarra DA, Ramadan FA, Choi KW et al. Loneliness and depression: bidirectional Mendelian randomization analyses using data from three large genome-wide association studies. Mol Psychiatry 2023;28:4594-601.
15. National Academies of Sciences, Engineering, and Medicine. Social isolation and loneliness in older adults: opportunities for the health care system. Washington: National Academies Press, 2020.
16. Wickramaratne PJ, Yangchen T, Lepow L et al. Social connectedness as a determinant of mental health: a scoping review. PLoS One 2022;17:e0275004.
17. Mykyta L. Living alone and feelings of depression among adults age 18 and older. Natl Health Stat Report 2024;199:1-11.
18. Mann F, Wang J, Pearce E et al. Loneliness and the onset of new mental health problems in the general population. Soc Psychiatry Psychiatr Epidemiol 2022; 57:2161-78.
19. Wray NR, Ripke S, Mattheisen M et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet 2018;50:668-81.
20. Levey DF, Stein MB, Wendt FR et al. Bi-ancestral depression GWAS in the Million Veteran Program and meta-analysis in >1.2 million individuals highlight new therapeutic directions. Nat Neurosci 2021;24:954-63.
21. Bedaso A, Adams J, Peng W et al. The relationship between social support and mental health problems during pregnancy: a systematic review and meta-analysis. Reprod Health 2021;18:162.
22. Serrano-Ripoll MJ, Meneses-Echavez JF, Ricci-Cabello I et al. Impact of viral epidemic outbreaks on mental health of healthcare workers: a rapid systematic review and meta-analysis. J Affect Disord 2020;277:347-57.
23. Penninkilampi R, Casey A-N, Singh MF et al. The association between social engagement, loneliness, and risk of dementia: a systematic review and meta-analysis. J Alzheimers Dis 2018;66:1619-33.
24. Lara E, Martin-Maria N, De la Torre-Luque A et al. Does loneliness contribute to mild cognitive impairment and dementia? A systematic review and meta-analysis of longitudinal studies. Ageing Res Rev 2019;52:7-16.
25. Kuiper JS, Zuidersma M, Oude Voshaar RC et al. Social relationships and risk of dementia: a systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev 2015;22:39-57.
26. Duffner LA, Deckers K, Cadar D et al. The role of cognitive and social leisure activities in dementia risk: assessing longitudinal associations of modifiable and non-modifiable risk factors. Epidemiol Psychiatr Sci 2022;31:e5.
27. National Academies of Sciences, Engineering, and Medicine. Enhancing community resilience through social capital and connectedness: stronger together! Washington: National Academies Press, 2021.
28. Cené CW, Beckie TM, Sims M et al. Effects of objective and perceived social isolation on cardiovascular and brain health: a scientific statement from the American Heart Association. J Am Heart Assoc 2022;11:e026493.
29. Valtorta NK, Kanaan M, Gilbody S et al. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. Heart 2016;102:1009-16.
30. Huang J, Xiao L, Zhao H et al. Living alone increases the risk of developing type 2 diabetes mellitus: a systematic review and meta-analysis based on longitudinal studies. Prim Care Diabetes 2024;18:1-6.
31. Park C, Majeed A, Gill H et al. The effect of loneliness on distinct health outcomes: a comprehensive review and meta-analysis. Psychiatry Res 2020;294: 113514.
32. Zhao Y, Guyatt G, Gao Y et al. Living alone and all-cause mortality in community-dwelling adults: a systematic review and meta-analysis. eClinicalMedicine 2022;54:101677.
33. Wang F, Gao Y, Han Z et al. A systematic review and meta-analysis of 90 cohort studies of social isolation, loneliness and mortality. Nat Hum Behav 2023;7: 1307-19.
34. Wang Y, Jiao Y, Nie J et al. Sex differences in the association between marital status and the risk of cardiovascular, cancer, and all-cause mortality: a systematic review and meta-analysis of 7,881,040 individuals. Glob Health Res Policy 2020;5:4.
35. Shor E, Roelfs DJ, Yogev T. The strength of family ties: a meta-analysis and meta-regression of self-reported social support and mortality. Social Networks 2013;35:626-38.
36. Shor E, Roelfs DJ, Curreli M et al. Widowhood and mortality: a meta-analysis and meta-regression. Demography 2012;49:575-606.
37. Shor E, Roelfs DJ, Bugyi P et al. Meta-analysis of marital dissolution and mortality: reevaluating the intersection of gender and age. Soc Sci Med 2012;75:46-59.
38. Shor E, Roelfs DJ. Social contact frequency and all-cause mortality: a meta-analysis and meta-regression. Soc Sci Med 2015;128:76-86.
39. Roelfs DJ, Shor E, Kalish R et al. The rising relative risk of mortality for singles: meta-analysis and meta-regression. Am J Epidemiol 2011;174:379-89.
40. Rico-Uribe LA, Caballero FF, Martin-Maria N et al. Association of loneliness with all-cause mortality: a meta-analysis. PLoS One 2018;13:e0190033.
41. Pinquart M, Duberstein PR. Associations of social networks with cancer mortality: a meta-analysis. Crit Rev Oncol Hematol 2010;75:122-37.
42. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med 2010;7:e1000316.
43. Holt-Lunstad J, Smith TB, Baker M et al. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspect Psychol Sci 2015;10:227-37.
44. Uchino BN, Landvatter J, Zee K et al. Social support and antibody responses to vaccination: a meta-analysis. Ann Behav Med 2020;54:567-74.
45. World Health Organization. Cardiovascular diseases. www.who.int.
46. Yang YC, Boen C, Gerken K et al. Social relationships and physiological determinants of longevity across the human life span. Proc Natl Acad Sci USA 2016; 113:578-83.
47. World Health Organization. Diabetes. www.who.int.
48. Brinkhues S, Dukers-Muijrers N, Hoebe C et al. Socially isolated individuals are more prone to have newly diagnosed and prevalent type 2 diabetes mellitus – the Maastricht study. BMC Public Health 2017;17:955.
49. Brinkhues S, Dukers-Muijrers N, Hoebe C et al. Social network characteristics are associated with type 2 diabetes complications: the Maastricht study. Diabetes Care 2018;41:1654-62.
50. Song Y, Nam S, Park S et al. The impact of social support on self-care of patients with diabetes: what is the effect of diabetes type? Systematic review and meta-analysis. Diabetes Educ 2017;43:396-412.
51. Manemann SM, Chamberlain AM, Roger VL et al. Perceived social isolation and outcomes in patients with heart failure. J Am Heart Assoc 2018;7:e008069.
52. Heidari Gorji MA, Fatahian A, Farsavian A. The impact of perceived and objective social isolation on hospital readmission in patients with heart failure: a systematic review and meta-analysis of observational studies. Gen Hosp Psychiatry 2019;60:27-36.
53. Motillon-Toudic C, Walter M, Séguin M et al. Social isolation and suicide risk: literature review and perspectives. Eur Psychiatry 2022;65:e65.
54. Foster HME, Gill JMR, Mair FS et al. Social connection and mortality in UK Biobank: a prospective cohort analysis. BMC Med 2023;21:384.
55. Elovainio M, Hakulinen C, Pulkki-Raback L et al. Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study. Lancet Public Health 2017;2:e260-6.
56. Valtorta NK, Kanaan M, Gilbody S et al. Loneliness, social isolation and risk of cardiovascular disease in the English Longitudinal Study of Ageing. Eur J Prev Cardiol 2018;25:1387-96.
57. Hakulinen C, Pulkki-Raback L, Virtanen M et al. Social isolation and loneliness as risk factors for myocardial infarction, stroke and mortality: UK Biobank cohort study of 479 054 men and women. Heart 2018;104:1536-42.
58. Hong JH, Nakamura JS, Berkman LF et al. Are loneliness and social isolation

equal threats to health and well-being? An outcome-wide longitudinal approach. SSM Popul Health 2023;23:101459.

59. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. J Behav Med 2006;29:377-87.
60. Hostinar CE, Sullivan RM, Gunnar MR. Psychobiological mechanisms underlying the social buffering of the hypothalamic-pituitary-adrenocortical axis: a review of animal models and human studies across development. Psychol Bull 2014;140:256-82.
61. Gunnar MR, Hostinar CE. The social buffering of the hypothalamic-pituitary-adrenocortical axis in humans: developmental and experiential determinants. Soc Neurosci 2015;10:479-88.
62. Cole SW. Human social genomics. PLoS Genet 2014;10:e1004601.
63. Eisenberger NI, Moieni M, Inagaki TK et al. In sickness and in health: the co-regulation of inflammation and social behavior. Neuropsychopharmacology 2017;42:242-53.
64. Uchino BN, Bowen K, Kent de Grey R et al. Social support and physical health: models, mechanisms, and opportunities. In: Fisher EB, Cameron LD, Christensen AJ et al (eds). Principles and concepts of behavioral medicine: a global handbook. New York: Springer, 2018:341-72.
65. Cohen S, McKay G. Social support, stress and the buffering hypothesis: a theoretical analysis. In: Taylor SE, Singer JE, Baum A (eds). Handbook of psychology and health, Vol. 4. London: Routledge, 2020:253-67.
66. Kent de Grey RG, Uchino BN, Trettevik R et al. Social support and sleep: a meta-analysis. Health Psychol 2018;37:787-98.
67. Shankar A, McMunn A, Banks J et al. Loneliness, social isolation, and behavioral and biological health indicators in older adults. Health Psychol 2011;30:377.
68. Uchino BN, Trettevik R, Kent de Grey RG et al. Social support, social integration, and inflammatory cytokines: a meta-analysis. Health Psychol 2018;37:462-71.
69. Hanna K, Cross J, Nicholls A et al. The association between loneliness or social isolation and food and eating behaviours: a scoping review. Appetite 2023;191:107051.
70. Miller J, King J, Trivers K. Vital signs: mammography use and association with social determinants of health and health-related social needs among women – United States, 2022. MMWR Morb Mortal Wkly Rep 2024;73:351-7.
71. DiMatteo MR. Social support and patient adherence to medical treatment: a meta-analysis. Health Psychol 2004;23:207-18.
72. Magrin ME, D'Addario M, Greco A et al. Social support and adherence to treatment in hypertensive patients: a meta-analysis. Ann Behav Med 2015;49:307-18.
73. Shahin W, Kennedy GA, Stupans I. The association between social support and medication adherence in patients with hypertension: a systematic review. Pharm Pract 2021;19:2300.
74. Adisa R, Olajide OO, Fakeye TO. Social support, treatment adherence and outcome among hypertensive and type 2 diabetes patients in ambulatory care settings in Southwestern Nigeria. Ghana Med J 2017;51:64-77.
75. Miller TA, Dimatteo MR. Importance of family/social support and impact on adherence to diabetic therapy. Diabetes Metab Syndr Obes 2013;6:421-6.
76. Smith TB, Workman C, Andrews C et al. Effects of psychosocial support interventions on survival in inpatient and outpatient healthcare settings: a meta-analysis of 106 randomized controlled trials. PLoS Med 2021;18:e1003595.
77. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300.
78. Howick J, Kelly P, Kelly M. Establishing a causal link between social relationships and health using the Bradford Hill guidelines. SSM Popul Health 2019;8:100402.
79. Holt-Lunstad J. The major health implications of social connection. Curr Dir Psychol Sci 2021;30:251-9.
80. Holt-Lunstad J. Social connection as a public health issue: the evidence and a systemic framework for prioritizing the "social" in social determinants of health. Annu Rev Public Health 2022;43:193-213.
81. VanderWeele TJ. Can sophisticated study designs with regression analyses of observational data provide causal inferences? JAMA Psychiatry 2021;78:244-6.
82. Shi X, Pan Z, Miao W. Data integration in causal inference. Wiley Interdiscip Rev Comput Stat 2023;15:e1581.
83. Sanderson E, Glymour MM, Holmes MV et al. Mendelian randomization. Nat Rev Methods Primers 2022;2:6.
84. Buecker S, Mund M, Chwastek S et al. Is loneliness in emerging adults increasing over time? A preregistered cross-temporal meta-analysis and systematic review. Psychol Bull 2021;147:787-805.
85. Surkalim DL, Luo M, Eres R et al. The prevalence of loneliness across 113 countries: systematic review and meta-analysis. BMJ 2022;376:e067068.
86. Gallup & Meta. The global state of social connections. https://www.gallup.com/analytics/509675/state-of-social-connections.aspx.
87. Kannan VD, Veazie PJ. US trends in social isolation, social engagement, and companionship – nationally and by age, sex, race/ethnicity, family income, and work hours, 2003-2020. SSM Popul Health 2022;21:101331.
88. Koscielniak M, Bojanowska A, Gasiorowska A. Religiosity decline in Europe: age, generation, and the mediating role of shifting human values. J Relig Health 2024;63:1091-116.
89. Höllinger F, Makula L. Religiosity in the major religious cultures of the world. Int J Sociol 2021;51:345-59.
90. Smock PJ, Schwartz CR. The demography of families: a review of patterns and change. J Marriage Fam 2020;82:9-34.
91. Barreto M, Qualter P, Doyle D. Loneliness inequalities evidence review. www.wcpp.org.uk.
92. National Academies of Sciences, Engineering, and Medicine. Social media and adolescent health. Washington: National Academies Press, 2024.
93. Haslam SA, McMahon C, Cruwys T et al. Social cure, what social cure? The propensity to underestimate the importance of social factors for health. Soc Sci Med 2018;198:14-21.
94. Holt-Lunstad J, Proctor AS. Blind spots in health perception: underestimation of social connection as a determinant of health. Submitted for publication.
95. Melfi CA, Drake BG, Tierney WM. The role of public opinion in drug resource allocation decisions. Pharmacoeconomics 1996;9:106-12.
96. Rosenstock IM. The health belief model and preventive health behavior. Health Educ Monogr 1974;2:354-86.
97. Kerr NA, Stanley TB. Revisiting the social stigma of loneliness. Pers Individ Differ 2021;171:110482.
98. World Health Organization. Constitution. www.who.int.
99. Prohaska T, Burholt V, Burns A et al. Consensus statement: loneliness in older adults, the 21st century social determinant of health? BMJ Open 2020;10:e034967.
100. Perlman D, Peplau LA. Toward a social psychology of loneliness. In: Gilmour R, Duck S (eds). Personal relationships. London: Academic Press, 1981:31-56.
101. O'Sullivan R, Burns A, Leavey G et al. Impact of the COVID-19 pandemic on loneliness and social isolation: a multi-country study. Int J Environ Res Public Health 2021;18:9982.
102. Serageldin I, Grootaert C. Defining social capital: an integrating view 1. In: Wiesner E (ed). Evaluation and development. New York: Routledge, 2017:201-17.
103. Moore S, Kawachi I. Twenty years of social capital and health research: a glossary. J Epidemiol Community Health 2017;71:513-7.
104. Valtorta NK, Kanaan M, Gilbody S et al. Loneliness, social isolation and social relationships: what are we measuring? A novel framework for classifying and comparing tools. BMJ Open 2016;6:e010799.
105. Holt-Lunstad J, Robles TF, Sbarra DA. Advancing social connection as a public health priority in the United States. Am Psychol 2017;72:517-30.
106. US National Center for Advancing Translational Sciences. New therapeutic uses. https://ncats.nih.gov/research/research-activities/ntu.
107. Lasgaard M, Løvschall C, Qualter P et al. Are loneliness interventions effective in reducing loneliness? A meta-analytic review of 128 studies. Eur J Public Health 2022;32(Suppl. 3):ckac129.266.
108. Beckers A, Buecker S, Casabianca E et al. Effectiveness of interventions tackling loneliness. Luxembourg: Publications Office of the European Union, 2022.
109. Collins LM, Baker TB, Mermelstein RJ et al. The multiphase optimization strategy for engineering effective tobacco use interventions. Ann Behav Med 2011;41:208-26.
110. Collins LM, Murphy SA, Nair VN et al. A strategy for optimizing and evaluating behavioral interventions. Ann Behav Med 2005;30:65-73.
111. Shah SGS, Nogueras D, van Woerden HC et al. Evaluation of the effectiveness of digital technology interventions to reduce loneliness in older adults: systematic review and meta-analysis. J Med Internet Res 2021;23:e24712.
112. McElfresh JJ, Skiba MB, Segrin CG et al. Interventions for loneliness among adult cancer survivors: a systematic review and meta-analysis. J Psychosoc Oncol 2021;39:509-33.
113. Hickin N, Kall A, Shafran R et al. The effectiveness of psychological interventions for loneliness: a systematic review and meta-analysis. Clin Psychol Rev 2021;88:102066.
114. Choi M, Kong S, Jung D. Computer and internet interventions for loneliness and depression in older adults: a meta-analysis. Healthc Inform Res 2012;18:191-8.
115. Eccles AM, Qualter P. Alleviating loneliness in young people – a meta-analysis of interventions. Child Adolesc Ment Health 2021;26:17-33.
116. Veronese N, Galvano D, D'Antiga F et al. Interventions for reducing loneliness: an umbrella review of intervention studies. Health Soc Care Community 2021;

29:e89-96.
117. Ellard OB, Dennison C, Tuomainen H. Interventions addressing loneliness amongst university students: a systematic review. Child Adolesc Ment Health 2023;28:512-23.
118. Gardiner C, Geldenhuys G, Gott M. Interventions to reduce social isolation and loneliness among older people: an integrative review. Health Soc Care Community 2018;26:147-57.
119. O'Rourke HM, Collins L, Sidani S. Interventions to address social connectedness and loneliness for older adults: a scoping review. BMC Geriatr 2018;18:214.
120. Spiegel D, Bloom JR, Kraemer HC et al. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. Lancet 1989;2:888-91.
121. Holt-Lunstad J, Perissinotto C. Social isolation and loneliness as medical issues. N Engl J Med 2023;388:193-5.
122. Reinhardt GY, Vidovic D, Hammerton C. Understanding loneliness: a systematic review of the impact of social prescribing initiatives on loneliness. Perspect Public Health 2021;141:204-13.
123. Costa A, Sousa CJ, Seabra PRC et al. Effectiveness of social prescribing programs in the primary health-care context: a systematic literature review. Sustainability 2021;13:2731.
124. Liz B, Alison B, Paul MW et al. Social prescribing: less rhetoric and more reality. A systematic review of the evidence. BMJ Open 2017;7:e013384.
125. Ibarra F, Baez M, Cernuzzi L et al. A systematic review on technology-supported interventions to improve old-age social wellbeing: loneliness, social isolation, and connectedness. J Healthc Eng 2020;2020:2036842.
126. Wister A, Fyffe I, O'Dea E. Technological interventions for loneliness and social isolation among older adults: a scoping review protocol. Syst Rev 2021;10:217.
127. Welch V, Ghogomu ET, Barbeau VI et al. Digital interventions to reduce social isolation and loneliness in older adults: an evidence and gap map. Campbell Syst Rev 2023;19:e1369.
128. Hawkley LC, Finch LE, Kotwal AA et al. Can remote social contact replace in-person contact to protect mental health among older adults? J Am Geriatr Soc 2021;69:3063-5.
129. Marraccini ME, Brier ZM. School connectedness and suicidal thoughts and behaviors: a systematic meta-analysis. Sch Psychol Q 2017;32:5-21.
130. Corcoran RP, Cheung ACK, Kim E et al. Effective universal school-based social and emotional learning programs for improving academic achievement: a systematic review and meta-analysis of 50 years of research. Educ Res Rev 2018;25:56-72.
131. Allen K, Kern ML, Vella-Brodrick D et al. What schools need to know about fostering school belonging: a meta-analysis. Educ Psychol Rev 2018;30:1-34.
132. Wilkins NJ, Verlenden JMV, Szucs LE et al. Classroom management and facilitation approaches that promote school connectedness. J Sch Health 2023;93:582-93.
133. Wigelsworth M, Verity L, Mason C et al. Social and emotional learning in primary schools: a review of the current state of evidence. Br J Educ Psychol 2022;92:898-924.
134. Weare K, Nind M. Mental health promotion and problem prevention in schools: what does the evidence say? Health Promot Int 2011;26(Suppl.1):i29-69.
135. Weatherson KA, O'Neill M, Lau EY et al. The protective effects of school connectedness on substance use and physical activity. J Adolesc Health 2018;63:724-31.
136. Steiner RJ, Sheremenko G, Lesesne C et al. Adolescent connectedness and adult health outcomes. Pediatrics 2019;144:e20183766.
137. Hawkley L. Public policy and the reduction and prevention of loneliness and social isolation. In: Hajek A, Riedel-Heller SG, König H-H (eds). Loneliness and social isolation in old age. London: Routledge, 2023:181-90.
138. Holt-Lunstad J. Social isolation and health. Health Affairs, June 21, 2020.
139. Lim MH, Qualter P, Ding D et al. Advancing loneliness and social isolation as a global health priority: taking three priority actions. Public Health Res Pract 2023;33:3332320.
140. Rudolph L, Caplan J, Ben-Moshe K et al. Health in all policies: a guide for state and local governments. Washington and Oakland: American Public Health Association and Public Health Institute, 2013.
141. Mahoney JL, Weissberg RP, Greenberg MT et al. Systemic social and emotional learning: promoting educational success for all preschool to high school students. Am Psychol 2021;76:1128-42.
142. Department of Agriculture, Trade and Consumer Protection, State of Wisconsin. Farmer Wellness Program. https://datcp.wi.gov.
143. Ali MM, West K, Teich JL et al. Utilization of mental health services in educational setting by adolescents in the United States. J Sch Health 2019;89:393-401.
144. Kirby J, Slone S. Social isolation and loneliness: State policies and interventions for the post-COVID era. Council of State Governments, 2022.
145. Lim MH, Eres R, Vasan S. Understanding loneliness in the twenty-first century: an update on correlates, risk factors, and potential solutions. Soc Psychiatry Psychiatr Epidemiol 2020;55:793-810.
146. Akhter-Khan SC, Au R. Why loneliness interventions are unsuccessful: a call for precision health. Adv Geriatr Med Res 2020;2:e200016.
147. Barreto M, Doyle DM, Qualter P. Changing the narrative: loneliness as a social justice issue. Polit Psychol 2024;45:157-81.
148. Welch V, Ghogomu E, Dowling S et al. In-person interventions to reduce social isolation and loneliness: an evidence and gap map. Campbell Syst Rev 2023;19:e1340.
149. Meehan DE, Grunseit A, Condie J et al. Social-ecological factors influencing loneliness and social isolation in older people: a scoping review. BMC Geriatr 2023;23:726.
150. World Health Organization. Health in all policies: Helsinki statement. Framework for country action. https://iris.who.int.
151. Nurminen M, Thoma-Otremba A, Casabianca E. Mapping of loneliness interventions in the EU. European Commission, 2023.
152. Caspi A, Harrington H, Moffitt TE et al. Socially isolated children 20 years later: risk of cardiovascular disease. Arch Pediatr Adolesc Med 2006;160:805-11.
153. Levine S, Malone E, Lekiachvili A et al. Health care industry insights: why the use of preventive services is still low. Prev Chronic Dis 2019;16:E30.
154. Bianco-Miotto T, Craig J, Gasser Y et al. Epigenetics and DOHaD: from basics to birth and beyond. J Dev Orig Health Dis 2017;8:513-9.
155. Hildreth JR, Vickers MH, Buklijas T et al. Understanding the importance of the early-life period for adult health: a systematic review. J Dev Orig Health Dis 2023;14:166-74.
156. Huang CX, Halfon N, Sastry N et al. Positive childhood experiences and adult health outcomes. Pediatrics 2023;152:e2022060951.
157. Abbott-Chapman J, Gall S, Ollington N et al. The association between childhood school engagement and attainment and adult education and health outcomes: preliminary findings from an interdisciplinary research project using longitudinal Australian cohort data. Presented at the Australian Association for Research in Education (AARE) International Research Conference, Hobart, November 2011.
158. Abbott-Chapman J, Martin K, Ollington N et al. The longitudinal association of childhood school engagement with adult educational and occupational achievement: findings from an Australian national study. Br Educ Res J 2014;40:102-20.
159. Bethell C, Jones J, Gombojav N et al. Positive childhood experiences and adult mental and relational health in a statewide sample: associations across adverse childhood experiences levels. JAMA Pediatr 2019;173:e193007.
160. Fletcher HK, Gallichan DJ. An overview of attachment theory: Bowlby and beyond. In: Fletcher HK, Flood A, Hare DJ (eds). Attachment in intellectual and developmental disability: a clinician's guide to practice and research. New York: Wiley Blackwell, 2016:8-32.
161. Hughes K, Bellis MA, Hardcastle KA et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health 2017;2:e356-66.
162. Hanson MA, Gluckman P. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev 2014;94:1027-76.
163. Chen Y, Cortes P, Kosar G et al. The impact of COVID-19 on workers' expectations and preferences for remote work. American Economic Association (AEA) Papers and Proceedings 2023;113:556-61.
164. Jiang Y, Lai P-L, Yang C-C et al. Exploring the factors that drive consumers to use contactless delivery services in the context of the continued COVID-19 pandemic. J Retail Consum Serv 2023;72:103276.
165. Kim S, Jang S, Choi W et al. Contactless service encounters among Millennials and Generation Z: the effects of Millennials and Gen Z characteristics on technology self-efficacy and preference for contactless service. J Res Interact Mark 2022;16:82-100.
166. Ahmed A, Abdulkareem AM. Big data analytics in the entertainment industry: audience behavior analysis, content recommendation, and revenue maximization. Reviews of Contemporary Business Analytics 2023;6:88-102.
167. Camilleri MA, Falzon L. Understanding motivations to use online streaming services: integrating the technology acceptance model (TAM) and the uses and gratifications theory (UGT). Span J Mark - ESIC 2021;25:217-38.
168. Oakman J, Kinsman N, Stuckey R et al. A rapid review of mental and physical health effects of working at home: how do we optimise health? BMC Public Health 2020;20:1825.
169. Holt-Lunstad J. Fostering social connection in the workplace. Am J Health Promot 2018;32:1307-12.
170. Granovetter MS. The strength of weak ties. Am J Sociol 1973;78:1360-80.

171. Kim M, Fernandez RM. What makes weak ties strong? Annu Rev Sociol 2023; 49:177-93.
172. Predmore ZS, Roth E, Breslau J et al. Assessment of patient preferences for telehealth in post-COVID-19 pandemic health care. JAMA Netw Open 2021;4: e2136405.
173. Rodriguez M, Pratt S, Bellet BW et al. Solitude can be good – if you see it as such: reappraisal helps lonely people experience solitude more positively. J Pers 2023; doi: 10.1111/jopy.12887.
174. Hoppmann CA, Lay JC, Pauly T et al. Social isolation, loneliness, and solitude in older adulthood. In: Coplan RJ, Bowker JC, Nelson LJ (eds). The handbook of solitude. Hoboken: Wiley Blackwell, 2021:178-89.
175. Haney C. Restricting the use of solitary confinement. Annu Rev Criminol 2018; 1:285-310.
176. Rahbari L. COVID-19 pandemic and the crisis of care: wellness discourses, neoliberal self-care, and (dis)infodemic. Soc Sci 2023;12:137.
177. Baker SA. Alt. Health Influencers: how wellness culture and web culture have been weaponised to promote conspiracy theories and far-right extremism during the COVID-19 pandemic. Eur J Cult Stud 2022;25:3-24.
178. Office of the US Surgeon General. Social media and youth mental health: the US Surgeon General's Advisory. www.hhs.gov.
179. Twenge JM, Haidt J, Joiner TE et al. Underestimating digital media harm. Nat Hum Behav 2020;4:346-8.
180. Odgers CL, Schueller SM, Ito M. Screen time, social media use, and adolescent development. Annu Rev Develop Psychol 2020;2:485-502.
181. Torous J. A path towards progress: lessons from the hard things about digital mental health. World Psychiatry 2022;21:419-20.
182. Valkenburg PM, Meier A, Beyens I. Social media use and its impact on adolescent mental health: an umbrella review of the evidence. Curr Opin Psychol 2022;44:58-68.
183. Torous J, Myrick K, Aguilera A. The need for a new generation of digital mental health tools to support more accessible, effective and equitable care. World Psychiatry 2023;22:1-2.
184. Capraro V, Lentsch A, Acemoglu D et al. The impact of generative artificial intelligence on socioeconomic inequalities and policy making. arXiv 2023; 2401.05377.
185. Campbell J. AI's future: utopia or dystopia? Experts weigh in on five possible outcomes. https://ainewstoday.co.uk.
186. Jones VK, Hanus M, Yan C et al. Reducing loneliness among aging adults: the roles of personal voice assistants and anthropomorphic interactions. Front Public Health 2021;9:750736.
187. Xie T, Pentina I. Attachment theory as a framework to understand relationships with social chatbots: a case study of Replika. Proceedings of the 55th Hawaii International Conference on System Sciences, Maui, January 2022.
188. Law T, Chita-Tegmark M, Rabb N et al. Examining attachment to robots: benefits, challenges, and alternatives. ACM Trans Hum Robot Interact 2022;11:1-18.
189. Baker RS, Hawn A. Algorithmic bias in education. Int J Artificial Intell Educ 2022; 32:1-41.
190. Morewedge CK, Mullainathan S, Naushan HF et al. Human bias in algorithm design. Nat Hum Behav 2023;7:1822-4.
191. World Health Organization. Social isolation and loneliness among older people: advocacy brief. Geneva: World Health Organization, 2021.
192. US Centers for Disease Control and Prevention. Social connectedness. www.cdc.gov.
193. Kovacic M, Mauri C, Nurminen M et al. Key messages and policy recommendations of the one day conference on "Loneliness in the European Union: policies at work". Luxembourg: Publications Office of the European Union, 2023.
194. Lim MH, Smith B. State of the nation report: social connections in Australia 2023. http://www.endingloneliness.com.au.
195. Fukuoka R, Nagano Y. Law enacted to battle growing problem of loneliness. The Asahi Shimbun, April 2, 2024.

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Where do neurodevelopmental conditions fit in transdiagnostic psychiatric frameworks? Incorporating a new neurodevelopmental spectrum

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Features of autism spectrum disorder, attention-deficit/hyperactivity disorder, learning disorders, intellectual disabilities, and communication and motor disorders usually emerge early in life and are associated with atypical neurodevelopment. These "neurodevelopmental conditions" are grouped together in the DSM-5 and ICD-11 to reflect their shared characteristics. Yet, reliance on categorical diagnoses poses significant challenges in both research and clinical settings (e.g., high co-occurrence, arbitrary diagnostic boundaries, high within-disorder heterogeneity). Taking a transdiagnostic dimensional approach provides a useful alternative for addressing these limitations, accounting for shared underpinnings across neurodevelopmental conditions, and characterizing their common co-occurrence and developmental continuity with other psychiatric conditions. Neurodevelopmental features have not been adequately considered in transdiagnostic psychiatric frameworks, although this would have fundamental implications for research and clinical practices. Growing evidence from studies on the structure of neurodevelopmental and other psychiatric conditions indicates that features of neurodevelopmental conditions cluster together, delineating a "neurodevelopmental spectrum" ranging from normative to impairing profiles. Studies on shared genetic underpinnings, overlapping cognitive and neural profiles, and similar developmental course and efficacy of support/treatment strategies indicate the validity of this neurodevelopmental spectrum. Further, characterizing this spectrum alongside other psychiatric dimensions has clinical utility, as it provides a fuller view of an individual's needs and strengths, and greater prognostic utility than diagnostic categories. Based on this compelling body of evidence, we argue that incorporating a new neurodevelopmental spectrum into transdiagnostic frameworks has considerable potential for transforming our understanding, classification, assessment, and clinical practices around neurodevelopmental and other psychiatric conditions.

Key words: Neurodevelopmental conditions, transdiagnostic approach, neurodevelopmental spectrum, autism spectrum disorder, attention-deficit/hyperactivity disorder, intellectual disabilities, learning disabilities, communication and motor disorders

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Difficulties with social communication, attention, learning, motor and cognitive abilities during development affect up to 15% of individuals worldwide, with many more experiencing subthreshold problems[1,2]. These features are listed as criteria for conditions including autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), intellectual disabilities, learning disorders, motor disorders (e.g., Tourette's syndrome, developmental coordination disorder), and various disorders of speech, language and communication (e.g., social pragmatic communication disorder) in traditional diagnostic manuals.

The latest editions of these manuals, the DSM-5[3] and the ICD-11[4], classify these conditions jointly as Neurodevelopmental Disorders, based on the "neurodevelopmental cluster" previously proposed within the DSM/ICD meta-structure[5,6]. The primary reasons that led to their inclusion in this DSM/ICD grouping are their early age of onset, relatively persistent course, salient cognitive difficulties, and high levels of co-occurrence with one another[5].

The limitations of categorical diagnostic systems for classifying neurodevelopmental and other psychiatric conditions are well documented[7-13]. Most notably, and of particular relevance to neurodevelopmental conditions, these systems do not provide effective tools to consider the widespread co-occurrence and overlap between purportedly distinct conditions, nor their within-disorder heterogeneity. Co-occurrence and heterogeneity pose serious barriers in both research (e.g., biomarker identification) and clinical (e.g., treatment planning) settings. Binary diagnostic categories also fail to recognize individuals with subthreshold but significantly impairing presentations, who would benefit from early support/treatment.

Transdiagnostic dimensional approaches – including the Hierarchical Taxonomy of Psychopathology (HiTOP)[8], hierarchical causal taxonomies[12,14], and the Research Domain Criteria (RDoC)[15,16] – offer alternative solutions by providing empirically-based frameworks for conceptualizing psychiatric conditions dimensionally. These models include dimensional constructs that cut across multiple conditions and account for their widespread co-occurrence.

Specific clinical features of many traditionally-defined disorders (e.g., psychotic, depressive and anxiety disorders) are well classified within most transdiagnostic dimensional models, for example through spectra/dimensions such as internalizing, externalizing and psychosis[17-19]. However, to date, the vast majority of studies examining the co-occurrence and structure of psychiatric conditions that inform current transdiagnostic frameworks have been limited to features of only some neurodevelopmental conditions (i.e., ADHD[8,14,20]). In addition, this literature (with few notable exceptions[21-23]) has predominantly focused on adult samples and paid limited attention to developmental processes[8,14,20]. As a result, current transdiagnostic dimensional frameworks largely omit the clinical features that characterize neurodevelopmental conditions.

More recently, researchers and clinicians have started to consider a transdiagnostic lens toward neurodevelopmental conditions[7,24-26], rather than focusing on individual disorders. These recent conceptualizations expand upon the DSM/ICD Neurodevelopmental Disorders grouping, which includes severity ratings for conditions such as ASD and intellectual disabilities, and conceptualizations of autism as belonging to an "autism spectrum"[3,4]. They are also broadly consistent with the notion of neurodiversity[27-29], which originated from an advocacy-based movement and has more recently been used as an umbrella term encompassing individual differences related to neurodevelopmental conditions.

As emphasized in some of these previous accounts[7,24-26], a transdiagnostic approach to neurodevelopmental conditions can promote a better understanding of the frequent co-occurrence of these conditions and their heterogeneity, both between individuals and within an individual across time[7,24,26]. Moreover, there have as yet been limited efforts toward taking an even broader transdiagnostic approach that spans across neurodevelopmental conditions and other psychiatric conditions to place the former within a broader psychiatric framework.

Individuals with neurodevelopmental conditions often experience other psychiatric conditions, such as internalizing and externalizing problems, either concurrently or at later stages of development[30,31]. Yet, these co-occurring or later emerging conditions are often neglected in clinical settings, so that people with neurodevelopmental diagnoses face significant barriers in receiving support for these additional conditions[32]. In response to these issues, individuals with neurodevelopmental conditions worldwide have ranked understanding the co-occurrence with other conditions and removing the above barriers as top priorities[32-35]. A joint transdiagnostic focus integrating both neurodevelopmental and other psychiatric conditions is essential for promoting more effective and holistic approaches to support people with neurodevelopmental and concurrent/subsequent mental health difficulties across the lifespan.

This paper aims to advance the transdiagnostic approach to neurodevelopmental conditions by formally introducing a new transdiagnostic "neurodevelopmental spectrum" and integrating it into extant transdiagnostic dimensional frameworks of psychiatric conditions (see Figure 1). We provide a broad review of the accumulating evidence in support of this proposed neurodevelopmental spectrum, including its structural (psychometric) coherence, validity and practical utility, and its placement within broader transdiagnostic frameworks of psychiatric conditions. Based on this evidence, we conceptualize this spectrum as a broad latent dimension reflecting the shared features and underpinnings of individual differences in attention, social communication, learning, motor and cognitive abilities that are most often expressed early in development, with a relatively stable developmental course, and accompanied by partly overlapping brain and socio-cognitive profiles.

We conclude that a critical mass of evidence has now accumu-

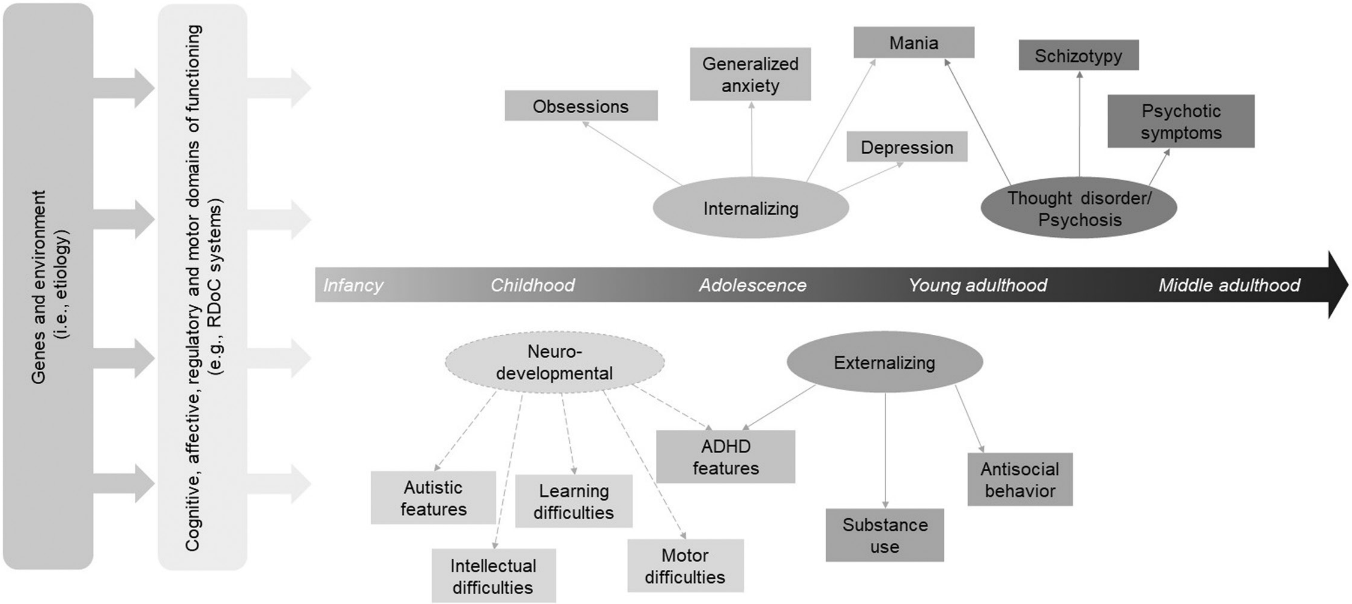

Figure 1 Graphic representation of the proposed neurodevelopmental spectrum alongside dimensions currently in transdiagnostic frameworks. ADHD – attention- deficit/hyperactivity disorder, RDoC – Research Domain Criteria.

lated supporting this new transdiagnostic neurodevelopmental spectrum. In contrast to the discrete DSM/ICD Neurodevelopmental Disorders diagnoses, this spectrum explicitly accounts for the co-occurrence between features of neurodevelopmental conditions, their heterogeneous presentation, their different severity throughout the population, and their intra-individual variability across diagnostic boundaries (i.e., an individual shifting from below to above the diagnostic threshold of a given condition, e.g. ASD, or between boundaries of different conditions, e.g. ASD and ADHD[36]).

Critically, our proposal also situates the neurodevelopmental spectrum into transdiagnostic frameworks of psychiatric conditions more broadly. Its explicit inclusion in these frameworks, already including spectra/dimensions capturing other clinical features, can promote a new understanding of the interplay between neurodevelopmental and other psychiatric conditions, thereby directly impacting future research and clinical practices.

It is worth noting from the outset that our use of the term "neurodevelopmental" is intended here as a label for the proposed new spectrum. The advantage of using this term is that it is in line with the terminology adopted in the DSM and ICD, and in most of the structural literature reviewed in this paper. Our use of the term does not imply that the "neural" developmental origins of these conditions have been fully elucidated, nor that other psychiatric conditions may not also have their roots in the brain or emerge early in development. For example, there have been proposals to recognize the "neurodevelopmental" origin of schizophrenia, given its overlap in etiological mechanisms with earlier-onset neurodevelopmental conditions[37,38]. Rare genetic syndromes, such as fragile-X and Prader-Willi syndromes, have also been considered neurodevelopmental disorders[39]. The proposed neurodevelopmental spectrum does not currently consider features of these other psychiatric and genetic conditions. However, the greater consideration of a cross-disorder and developmental perspective promoted by the inclusion of this spectrum in transdiagnostic frameworks offers the potential to enhance our understanding of the developmental pathways to other psychiatric conditions and the co-occurrence between a broad range of clinical features (including neurodevelopmental and behavioral challenges in individuals with genetic syndromes).

STRUCTURAL EVIDENCE

Building on research and clinical observations regarding the co-occurrence among neurodevelopmental conditions[40] and between these conditions and other psychiatric conditions[31,41], a growing number of factor analytic studies have included assessments of neurodevelopmental features. This has allowed for investigation of covariation within and across neurodevelopmental and other psychiatric conditions, with available studies providing key evidence for a neurodevelopmental spectrum and supporting its placement among other more established spectra/dimensions in transdiagnostic frameworks.

Studies that identified a neurodevelopmental factor

A factor explicitly called "neurodevelopmental" was first delineated alongside other psychiatric dimensions in a study using exploratory factor analysis on items of the Child Behavior Checklist (CBCL) in almost 10,000 children from the Adolescent Brain Cognitive Development (ABCD) study[25]. Results showed a transdiagnostic structure including a neurodevelopmental factor along with externalizing, internalizing, somatoform and detachment factors. This neurodevelopmental factor included features of ADHD (e.g., inattention, hyperactivity), aspects of motor disorders (e.g., poor coordination, twitching), features conceptually overlapping between ASD and obsessive-compulsive disorder (OCD) (e.g., repetitive thoughts/obsessions and behaviors/compulsions, strange ideas), and poor school performance. A narrower inattentive neurodevelopmental factor, mainly defined by ADHD features, was also delineated using Adult-Self Report (ASR) items in adult parents of ABCD participants.

Interestingly, these neurodevelopmental factors first emerging in three-factor models were highly correlated with both broad internalizing and externalizing factors in the higher-level two-factor models. This finding suggests that the newly emerging factor is not a mere partition of a higher-order externalizing spectrum/dimension, but rather has associations with both internalizing and externalizing problems.

The neurodevelopmental factor was replicated in six subsequent studies. Using an equivalent analytic approach to the aforementioned ABCD study[25], a neurodevelopmental factor capturing inattention, hyperactivity/impulsivity, executive function problems, and learning difficulties was identified in a transdiagnostic sample enriched for problems with attention and learning[42]. This factor emerged along with internalizing and social maladjustment factors. A study on the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort at ages 7 and 13 years showed superior fit of correlated factor and bifactor models including a neurodevelopmental factor (ADHD and ASD scales) alongside emotional and behavioral factors relative to models only including two emotional and behavioral/neurodevelopmental factors[43].

Further, two studies of several hundreds of thousands children and adults from the Swedish population tested a neurodevelopmental factor (defined by diagnoses) within bifactor structures also including other specific factors (e.g., externalizing, internalizing) and a general psychopathology (p) factor[44,45]. One of these studies also modeled an ADHD factor separately and showed significantly stronger phenotypic and genetic associations of this factor with the neurodevelopmental factor than with externalizing and internalizing factors when controlling for p, congruent with the inclusion of ADHD in a neurodevelopmental spectrum (rather than in the externalizing spectrum).

Another recent study of Swedish adult twins identified a neurodevelopmental factor, capturing features of ADHD (inattention and disorganization) and ASD (social difficulties), along with internalizing, substance and impulsivity factors[46]. Finally, a recent study exploring the data-driven hierarchical structure of the full set of DSM-5 clinical features in separate primary and hold-out adult population-based samples revealed a neurodevelopmental factor along with other major transdiagnostic dimensions[47]. This broad neurodevelopmental factor included features of ASD, ADHD, and learning, communication, language and speech difficulties.

Findings from these studies are also in line with two additional studies that modeled a neurodevelopmental factor using various neurodevelopmental features and traits through confirmatory factor analysis[48,49]. However, as these studies did not include other psychiatric features alongside neurodevelopmental indicators, they cannot be used to determine the placement of the neurodevelopmental factor within a broader transdiagnostic structure.

Other evidence supporting the delineation of a neurodevelopmental spectrum

Several other lines of research, despite not explicitly using the term "neurodevelopmental", support the integration of the proposed spectrum into transdiagnostic dimensional models. First, an exploratory factor analysis[50] and subsequent confirmatory factor analysis[51] of the CBCL and a questionnaire assessing ASD and related developmental problems (Children's Social Behavior Questionnaire), in an epidemiological child and adolescent cohort, found "attention and orientation" and ASD factors, together with internalizing, externalizing and p factors. Of note, ADHD features did not cluster with externalizing, but rather with orientation features of ASD, and several ASD scales had significant loadings from both the attention and orientation factor and the ASD factor. Moreover, item-level analyses suggested that ASD and ADHD features clustered together in a model including an ASD/ADHD factor and internalizing and externalizing factors, and only differentiated into two separate factors in models with at least eight narrower factors[52]. This indicates that some features of ASD and ADHD may form a broad spectrum that may be further differentiated in more specific factors[52].

Second, studies incorporating both personality and mental health measures have identified factors similar to the neurodevelopmental spectrum. A recent exploratory factor analysis of items from ADHD, ASD, and questionnaires measuring normal-range personality and psychopathology in adults, found that inattention, hyperactivity/impulsivity, and pragmatic language difficulties clustered together, whereas aloofness loaded onto detachment factors[53,54]. Another study in children and adolescents found that items of distractibility, organization, achievement, hyperactivity, and intelligence loaded together on an "organization" factor and separately from items belonging to positive personality, behavior problems, and internalizing factors[55].

Third, several previous studies using bifactor models in samples of children, adolescents and adults showed that indicators of ASD or ADHD (especially inattention) were solely or predominantly captured by the p factor, with minor or non-significant loadings onto the externalizing factor[56-64]. This suggests that ASD and ADHD may be better captured by a different factor not modeled in these studies, such as a neurodevelopmental factor. Similarly, factor analytic studies using measures from the Achenbach System of Empirically Based Assessment (ASEBA) in dozens of samples from preschool to old adult age, and across societies and raters, indicate that the attention problems scale is not subsumed within the externalizing scale (aggregating rule breaking and aggression) or the internalizing scale (anxious/depressed, withdrawn/depressed, somatic complaints)[21,65-71]. This is consistent with studies identifying a factor capturing features of ADHD separately from externalizing factors[72-80].

Summary of the structural evidence

Overall, the studies reviewed here provide accumulating evidence supporting the robust factor structure of the neurodevelopmental spectrum alongside other transdiagnostic spectra/dimensions, providing a strong argument for the inclusion of this spectrum in transdiagnostic dimensional frameworks. Available studies indicate that features of ADHD, ASD, intellectual disability, and learning, communication and motor disorders can be conceptualized within this dimension (see Table 1).

The studies reviewed here suggest the inclusion of ADHD features, particularly inattention, in the proposed neurodevelopmental spectrum, with impulsivity being captured by both neurodevelopmental and externalizing spectra in some studies[25,42]. This is inconsistent with studies that modeled ADHD exclusively as an indicator of externalizing factors[81-89], which informed current transdiagnostic frameworks typically placing ADHD under a (disinhibited) externalizing spectrum[14,18].

However, it should be noted that, unlike recent studies identifying a neurodevelopmental or neurodevelopmental-consistent factor, the studies placing ADHD under externalizing factors did not include features of other neurodevelopmental conditions. Further, these studies only examined diagnoses or scale total scores, resulting in only one or two ADHD indicators – an insufficient number for the emergence of a separate neurodevelopmental/ADHD factor. The use of diagnoses in this context may also be particularly problematic, because children with ADHD with high hyperactivity-impulsivity are more likely to receive an ADHD diagnosis, especially when comorbid with oppositional defiant disorder (ODD) or conduct disorder (CD), compared to children only showing inattentive features, who are often misdiagnosed or underdiagnosed[90]. This artificially inflates the covariation between ADHD and ODD/CD and may result in an incorrect placement within the externalizing spectrum.

Crucially, before the DSM-5 and ICD-11, ADHD and ASD could not be diagnosed together in the same individual, and, since ASD is typically diagnosed earlier in development, an additional ADHD diagnosis was not possible[91]. Studies including ADHD diagnoses prior to the latest editions of those diagnostic manuals, therefore, likely missed a sizeable portion of the ADHD population with predominant neurodevelopmental and autistic features.

A few limitations of the available literature should be noted. Most of the studies used samples with wide age ranges and cross-

Table 1 Summary of structural evidence supporting the proposed neurodevelopmental spectrum

	Diagnoses						Features/symptoms/traits											
	ADHD	ASD	LD	ID	Motor	ODD	Inatt	Hyp/Imp	Aut	Soc	Tho	Lear	Cog	Com	Mot	Con	Opp	Other
Neurodevelopmental factor																		
First order																		
Martin et al[48]							+	+	+	+								
Michelini et al[25]							+	+	+	+	+				+			+
Addicoat et al[49]								+				+	+		+			
Holmes et al[42]							+	+				+	+					
Pettersson et al[46]							+		+	+								
Forbes et al[47]								+	+	+		+		+				
Bifactor																		
Du Rietz et al[44]		+	+	+	+													
Pettersson et al[45]	+	+																
Riglin et al[43]							+	+	+									
Similar factor																		
First order																		
Hartman et al[72]							+	+								+	+	
Lahey et al[79]							+	+									+	
Hartman et al[52]							+		+		+							
Ivanova et al[67]							+											
Farmer et al[80]	+					+												
Slobodskaya[55]							+	+										
Noordhof et al[50]							+		+									
Niarchou et al[74]							+	+										
Pettersson et al[75]							+	+										
Haltigan et al[71]							+											
Moore et al[76]							+	+	+		+				+			
Clark et al[78]							+	+		+								+
Stanton et al[53]							+	+	+					+				
Stanton et al[54]							+	+	+					+				
Bifactor																		
Murray et al[73]							+	+										
Bloemen et al[51]							+		+									
McElroy et al[70]							+											
Miller et al[77]							+											

Studies are split between those that modeled a neurodevelopmental (or similar) factor as a first-order one (e.g., within correlated factor models) and those that modeled it as a specific factor in a bifactor model (i.e., where some of the variance in relevant indicators was captured by a general psychopathology factor). The + means that the indicator was included in the analysis and loaded ≥0.30 onto neurodevelopmental (or similar) factor. ADHD – attention-deficit/hyperactivity disorder, ASD – autism spectrum disorder, LD – learning disorders, ID – intellectual disabilities, Motor – motor disorders, ODD – oppositional defiant disorder, Inatt – inattention/attention problems, Hyp/Imp – hyperactivity/impulsivity, Aut – autism spectrum features, Soc – social problems, Tho – thought problems, Lear – learning difficulties, Cog – general or specific (e.g., executive functioning) cognitive abilities, Com – communication, language and speech difficulties, Mot – motor features, Con – conduct problems, Opp – oppositionality, Other – features of poor functioning or general psychopathology not belonging to specific conditions.

sectional designs, precluding the examination of developmental effects. This limitation is common to many studies on the structure of psychiatric conditions, but especially problematic for delineating a neurodevelopmental spectrum with its roots in early development. Another limitation is that the majority of studies focused on ADHD and to a lesser extent ASD, while only a minority included learning, motor, intellectual and communication difficulties (see Table 1). While the few available studies consistently support the inclusion of these latter conditions in a neurodevelopmental spectrum, future studies with broad assessments of neurodevelopmental features are warranted.

VALIDITY EVIDENCE

Besides evidence of its structural coherence, the proposed neurodevelopmental spectrum is supported by multiple lines of research establishing its validity, in line with validators commonly used in psychiatric nosology[5,17-19].

Genetics

Neurodevelopmental conditions run in families, with higher rates in family members of affected individuals[92]. Twin studies provide strong evidence that neurodevelopmental conditions are highly heritable (with an average meta-analytic heritability of 0.66, ranging from 0.62 for specific learning disorders to 0.86 for intellectual disabilities).

Further, these conditions share a substantial degree of genetic influences with one another (the meta-analytic genetic correlation across neurodevelopmental conditions is 0.36, ranging from 0.07 for ADHD-specific learning disorders to 0.90 for ADHD-motor disorders)[92], consistent with a neurodevelopmental spectrum, and show a more modest genetic overlap with other psychiatric conditions (e.g., 0.10 to 0.31 with schizophrenia, but also 0.62 with disruptive disorders)[1,93-96].

Notably, the strong shared genetic influences between ASD, ADHD, the broader autism phenotype, intellectual disabilities; coordination, speech and language problems; and other social problems[95,97-104] can be captured by a latent genetic neurodevelopmental factor[105]. Recent meta-analyses and reviews of twin and family studies indicate that up to ~80% of the phenotypic correlation between ASD, ADHD and other neurodevelopmental conditions, as well as conditions that also typically emerge earlier in development, such as OCD, can be explained by shared genetic influences[92,93,106].

Consistent with findings from twin studies, recent genome-wide association studies (GWAS) have also found evidence of considerable genetic overlap between neurodevelopmental conditions at the level of common single nucleotide polymorphisms (SNPs)[107-111]. In the largest GWAS conducted on ASD to date (18,000 cases and 28,000 controls), one of the most robust genetic correlations was between ASD and ADHD (r_g=.36)[108].

To model the genetic covariance structure among multiple conditions/traits (including ASD and ADHD) using GWAS summary statistics, factor analytic methods such as genomic structural equation modeling (GenomicSEM) have been developed[112]. Recent findings using this approach have shed new light on the genetic basis of a neurodevelopmental factor that appears to include ASD, ADHD and Tourette's syndrome[109,113-115]. Further, findings from GenomicSEM studies have thus far consistently converged on the existence of a neurodevelopmental factor that is genetically separable from other factors (i.e., internalizing, externalizing, psychosis[114,115]).

Several of the genes associated with ADHD[107] and ASD[108] are also more generally involved in neurodevelopmental processes. Regarding ADHD, *FOXP2* is involved in synapse formation and speech and learning development[108,116-118]; *SORCS3* encodes a brain-expressed transmembrane receptor important for neuronal development and plasticity[119,120]; *SEMA6D* appears to play a role in neuronal wiring during embryonic brain development[120,121]; and *ST3GAL3* and *MEF2C* have been associated with severe intellectual disability[120,122-124]. Similarly, regarding ASD, strong enrichment was observed for regulatory elements in the brain regions involved in prenatal neurodevelopment[108]. This is in line with studies of genes (e.g., *SHANK3*, *MEF2C*) that disrupt early synaptic function in genetic syndromes such as the Rett syndrome and the Phelan-McDermid syndrome, which often show intellectual disability, autistic features, and ADHD features[125].

Building on GWAS discoveries, polygenic risk scores seem to show robust associations across neurodevelopmental features, rather than just for individual neurodevelopmental conditions [126,127]. For example, in a large cohort study of children, an ADHD polygenic risk score was associated with inattention and hyperactivity but also language difficulties, and an ASD polygenic risk score was associated with inattention, hyperactivity, language and motor difficulties, whereas a schizophrenia polygenic risk score did not show significant associations with neurodevelopmental features[128]. Both ADHD and ASD polygenic risk scores further predicted a neurodevelopmental spectrum based on exploratory factor analysis delineated in the ABCD study[129].

It is important to note that genomic studies of most psychiatric conditions are still in their infancy. As such, the genetic architecture of neurodevelopmental and other psychiatric conditions may change as sample sizes increase and new genomic data become available. Although GenomicSEM research has now been conducted with ASD and ADHD, other conditions that are hypothesized to be included in the neurodevelopmental spectrum, such as motor disorders and intellectual disabilities, have yet to be considered, due to the absence of GWAS of these phenotypes. It is critical that these omissions are addressed in future genomic studies of the neurodevelopmental spectrum.

Environmental risk factors

While the above-reviewed research indicates relatively large genetic influences for neurodevelopmental conditions and their covariation, meta-analytic evidence also demonstrates modest to moderate environmental influences[92]. Associations have been found of various forms of pre- and peri-natal stress[130-134], preterm birth[135,136] and environmental toxicant exposure (e.g., lead)[137-141] with neurodevelopmental conditions, including ASD, ADHD, intellectual disabilities, and learning and motor difficulties, as well as associated cognitive profiles. This pattern is consistent with an underlying dimension of liability to all neurodevelopmental conditions influenced by the aforementioned environmental exposures.

However, there are two important caveats when interpreting this evidence. First, it remains unclear whether and how specific these associations are to clinical features of the proposed neurodevelopmental spectrum relative to features captured by other spectra/dimensions[133,142]. Shared environmental risk factors, similar to genetics, may contribute to the co-occurrence between neurodevelopmental conditions and other psychiatric conditions. Yet, it is also possible that the same environmental factors are associated with different transdiagnostic conditions at different points in development, pointing to some specificity. For example, the same environmental exposure may increase risk for neurodevelopmental conditions in infancy/childhood and for psychosis in adolescence/adulthood. Second, establishing an association between environmental risk factors and neurodevelopmental conditions does not necessarily imply a causal effect. For example, accounting for familial and other confounders often results in attenuated associations[135,143]. However, a recent systematic review of twin and sibling studies, which controlled for familial and other shared confounders, did find suggestive evidence of a causal effect of pre-natal exposures for ASD and ADHD[130].

Developmental course

Additional evidence supporting the validity of the proposed neurodevelopmental spectrum pertains to the similarities in developmental course displayed by features clustering in this dimension. A key characteristic of all neurodevelopmental conditions is that they typically emerge early in development. The first features of some conditions – such as ASD, language and communication disorders, and developmental coordination disorder – are often recognizable before school age[144-150]. Other conditions, such as ADHD and learning disabilities, may be detected during the preschool period, but formal diagnosis usually does not occur until the child enters the school system and the skills associated with these conditions are evaluated[31,151]. Nevertheless, on average, neurodevelopmental features tend to emerge earlier than most other psychiatric conditions[152] (see Figure 1).

Regarding developmental trajectories, individuals with neurodevelopmental conditions tend to show persisting features over development, with some degree of improvement often seen with maturation[31,153,154]. Rates of diagnostic stability vary widely between studies (from ~20% to 100%)[31,155-159], particularly for ADHD and ASD. This instability may be explained by methodological differences, with lower persistence rates generally reported in population-based samples than in clinical samples and in studies relying on strict diagnostic thresholds[31,36,160,161]. Nevertheless, research has shown that most individuals with neurodevelopmental conditions show worse functional outcomes into adulthood relative to neurotypical individuals[31,154,162,163].

With regard to specific clinical features, inattention and socio-communication difficulties follow a relatively stable developmental pattern[154,164], while other features may change or be manifested differently with age and development, or even be replaced by features of other psychiatric conditions (heterotypic continuity). As an example, motor hyperactivity tends to decline over childhood and adolescence, but is often replaced by a feeling of inner restlessness in adulthood, which is also common in internalizing conditions[31]. In addition, it has been suggested that support strategies and interventions may not alter the natural course of neurodevelopmental conditions, but rather provide skills to compensate for stable underlying problems[31].

Altogether, evidence suggests similarities in developmental course between different neurodevelopmental conditions, namely an early onset and persistent course, with some degree of heterogeneity among individuals with the same condition[7,165,166]. Transdiagnostic approaches seeking to parse individuals with different neurodevelopmental conditions through more specific data-driven subdimensions cutting across diagnostic boundaries are particularly valuable for characterizing variability in developmental course[7,167]. For example, individuals with features of multiple neurodevelopmental conditions – consistent with high score on an overarching neurodevelopmental spectrum – commonly display more persisting symptom trajectories and worse long-term outcomes, including psychiatric comorbidities[153,154,168]. Future research should systematically evaluate the presence of different transdiagnostic neurodevelopmental subdimensions and how they may be linked to other psychiatric conditions, which could inform the design of transdiagnostic early interventions and support strategies.

Temperamental antecedents and personality

There appears to be both consistency and specificity in the temperamental traits that characterize neurodevelopmental conditions, though most of the existing research has been limited to ASD and ADHD, and to a lesser extent intellectual disabilities and communication disorders.

Lower levels of effortful control are common across all neurodevelopmental conditions[169-178]. Higher levels of negative emotionality are also frequent across these conditions, though the expression of this domain may partly differ across conditions, with distress, fear, shyness and sadness predominant in ASD and intellectual disabilities, while anger predominates in ADHD[169,179]. Positive emotionality/surgency also shows specificity across neurodevelopmental conditions, with higher levels in ADHD but lower levels in ASD and intellectual disabilities[169,170,178-181].

Although less common, longitudinal prospective studies highlight early temperamental indicators of lower effortful control, and higher negative emotionality and positive emotionality/surgency, as predicting ADHD symptom trajectories[182]; and lower effortful control in toddlerhood as predicting ASD diagnosis in early childhood[183]. Of note, lower effortful control and higher negative emotionality have also been associated with other psychiatric conditions, and may represent more general transdiagnostic indicators[182,184].

Cognitive and socio-emotional profiles

Neurodevelopmental conditions are characterized by difficulties in cognition, social interaction, and communication that emerge early in development and persist into later life[5,146]. Early cognitive challenges are a key feature of these conditions, though the nature of challenges may vary among different conditions, ranging from impairments specific to core processes and abilities, while other capacities are relatively preserved, to more generalized problems [185-187].

Executive functioning deficits cut across ASD, ADHD, motor disorders, and learning disabilities[7,31,188,189]. The ABCD study found that, among transdiagnostic dimensions, the neurodevelopmental factor showed the strongest association with executive functioning[190].

Studies directly comparing children with ASD and ADHD showed similarities during early development in attention, response inhibition, working memory, verbal fluency, preparatory processes, and concept formation, with some differences more likely to be quantitative rather than qualitative[145,191,192]. Similar cognitive challenges have also been reported in other neurodevelopmental conditions, such as language disorders, developmental coordination disorder, and Tourette's syndrome[193-195], but transdiagnostic comparison studies are lacking.

Early atypicalities in sensory processing (e.g., hyper-sensitivity) have been consistently reported in autistic children[196,197], but are also found in children with ADHD[198]. Further, motor skills, such as motor coordination, are impaired across developmental coordination disorder, Tourette's syndrome, ASD and ADHD[145,158,199], and communication/language problems characterize not just language and speech disorders but also to some extent ASD and ADHD[145,195,200].

With regard to social skills, children with ASD, ADHD, motor disorders and learning disabilities show social impairments relative to their peers[7,193,201,202]. There does appear to be some specificity in social impairment, with autistic children showing more atypical social skills[7,189,203,204], whereas children with ADHD show relatively intact social skills knowledge but more maladaptive social behavior[205]. Perhaps due to impairments in self-regulation and inhibitory control[206], both ASD and ADHD are also associated with elevated emotional dysregulation, including emotional lability and irritability[207-209].

Although there is evidence of characteristic cognitive and socio-emotional profiles for neurodevelopmental conditions, similar cognitive challenges have also been found for other psychiatric conditions[51,210]. However, because few studies comprehensively examined cognitive functions across the above conditions (with the notable exception of ADHD and disruptive behavior disorders [211,212]), the specificity of these cognitive profiles to neurodevelopmental conditions remains to be clarified in future transdiagnostic studies. Another important direction will be to address the wide heterogeneity in cognitive and socio-emotional profiles across neurodevelopmental conditions more systematically, by developing multidimensional models that integrate both clinical features and functioning abilities.

Neurobiological profiles: neuroimaging

Structural and functional magnetic resonance imaging (MRI) studies suggest largely shared patterns of brain structure and functioning in networks important for executive function and cognitive/motor control across neurodevelopmental conditions[213-217], supporting the proposed neurodevelopmental spectrum.

Specifically, similar patterns of grey matter structure have been observed in frontal, temporal, parietal and striato-thalamic networks supporting cognitive control and goal-directed decision-making across ASD and ADHD[218-224]. Mega- and meta-analyses have found associations of ASD and ADHD with lower grey matter volume in ventromedial orbitofrontal cortex and basal ganglia, amygdala and hippocampus, and with lower cortical surface area and thickness in frontal, temporal and parietal regions[220-222,225-232]. Neuroanatomical findings may, however, vary with development (e.g., evidence of increased total brain volume in ASD during infancy/early childhood[224]) and have been somewhat less consistent in studies of ASD compared to ADHD.

Few studies have compared neurodevelopmental conditions directly, but these findings are consistent with a recent cross-disorder study showing commonalities in cortical regions implicated in socio-emotional and executive functions across ASD and ADHD (as well as OCD)[233]. Additional cross-disorder mega- and meta-analyses further indicate a range of structural brain features shared between ASD and ADHD, such as lower cortical thickness and surface area, though some divergent findings have also been observed, possibly due to the fact that some studies analyzed summary statistics rather than raw data[234-236].

While the majority of studies have focused on ASD and ADHD, structural MRI studies of other neurodevelopmental conditions have shown more mixed findings, likely owing to the use of smaller samples[237-242]. Larger comparative studies investigating all neurodevelopmental conditions, as well as other psychiatric conditions, are needed.

As to brain functioning, atypical activations within fronto-striatal brain circuitry and basal ganglia appear to be most commonly implicated across ASD, ADHD, and speech and language disorders. Meta-analyses show underactivation related to cognitive and inhibitory control in lateral/medial fronto-striatal networks in ADHD[222,243,244]. Similarly, a whole-brain meta-analysis of functional MRI studies of cognitive control in ASD found underactivation in salience and executive networks, including lateral and medial frontal regions and left cerebellum, and overactivation in right temporo-parietal regions, including areas of the default-mode network[218,221]. Moreover, shared reductions in dorsolateral prefrontal cortex and precuneus activation during higher-order cognitive functions and resting state have been observed across ASD and ADHD[245-248].

Fewer studies have investigated the neural underpinnings of other neurodevelopmental conditions using functional MRI. Regarding specific learning disabilities, dyslexia has been associated with primarily left-lateralized underactivation in lateral temporal, inferior parietal, and fusiform regions, as well as overactivation in motor cortex and the anterior insula[249-251], whereas dyscalculia is associated with number-relevant parietal regions and prefrontal and occipital regions[252]. Initial data in Tourette's syndrome suggest that functional dysregulation in basal ganglia and limbic regions related to the suppression of tics may overlap with functional abnormalities and related cognitive control difficulties seen in ADHD[253].

Shared alterations across ASD and ADHD have been found in structural connectivity, particularly in white matter tracts connecting prefrontal regions to other regions[254,255], as well as in functional connectivity in large-scale brain networks, particularly in the default-mode network and fronto-parietal attention-related salience networks[248,256-261]. Such cross-disorder overlap is also reflected in recent data from the ABCD study showing the association between a neurodevelopmental factor derived from exploratory factor analysis[25] and resting state functional connectivity involving the default-model, cingulo-opercular and dorsal attention networks[262]. Associations with functional connectivity were significant even after controlling for a general psychopathology factor and did not emerge for other psychopathological dimensions (e.g., internalizing, externalizing), suggesting the specificity of these atypical functional connectivity profiles to neurodevelopmental features.

Functional connectivity studies in motor disorders are somewhat more limited, but those directly comparing developmental coordination disorder and ADHD have found evidence for shared abnormalities across disorders in motor circuitry, pointing to a common neural substrate[263,264].

Overall, the available evidence indicates an overlap in candidate diagnostic biomarkers of brain structure and functioning across neurodevelopmental conditions, particularly ASD and ADHD. Structural and functional atypicalities in frontal and striato-thalamic regions implicated in attention and cognitive control, and abnormalities in resting-state functional connectivity networks, particularly the default mode and dorsal attention networks, may be a unifying feature across a neurodevelopmental spectrum. While initial evidence points to brain patterns that may be common across neurodevelopmental features but discriminate them from other psychiatric features[262], future studies should systematically assess the extent of possible neurodevelopmental-specific neuroimaging biomarkers.

Neurobiological profiles: neurophysiology

Evidence from neurophysiological studies, particularly based on electroencephalography (EEG), complements knowledge from neuroimaging studies. Reductions in event-related potentials (ERP) amplitudes reflecting early sensory perception, such as N1 and mismatch negativity (MMN), have been commonly reported in ASD[265,266] and dyslexia[267,268], whereas associations with ADHD and developmental coordination disorder appear more consistent for reduced MMN[265,269] than for N1 components[270].

Atypical N170 amplitudes in response to facial stimuli have been studied almost exclusively in ASD, and large studies in other conditions are needed[271,272]. Studies of ERPs indexing goal-directed behavior indicate reduced N2 and error-related negativity (ERN) components in ASD[266,273], ADHD[273,274], specific learning disabilities[275,276] and developmental coordination disorder[277], whereas increased ERNs are commonly associated with Tourette's syndrome[273]. The latter finding might be explained by the close link between Tourette's syndrome and OCD, as OCD is also associated with increased ERN, potentially suggesting that Tourette's syndrome might be jointly captured by internalizing and neurodevelopmental spectra. Further, reduced P3 components in response to visual and auditory stimuli have been repeatedly associated with ASD[278,279], ADHD[280,281], specific learning disabilities[276], Tourette's syndrome[282], and developmental coordination disorder[269,283,284].

With regard to resting-state EEG studies, elevated power in slow oscillations (delta and theta), thought to reflect delayed cortical maturation, have repeatedly been associated with ASD[285], ADHD[286,287], and learning difficulties[288,289]. Reduced alpha and beta power have also commonly been associated with these conditions[290-292], although findings for alpha power have been more mixed in ADHD[287,293]. Emerging findings suggest shared alterations in intra-individual EEG variability[294,295] and EEG connectivity[296-298] between ASD and ADHD. Similarly, a recent study of children with ASD or ADHD and controls found a data-driven cluster largely reflecting a transdiagnostic neurodevelopmental subgroup based on functional connectivity measured with magnetoencephalography (MEG)[299].

These findings support the validity of the proposed neurodevelopmental spectrum, in that they delineate neurophysiological profiles mapping onto neural mechanisms shared across neurodevelopmental conditions. However, similar to the neuroimaging literature, the strongest evidence pertains to ASD and ADHD, warranting replication and extension in transdiagnostic studies of neurodevelopmental and other psychiatric conditions.

Other neurobiological profiles

The literature on peripheral diagnostic biomarkers provides further evidence in support of the neurodevelopmental spectrum. Meta-analyses and reviews indicate that reduced levels of serum vitamin D levels[300-303] and blood zinc levels[304-307] are associated with ASD, ADHD, intellectual and learning difficulties. Blood levels of brain-derived neurotrophic factor (BDNF) were found elevated in both ASD and ADHD[308,309]. However, the strength of the evidence for these biomarkers varied in these meta-analyses and was often rated as weak, indicating that larger and more rigorous studies are needed.

Service organization and efficacy of support and intervention approaches

Patterns of service organization and efficacy of support and intervention strategies provide additional evidence for the validity of the proposed neurodevelopmental spectrum.

Given the high rates of co-occurrence across neurodevelopmental conditions, the need for multifaceted professional care that adequately addresses varied symptom presentations and needs beyond diagnostic categories has been widely advocated[310,311]. In fact, in several countries, clinical services are already organized to provide care for features spanning the neurodevelopmental conditions[312], with service-user organizations actively advocating for a shift toward transdiagnostic neurodevelopmental services in countries where care is still based on discrete conditions[313].

Evidence from treatment studies shows that stimulant medication broadly improves features of inattention, hyperactivity and impulsivity[314]; academic performance in math productivity, math accuracy and reading speed[315]; outcomes related to motor coordination[316], and cognitive performance in children with ADHD but also ASD[317]. These effects across neurodevelopmental conditions suggest that medication is not acting upon mechanisms specific for one diagnostic category, but instead on shared underlying processes[315,317,318]. It is important to note, however, that some core features of ASD, such as social interaction and stereotypical behaviors, do not show improvements with stimulants[318], highlighting heterogeneity.

Regarding response to psychosocial interventions, initial evidence indicates that transdiagnostic traits (executive functioning and emotion regulation) predict efficacy of an intensive behavioral treatment program targeting school readiness over and above ASD and ADHD diagnoses[206], further supporting the validity of the proposed spectrum. Since most transdiagnostic studies have focused on ASD and ADHD, additional research is needed to conclusively determine whether transdiagnostic psychosocial interventions can provide similarly efficacious benefits across other neurodevelopmental conditions.

Summary of the validity evidence

Overall, there is a broad degree of similarity in genetic, neuroimaging, neurophysiological and other biomarkers, as well as in developmental, cognitive, socio-emotional, temperamental/personality profiles, and patterns of service organization and treatment efficacy, across neurodevelopmental conditions (see Table 2). Evidence is most convincing for ASD and ADHD, as these conditions have been investigated to a much greater extent than other neurodevelopmental conditions.

Many studies support a dimensional approach, highlighting within-diagnosis variability and between-diagnosis overlap, motivating the search for shared patterns of brain-behavior associations across neurodevelopmental conditions. However, most studies have only considered one condition or symptom dimension in small samples, highlighting an acute need for larger studies using transdiagnostic samples with neurodevelopmental and other psychiatric conditions.

Besides broad similarities supporting the coherence of a neurodevelopmental spectrum, findings suggesting some differences between neurodevelopmental conditions, if replicated, would be consistent with the possible delineation of subdimensions (e.g., inattention, social difficulties) within this broad spectrum.

Two points are worth noting. First, multiple and different causes and configurations of underlying mechanisms may give rise to shared phenotypes across neurodevelopmental and other psychiatric conditions (i.e., equifinality[319]). At the same time, the same underlying cause or mechanism may result in phenotypic variation and different outcomes within neurodevelopmental conditions (i.e., multifinality[319]). Further transdiagnostic research using etiological and developmental approaches will be important for elucidating these equifinal and multifinal pathways, and for informing clinical decisions and applications based on underlying mechanisms and developmental processes.

Second, while the reviewed validity evidence points to commonalities across neurodevelopmental conditions, the extent of the overlap with other psychiatric conditions remains largely unclear. For example, similar temperamental, cognitive and neural profiles may also be found in the context of later-onset psychiatric conditions, such as depressive and psychotic disorders[9]. Yet, studies of other psychiatric conditions rarely examine whether these findings may be explained by co-occurrence with earlier-onset features of neurodevelopmental conditions. The systematic inclusion of neurodevelopmental features and conditions in future longitudinal transdiagnostic studies will be crucial to clarify this issue.

UTILITY EVIDENCE

Although a DSM/ICD-based categorical approach for research and practice still represents the *status quo*, transdiagnostic dimensional approaches are increasingly being adopted in research as well as clinical services for neurodevelopmental conditions[7,26,320], supported by growing evidence suggesting their utility.

Reliability and measurement

To contextualize the potential utility of dimensional alternatives, it is useful to consider evidence for the limited reliability of categorically-defined neurodevelopmental conditions. Most evaluations of reliability of these conditions have focused on ASD and ADHD, whereas data are lacking for other neurodevelopmental conditions (with a few exceptions[321]). Interrater reliability (i.e., the extent to which two raters agree) has generally been

Table 2 Summary of validity evidence supporting the proposed neurodevelopmental spectrum

	Diagnoses/features						Neurodevelopmental (or similar) factor
	ADHD	ASD	Learn	ID	Comm	Motor	
Genetics							
Family/twin studies	++	++	+	+	+	+	+
Molecular genetics/genomics	+	+			+	+	+
Environmental risk							
Early stress exposure	++	++	+	+		+	
Preterm birth	+	+					
Toxicant exposure (e.g., lead)	+	++	+	+			
Developmental course							
Early age of onset	+	++	+	+	++	++	
High chronicity/stability	+	++	+	+	++	+	
Temperamental antecedents							
Low effortful control	++	+	+	+	+	+	
High negative emotionality	++	++	+	+	+	+	
High positive emotionality	+						
Low positive emotionality		+		+			
Cognitive and socio-emotional difficulties							
Executive functioning	++	++	++	+		++	+
Sensory processing	++	++					
Motor coordination	+	+				++	
Language problems	+	+			++		
Theory of mind	+	++					
Emotional dysregulation	++	+					
Neurobiology							
Brain volumes	++	+	+			+	
Brain activity (fMRI)	++	++	+		+	+	
Structural connectivity	+	+					
Functional connectivity	+	+				+	+
Event-related potentials	++	++	+		+	+	
EEG spectral power	+	+	+		+	+	
Other biomarkers							
Reduced serum vitamin D	+	+	+	+			
Reduced blood zinc	+	+	+	+			
Elevated BDNF expression	+	+					
Service organization and treatment							
Broad neurodevelopmental services	+	+	+	+	+	+	
Efficacy of stimulant medication	++		+			+	

++ means repeatedly replicated finding, + means some evidence for effect. ADHD – attention-deficit/hyperactivity disorder/features, ASD – autism spectrum disorder/ features, Learn – learning disorders/problems, ID – intellectual disabilities, Comm – communication disorders/problems, Motor – motor disorders/ features, fMRI – functional magnetic resonance imaging, EEG – electroencephalography, BDNF – brain-derived neurotrophic factor.

found to be low to barely adequate for both ASD[322-325] and ADHD [326-328], and even lower for specific ADHD subtypes[329].

Interrater reliability estimates for ASD and ADHD diagnoses are also generally lower than for other psychiatric diagnoses [323,324,330,331]. One important consideration is that, unlike diagnoses of most other psychiatric conditions, diagnoses of neurodevelopmental conditions are often made using parent and other informant (e.g., teacher) reports rather than relying solely on self-report, especially at younger ages. As cross-informant discrepancies must be resolved when making a diagnosis, despite often reflecting unique information that each reporter has access to rather than errors, this can lead to low interrater reliability[332].

Interrater reliability is consistently higher for neurodevelopmental features and specific symptom dimensions. For example, interrater reliability for diagnostic features of ASD (e.g., reciprocal social interaction, communication, repetitive and restricted behavior) has been found to be higher than for the diagnosis[323,324,331]. ADHD symptom dimensions (inattention and hyperactivity-impulsivity dimensions) similarly show higher interrater reliability than the diagnosis[329].

Moreover, estimates of test-retest reliability (a measure of temporal stability) also tend to be higher for dimensional conceptualizations of neurodevelopmental conditions relative to categorical ones. Whereas findings for categorical diagnoses of ASD[324,333] and ADHD[334-336] have varied substantially, dimensional studies examining inattention, hyperactivity, and sluggish cognitive tempo features of ADHD[333,337,338], as well as social, communication, sensory and motor features of ASD[339-341], have consistently shown high stability. Overall, there is extensive evidence that spectra/dimensions of neurodevelopmental and other psychiatric features show superior temporal stability compared to diagnostic categories[43,62,337,342-344].

The relatively lower reliability found for neurodevelopmental categories compared to dimensions may be due in part to the high co-occurrence between neurodevelopmental diagnoses and their transdiagnostic features (e.g., similarities in symptoms). These issues pose significant challenges to differential diagnosis among the neurodevelopmental conditions[345]. For example, the interrater reliability for the DSM-IV autism disorder diagnosis – one of five DSM-IV pervasive developmental disorder (PDD) diagnoses – was generally adequate-to-good for the diagnosis of autism versus non-PDD conditions[326,345], but lower for the differential diagnosis of autism versus other PDD[326,345].

Moreover, it is difficult to partition true dimensional and transdiagnostic features into discrete diagnostic categories. For example, clinicians commonly report uncertainty when determining whether individuals with significant social difficulties meet criteria for ASD versus other neurodevelopmental conditions[346], and the feature of elevated inattention that is key for ADHD is also commonly seen in children with other neurodevelopmental conditions, as well as other psychiatric conditions[97,347].

Notably, standard diagnostic measures for children and adolescents – e.g., the Diagnostic Interview for Children and Adolescents (DICA)[348] – assess ADHD but rarely include other neurodevelopmental conditions, and most adult diagnostic interviews – e.g., the Structured Clinical Interview for DSM-5 (SCID-5)[349] – do not include any neurodevelopmental conditions. As such, these conditions are rarely assessed alongside other psychiatric conditions (because doing so would require the addition of another diagnostic assessment and increase burden on researchers/clinicians and patients). This means that the differential diagnosis of neurodevelopmental conditions versus other psychiatric conditions is rarely done in research or clinical contexts, making it difficult to evaluate or differentiate transdiagnostic features (e.g., attention problems due to ADHD or to depression) and contributing to their artificial separation in research and clinical practices[32].

Challenges in the reliable assessment of categorical neurodevelopmental diagnoses have important implications. For example, the DSM-5 introduced several changes in the new ASD diagnosis, now encompassing all five DSM-IV PDD diagnoses. This shift has resulted in more severe presentations in individuals receiving a DSM-5 ASD diagnosis compared to those with a DSM-IV diagnosis, but in fewer DSM-5 diagnoses in individuals who had previously met criteria for DSM-IV PDD diagnoses[350,351]. At the same time, many individuals who do not meet criteria for a DSM-5 diagnosis nonetheless still show features of ASD[350,351] and other psychiatric conditions[30]. A shift toward transdiagnostic dimensional assessments that do not rely on strict diagnostic cutoffs would avoid these problems, because dimensional approaches allow for the assessment of key features of neurodevelopmental and other psychiatric conditions, as well as of symptom severity and functional impairment, likely leading to a better identification of treatment targets.

Consistent with recognition of the usefulness of a dimensional approach, there is a long history of dimensional measures for ADHD[352-356], such as the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale (SWAN)[353], the Adult ADHD Self-Report Scale (ASRS)[355], and scales included in the ASEBA system[21]. There has also been a recent move toward dimensional measures for ASD[41,357], such as the Social Responsiveness Scale (SRS)[358], the Autism Symptom Dimensions Questionnaire (ASDQ)[359], and the Repetitive Behavior Scale-Revised (RBS-R)[360].

These dimensional measures carry multiple advantages, as they are readily adopted in clinical settings (especially when conducting full diagnostic assessments is not feasible or preferred) and show improved interrater reliability and prediction of functioning and impairment relative to categorical ASD and ADHD diagnoses[358-362]. However, most of these assessment tools are still focused on features of individual conditions, rather than providing a transdiagnostic assessment of all neurodevelopmental conditions, as well as other psychiatric conditions.

Dimensional measures for neurodevelopmental conditions other than ASD and ADHD are also still uncommon, with a few exceptions[363,364]. In addition, measurement invariance is rarely considered or explicitly evaluated, but it is important to establish when considering assessments across informants, age, sex/gender, and other sociodemographic and clinical characteristics. Notably, initial work with some standard dimensional measures of ASD indicates a lack of measurement invariance for birth sex that obscures sex-specific patterns of ASD symptoms among boys and girls[365].

Overall, it is clear from decades of research that – as for dimensional conceptualizations of internalizing, externalizing and psychotic conditions[8,366] – dimensional measures of neurodevelopmental conditions show higher reliability than categorical indicators[7,41]. The development of new transdiagnostic dimensional measures that span across features of all neurodevelopmental and psychiatric conditions and do not rely on strict diagnostic cutoffs will likely further improve reliability. In turn, better reliability of measures can result in more robust research efforts, greater utility in clinical settings, and improved clinical care.

Explanatory and prognostic utility

A critical aspect of the utility of a model or framework is its ability to explain and predict clinical phenomena, risk factors, and outcomes. The heterogeneity intrinsic to neurodevelopmental diagnostic categories has long been regarded as a significant barrier to explanatory and prognostic utility[367-371]. The transdiagnostic nature of risk factors, cognitive and socio-emotional profiles, and developmental course across neurodevelopmental conditions (as reviewed above) further points to the limited explanatory and prognostic value of categorical diagnoses.

Conversely, a growing body of evidence indicates that a transdiagnostic neurodevelopmental spectrum, or narrower dimensions included within this spectrum (e.g., inattention), can improve explanatory and prognostic utility over a categorical approach, in line with meta-analytic evidence showing greater validity of dimensional conceptualizations relative to categorical ones for a wide range of psychiatric conditions[366].

In the Canadian 2006 Participation and Activity Limitation Survey (ages 5-14; weighted N=120,700), a factor capturing neurodevelopmental and related functional characteristics fully mediated the relationship between an ASD diagnosis and child and family health and well-being outcomes (e.g., involvement in school activities, family psychological well-being)[372]. The direct effects of the neurodevelopmental factor on these outcomes were roughly twice as large as the effects of ASD diagnosis, and these latter effects disappeared when the neurodevelopmental factor was added into the model[372], indicating the superior explanatory utility of the dimensional approach.

Longitudinal evidence from three cohorts (total N=1,253) further showed that a model including a neurodevelopmental factor primarily capturing ADHD features, measured in early childhood, predicted pre-adolescent psychiatric psychopathology and psychosocial functioning about two times more strongly than meeting criteria for a DSM diagnosis[373].

These findings align with replicated evidence that continuous dimensions of inattention and hyperactivity-impulsivity show greater predictive utility and temporal stability than DSM ADHD inattentive, hyperactive-impulsive, and combined type diagnoses[329,374-377], speaking to the utility of a dimensional approach and the limited validity of categorical diagnostic specifiers.

Several studies also indicate that neurodevelopmental factors show stronger associations with a range of important risk factors and outcomes – including global executive functioning, brain functioning, developmental delays, learning problems, psychosocial functioning, medication use, and service utilization – than general factors comprising other psychiatric conditions and clinical features[25,42,190,233,262,373,379]. A large Swedish population study (N=1,093,788) showed that a neurodevelopmental factor was associated with reduced fetal growth to a greater extent than internalizing, externalizing, psychosis, and general psychopathology factors[45]. These associations remained significant even in sibling analyses controlling for unmeasured familial confounding.

A transdiagnostic neurodevelopmental spectrum has also been found to show improved utility over specific neurodevelopmental features. For example, a large longitudinal study on a UK birth cohort (N=10,054) found that a broad childhood neurodevelopmental factor predicted adult mood problems more stably and to a larger extent than more narrow dimensions capturing motor and cognitive difficulties[49].

Overall, these findings indicate that a transdiagnostic characterization of neurodevelopmental conditions can better explain and enhance prediction of important outcomes beyond categorical approaches, and provides incremental validity even over dimensional indicators of other psychiatric conditions and clinical features[202].

Clinical utility

Clinical utility includes the extent to which shifting toward a transdiagnostic dimensional approach for neurodevelopmental conditions would reflect clinician acceptability and preference; facilitate practical implementation in clinical settings, patient conceptualization, communication among practitioners, patients and family members, clinical decision-making, and treatment selection/planning; and improve outcomes for individuals, families and clinicians[379].

Several lines of evidence indicate that transdiagnostic dimensional approaches in general[17-19], and to neurodevelopmental conditions more specifically[7,202,320,380], provide more clinically useful assessment and treatment targets than diagnostic categories.

Research on practitioner ratings has found that clinicians report a preference for and greater acceptability, feasibility and clinical utility of a transdiagnostic dimensional approach to diagnosis in both child and adult patients, including those with ADHD[326]. This is consistent with data showing that practitioners focus more on symptom severity than diagnostic categories in clinical decision-making[381]. Notably, child and adult patients (and parents of child patients) also reported that the transdiagnostic approach was likely to be more helpful to the clinician in understanding their problems and needs[326].

Another piece of evidence directly pointing to the clinical utility of a dimensional approach to neurodevelopmental conditions is the widespread implementation of dimensional assessments in clinical settings[382], particularly for ADHD[353–355,383,384], but also more recently for ASD[41,357-360,385] and intellectual disabilities[363,386]. As a singular diagnosis does not provide clinicians with an accurate picture of the individual patient, dimensional assessments are routinely used in clinical care to yield a more complete conceptualization of an individual's strengths, weaknesses and needs beyond their categorical diagnosis[7,382,387-390].

This is illustrated by a recent field trial on the utility of newly-developed behavioral indicators for assessing the severity of intellectual disabilities, included within the Clinical Descriptions and Diagnostic Requirements for ICD-11 neurodevelopmental disorders[363]. Findings showed positive practitioner ratings regarding ease of administration, as well as clinical utility for treatment selection, prognostication, and communication with other health care and educational professionals[363].

Regarding support and treatment strategies, there is evidence that targeting the social difficulties common across many neurodevelopmental conditions by designing interventions around social skills rather than diagnoses may be more helpful and cost-effective[202,391]. Dimensional assessments can also be useful for monitoring treatment efficacy and clinical improvements over time[387,389,392]. Broadening the transdiagnostic focus across both neurodevelopmental and psychiatric conditions is likely to promote the development of preventive strategies to avert the emergence of later-onset mental health challenges in individuals with neurodevelopmental conditions. This is in line with recent proposals for a stepped-care personalized health model for ASD tailored to autistic individuals' and families' needs, strengths and challenges[390].

Finally, the clinical utility and acceptability of the proposed transdiagnostic dimensional approach are reflected in stakeholders' clinical priorities. Advocacy organizations and individuals with neurodevelopmental conditions have highlighted the unmet support needs resulting from the use of traditional categorical approaches in clinical settings[33,34,393]. As a solution to these challenges, they have actively called for a shift toward clinical services supporting multiple neurodevelopmental conditions and including dimensional assessments for neurodevelopmental and co-occurring conditions[313,382].

Emerging evaluations of clinical services adopting such an approach in the UK have shown improvements in capacity for support and satisfaction from patients, families and practitioners, along with reductions in waiting lists, re-referrals to different assessments (e.g., for learning difficulties in a child initially assessed in an ADHD clinic), and economic cost[383]. These encouraging data point to the clinical utility of a transdiagnostic dimensional approach to neurodevelopmental conditions and support the extension of this approach to other counties[394].

IMPLICATIONS

Integrating the proposed neurodevelopmental spectrum into transdiagnostic approaches to psychiatric conditions can have several important implications.

Research implications

From a research perspective, our proposal to situate the neurodevelopmental spectrum in transdiagnostic models of psychiatric conditions can provide a formal framework for characterizing the common developmental continuity and co-occurrence among neurodevelopmental conditions and between them and other psychiatric conditions. Progress in this area has been slow, as research based on categorical approaches has typically considered neurodevelopmental conditions separately from one another and from other psychiatric conditions. This is at odds with how these conditions manifest clinically, and has led researchers, advocacy organizations, and people with lived experience to call for more transdiagnostic work across neurodevelopmental conditions and psychiatric comorbidities[7,25,32-35,395]. The notion of a neurodevelopmental spectrum and its explicit consideration alongside other transdiagnostic spectra/dimensions can directly respond to these issues by promoting a more holistic characterization of their frequent overlap across development.

Moreover, inclusion of the proposed neurodevelopmental spectrum into transdiagnostic models can have important implications for elucidating the etiological and developmental underpinnings of neurodevelopmental and other psychiatric conditions. Categorical approaches have encouraged etiological and developmental research focused on individual conditions, often not considering whether research participants also present with (or have a prior history of) other conditions. As a result, it has not been possible to clarify to what extent the risk factors and mechanisms identified for any individual condition are specific to that condition, shared across multiple conditions, or explained by unmeasured comorbidities[9]. Incorporating the neurodevelopmental spectrum into transdiagnostic models can allow researchers to pinpoint etiological and developmental processes that are specific to that spectrum (or its constituent subdimensions) and those shared with other transdiagnostic spectra/dimensions. Further, since earlier developmental expressions of neurodevelopmental features often precede more severe presentations and significant impairment[145], the proposed transdiagnostic approach can generate new insights into developmental processes more generally, which are key to early identification and prevention.

In addition, by encouraging a broad assessment of the degree of functioning and challenges displayed by each individual, the dimensional approach intrinsic to the proposed transdiagnostic conceptualization can also help consolidate understanding that neurodevelopmental conditions are on a continuum with typical functioning and subthreshold presentations[7,26], just like their common psychiatric comorbidities[12,17-19]. A dimensional approach characterizing the entire population-level distribution of multiple neurodevelopmental features will also encourage researchers to move away from the known limitations of case-control studies[7,11,17]. This is especially valuable for conditions with lower diagnostic prevalence rates (e.g., ASD), for which recruitment of eligible individuals into studies is challenging.

Overall, including the proposed neurodevelopmental spectrum in transdiagnostic frameworks can foster approaches to characterize co-occurring profiles, heterogeneity, mechanisms, and developmental processes, as well as promote significant refinement of theoretical and etiological models of neurodevelopmental and other psychiatric features. This can have important effects on stratification, biomarker discovery, and future clinical practices.

Clinical implications

From a clinical perspective, our proposal has implications for early identification, prevention, treatment planning, and transdiagnostic interventions. First, as neurodevelopmental conditions share many overlapping early features, focusing on transdiagnostic domains rather than single measures of separate diagnostic categories can improve early identification and optimize early intervention[391]. This has direct clinical implications, for example, in addressing issues of diagnostic overshadowing[33,396], such as when receiving a diagnosis of ASD leads to delayed diagnosis of other neurodevelopmental conditions (e.g., ADHD) or other psychiatric conditions (e.g., depression).

Second, a broader assessment of various neurodevelopmental features, alongside features of other psychiatric conditions, can yield a fuller evaluation of an individual's specific strengths, difficulties and needs than possible when focusing on categorical diagnoses. It can also allow for the assessment of gradations in functioning in multiple domains. This can both identify areas of strength, that may be emphasized, and allow for earlier identification of difficulties before they become severe enough to meet the level of a diagnosis. As a result, a transdiagnostic approach can directly address the priorities of individuals with neurodevelopmental conditions and their families, proving more clinically acceptable and less stigmatizing than categorical diagnostic approaches[10,32,33].

Third, neurodevelopmental conditions increase the risk for other psychiatric conditions in adolescence and adulthood[31,49,151,153,395], but this risk is non-specific across the neurodevelopmental spectrum[49,397]. A transdiagnostic approach to assessing the neurodevelopmental spectrum, instead of focusing on individual diagnoses, offers greater explanatory power for predicting important outcomes. Characterizing risk pathways between a broad neurodevelopmental spectrum and subsequent psychiatric conditions can improve prevention and timely diagnostic assessment[395].

Finally, the proposed transdiagnostic dimensional approach can increase access to needed services. Clinicians, users and their families, and advocates speak to the need for approaches and services that recognize mental health complexity[33,391,398,399], including service delivery based on severity, functioning and prognosis, rather than limiting access to only those who have received a specific diagnosis[33,400,401]. Under the current categorical approach, an individual displaying impairing features of several neurodevelopmental conditions, but not reaching diagnostic cut-offs for any specific diagnosis, can be denied care. Instead, taking a more universal approach to providing services focused on broad neurodevelopmental features can enable prompt recognition and support based on individual needs, helping to address barriers to care, including structural inequities related to immigration, race and ethnicity[402-404]. Additionally, such an approach may be destigmatizing, since it will encourage moving away from diagnostic labels towards a focus on individual challenges as well as strengths[10,405].

FUTURE DIRECTIONS

An important future step is to map the finer-grained structure of the neurodevelopmental spectrum by investigating its specific subdimensions (e.g., inattention, repetitive behaviors, reading difficulties). This work may build on previous studies on the structure of individual neurodevelopmental conditions. For example, the most replicated structure of ADHD includes separate inattention, hyperactivity and impulsivity factors[199,406], whereas the ASD literature has identified between three (communication, social interaction, and restrictive/repetitive behaviors)[407,408] and five (somewhat varying across studies)[199,409-412] factors.

Studies spanning subdimensions of neurodevelopmental and other transdiagnostic spectra/dimensions can shed light on whether certain neurodevelopmental features may partly overlap with other more established spectra/dimensions. For example, some studies conformant with the HiTOP model suggest that impulsive features of ADHD and aloofness features of ASD may be also partly accounted for, respectively, by disinhibited externalizing[25] and detachment[53] spectra.

Additionally, features currently included within other spectra/dimensions may be better captured by the new neurodevelopmental spectrum. For example, repetitive thinking and behaviors characterizing OCD (typically included in internalizing factors) may show stronger clustering with neurodevelopmental features[25], in line with evidence that they are common also in ASD and Tourette's syndrome and not always associated with obsessions[199].

There is also a critical need for prospective longitudinal studies of unselected epidemiological samples first assessed early in life and then repeatedly into childhood, adolescence and adulthood. Although such studies are resource and time intensive, they are the only way to capture the development, temporal ordering, and dynamic course of neurodevelopmental and other psychiatric conditions. Of particular importance for comprehensive etiological models of psychiatric conditions is a better understanding of the stability of the proposed neurodevelopmental spectrum, and the continuity or discontinuity of neurodevelopmental conditions with one another and with other psychiatric conditions captured by other broad spectra/dimensions. Investigations that track features and behaviors of neurodevelopmental and other psychiatric conditions across key developmental periods and the entire lifespan are also needed to examine equifinality and multifinality[319].

Including neurodevelopmental features alongside other psychiatric features in transdiagnostic studies is also necessary to further evaluate the validity evidence for the neurodevelopmental spectrum, in line with validators commonly used in psychiatric nosology[5,17-19]. The existing research reviewed in this paper identifies commonalities across neurodevelopmental conditions for psychiatric nosology validators. However, because this research rarely includes features of both neurodevelopmental and other psychiatric conditions, it remains unclear whether these validators are specific to the neurodevelopmental spectrum. Future studies should establish associations with validators specific to the neurodevelopmental spectrum or transdiagnostically associated with multiple spectra (particularly concerning environmental risk factors and temperament/personality profiles), as well as associations relevant to specific developmental periods.

Of note, this is also an issue for the validity of other, well-established internalizing, externalizing and psychosis spectra[17-19], because that research likewise has rarely included neurodevelopmental conditions, meaning that unexamined co-occurrence with earlier-onset features of neurodevelopmental conditions may account for findings. Therefore, the inclusion of a neurodevelopmental spectrum in transdiagnostic psychiatric frameworks is necessary to evaluate the validity evidence for transdiagnostic spectra more generally.

Studies of this kind will require the development of new and expanded measures that comprehensively cover the range of features and behaviors captured in transdiagnostic frameworks of psychiatric conditions, including neurodevelopmental ones. Although strict cut-offs are antithetical to the transdiagnostic dimensional approach we describe here, incorporating clinically useful thresholds that identify individuals in need of additional supports can improve implementation, conceptualization, communication, treatment selection/planning, and outcomes for individuals, families and clinicians[344].

Finally, an important future direction will be to engage multiple stakeholders – including people with lived experience, families, advocates, researchers and clinicians – in broader discussions (e.g., through participatory research approaches) on the acceptability of applying and implementing the proposed transdiagnostic approach to neurodevelopmental and other psychiatric conditions in clinical settings. Translating our proposed transdiagnostic approach into clinical care has the potential to transform how co-occurring mental health problems are detected and supported. Yet, integrating a neurodevelopmental spectrum in transdiagnostic psychiatric frameworks (e.g., HiTOP) may also suggest that features of ASD, ADHD and other neurodevelopmental conditions should be exclusively seen as forms of psychopathology. This issue is non-trivial, as many individuals with neurodevelopmental conditions do not recognize these conditions as pathological, but rather as forms of neurodiversity[27-29] or aspects of their own identity (as evidenced by the preference for identity-first language expressed by certain groups)[27].

At the same time, the neurodiversity framework encourages research and clinical efforts on issues important to people with neurodevelopmental conditions, with the potential to improve their lives[27,28,313]. As prompt recognition and access to support are top priorities of people with lived experience and advocacy groups worldwide[32-35], the benefits arising from our proposed approach could outweigh the potential risks associated with considering a neurodevelopmental spectrum alongside other transdiagnostic psychopathology spectra/dimensions. Moreover, transdiagnostic dimensional approaches promote a view of each person as a whole, with individual challenges and strengths, and are less pathologizing/stigmatizing than categorical approaches[10], which are still prevailing in clinical care.

CONCLUSIONS

The evidence discussed in this paper provides a compelling case for the inclusion of the neurodevelopmental spectrum into transdiagnostic frameworks of psychiatric conditions. Research and clinical practices have for too long focused on neurodevelopmental conditions in isolation, ignoring their high rates of co-occurrence with one another and other psychiatric conditions.

Our proposal promotes a shift towards a joint transdiagnostic and dimensional approach to neurodevelopmental and frequently co-occurring problems across development both in research and clinical settings. Future research and implementation work are needed, but our proposed approach can already be used to guide innovative studies and design transdiagnostic assessments and clinical protocols.

This approach can provide more accurate conceptualization, holistic assessment and individualized support for neurodevelopmental features alongside other frequently co-occurring conditions, thereby meeting the needs of each individual.

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REFERENCES

1. Arora NK, Nair MKC, Gulati S et al. Neurodevelopmental disorders in children aged 2-9 years: population-based burden estimates across five regions in India. PLoS Med 2018;15:e1002615.
2. Zablotsky B, Black LI, Maenner MJ et al. Prevalence and trends of developmental disabilities among children in the United States: 2009-2017. Pediatrics 2019;144:e20190811.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Washington: American Psychiatric Publishing, 2013.
4. World Health Organization. International classification of diseases, 11th revision. Geneva: World Health Organization, 2022.
5. Andrews G, Pine DS, Hobbs MJ et al. Neurodevelopmental disorders: cluster 2 of the proposed meta-structure for DSM-V and ICD-11. Psychol Med 2009;39:2013-23.
6. Andrews G, Goldberg DP, Krueger RF et al. Exploring the feasibility of a meta-structure for DSM-V and ICD-11: could it improve utility and validity? Psychol Med 2009;39:1993-2000.
7. Astle DE, Holmes J, Kievit R et al. Annual Research Review: The transdiagnostic revolution in neurodevelopmental disorders. J Child Psychol Psychiatry 2022;63:397-417.
8. Kotov R, Krueger RF, Watson D et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): a dimensional alternative to traditional nosologies. J Abnorm Psychol 2017;126:454-77.
9. Michelini G, Palumbo IM, DeYoung CG et al. Linking RDoC and HiTOP: a new interface for advancing psychiatric nosology and neuroscience. Clin Psychol Rev 2021;86:102025.
10. Lahey BB, Tiemeier H, Krueger RF. Seven reasons why binary diagnostic categories should be replaced with empirically sounder and less stigmatizing dimensions. JCPP Adv 2022;2:e12108.
11. Uher R, Rutter M. Basing psychiatric classification on scientific foundation: problems and prospects. Int Rev Psychiatry 2012;24:591-605.

12. Lahey BB, Moore TM, Kaczkurkin AN et al. Hierarchical models of psychopathology: empirical support, implications, and remaining issues. World Psychiatry 2021;20:57-63.
13. Doyle CM, Lasch C, Vollman EP et al. Phenoscreening: a developmental approach to Research Domain Criteria-motivated sampling. J Child Psychol Psychiatry 2021;62:884-94.
14. Lahey BB, Krueger RF, Rathouz PJ et al. A hierarchical causal taxonomy of psychopathology across the life span. Psychol Bull 2017;143:142-86.
15. Cuthbert BN. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry 2014;13:28-35.
16. Sanislow CA, Morris SE, Cuthbert BN et al. Development and environment in the National Institute of Mental Health (NIMH) Research Domain Criteria. J Psychopathol Clin Sci 2022;131:653-9.
17. Kotov R, Jonas KG, Carpenter WT et al. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): I. Psychosis superspectrum. World Psychiatry 2020;19:151-72.
18. Krueger RF, Hobbs KA, Conway CC et al. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): II. Externalizing superspectrum. World Psychiatry 2021;20:171-93.
19. Watson D, Levin-Aspenson HF, Waszczuk MA et al. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): III. Emotional dysfunction superspectrum. World Psychiatry 2022;21:26-54.
20. Caspi A, Houts RM, Belsky DW et al. The p factor: one general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci 2014;2:119-37.
21. Achenbach TM, Ivanova MY, Rescorla LA. Empirically based assessment and taxonomy of psychopathology for ages 1½-90+ years: developmental, multi-informant, and multicultural findings. Compr Psychiatry 2017;79:4-18.
22. Casey BJ, Oliveri ME, Insel T. A neurodevelopmental perspective on the Research Domain Criteria (RDoC) framework. Biol Psychiatry 2014;76:350-3.
23. MacNeill LA, Allen NB, Poleon RB et al. Translating RDoC to real-world impact in developmental psychopathology: a neurodevelopmental framework for application of mental health risk calculators. Dev Psychopathol 2021;33:1665-84.
24. Dadds MR, Frick PJ. Toward a transdiagnostic model of common and unique processes leading to the major disorders of childhood: the REAL model of attention, responsiveness and learning. Behav Res Ther 2019;119:103410.
25. Michelini G, Barch DM, Tian Y et al. Delineating and validating higher-order dimensions of psychopathology in the Adolescent Brain Cognitive Development (ABCD) study. Transl Psychiatry 2019;9:261.
26. Knott R, Johnson BP, Tiego J et al. The Monash Autism-ADHD genetics and neurodevelopment (MAGNET) project design and methodologies: a dimensional approach to understanding neurobiological and genetic aetiology. Mol Autism 2021;12:55.
27. Baron-Cohen S. Editorial Perspective: Neurodiversity – a revolutionary concept for autism and psychiatry. J Child Psychol Psychiatry 2017;58:744-7.
28. Fletcher-Watson S. Transdiagnostic research and the neurodiversity paradigm: commentary on the transdiagnostic revolution in neurodevelopmental disorders by Astle et al. J Child Psychol Psychiatry 2022;63:418-20.
29. Sonuga-Barke E, Thapar A. The neurodiversity concept: is it helpful for clinicians and scientists? Lancet Psychiatry 2021;8:559-61.
30. Romero M, Aguilar JM, Del-Rey-Mejías Á et al. Psychiatric comorbidities in autism spectrum disorder: a comparative study between DSM-IV-TR and DSM-5 diagnosis. Int J Clin Health Psychol 2016;16:266-75.
31. Franke B, Michelini G, Asherson P et al. Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. Eur Neuropsychopharmacol 2018;28:1059-88.
32. Emerging Minds. Embracing complexity in neurodevelopment research. https://emergingminds.org.uk.
33. Embracing Complexity. Towards new approaches for supporting people with neurodevelopmental conditions. https://embracingcomplexity.org.uk.
34. Bisset M, Brown LE, Bhide S et al. Practitioner Review: It's time to bridge the gap – understanding the unmet needs of consumers with attention-deficit/hyperactivity disorder – a systematic review and recommendations. J Child Psychol Psychiatry 2023;64:848-58.
35. Pukki H, Bettin J, Outlaw AG et al. Autistic perspectives on the future of clinical autism research. Autism Adulthood 2022;4:93-101.
36. Tunç B, Pandey J, St John T et al. Diagnostic shifts in autism spectrum disorder can be linked to the fuzzy nature of the diagnostic boundary: a data-driven approach. J Child Psychol Psychiatry 2021;62:1236-45.
37. Chien YL, Lin HY, Tung YH et al. Neurodevelopmental model of schizophrenia revisited: similarity in individual deviation and idiosyncrasy from the normative model of whole-brain white matter tracts and shared brain-cognition covariation with ADHD and ASD. Mol Psychiatry 2022;27:3262-71.
38. Owen MJ, O'Donovan MC. Schizophrenia and the neurodevelopmental continuum: evidence from genomics. World Psychiatry 2017;16:227-35.
39. Trickett J, Heald M, Oliver C et al. A cross-syndrome cohort comparison of sleep disturbance in children with Smith-Magenis syndrome, Angelman syndrome, autism spectrum disorder and tuberous sclerosis complex. J Neurodev Disord 2018;10:9.
40. Dewey D. What is comorbidity and why does it matter in neurodevelopmental disorders? Curr Develop Disord Rep 2018;5:235-42.
41. Rosen NE, Lord C, Volkmar FR. The diagnosis of autism: from Kanner to DSM-III to DSM-5 and beyond. J Autism Dev Disord 2021;51:4253-70.
42. Holmes J, Mareva S, Bennett MP et al. Higher-order dimensions of psychopathology in a neurodevelopmental transdiagnostic sample. J Abnorm Psychol 2021;130:909-22.
43. Riglin L, Thapar AK, Leppert B et al. Using genetics to examine a general liability to childhood psychopathology. Behav Genet 2020;50:213-20.
44. Du Rietz E, Pettersson E, Brikell I et al. Overlap between attention-deficit hyperactivity disorder and neurodevelopmental, externalising and internalising disorders: separating unique from general psychopathology effects. Br J Psychiatry 2021;218:35-42.
45. Pettersson E, Larsson H, D'Onofrio B et al. Association of fetal growth with general and specific mental health conditions. JAMA Psychiatry 2019;76:536-43.
46. Pettersson E, Larsson H, D'Onofrio BM et al. Associations between general and specific psychopathology factors and 10-year clinically relevant outcomes in adult Swedish twins and siblings. JAMA Psychiatry 2023;80:728-37.
47. Forbes MK, Baillie AJ, Batterham P et al. Reconstructing psychopathology: a data-driven reorganization of the symptoms in DSM-5. https://osf.io/preprints/psyarxiv/7um9a.
48. Martin J, Hamshere ML, Stergiakouli E et al. Neurocognitive abilities in the general population and composite genetic risk scores for attention-deficit hyperactivity disorder. J Child Psychol Psychiatry 2015;56:648-56.
49. Addicoat A, Thapar AK, Riglin L et al. Adult mood problems in children with neurodevelopmental problems: evidence from a prospective birth cohort followed to age 50. Soc Psychiatry Psychiatr Epidemiol 2020;55:351-8.
50. Noordhof A, Krueger RF, Ormel J et al. Integrating autism-related symptoms into the dimensional internalizing and externalizing model of psychopathology. The TRAILS Study. J Abnorm Child Psychol 2015;43:577-87.
51. Bloemen AJP, Oldehinkel AJ, Laceulle OM et al. The association between executive functioning and psychopathology: general or specific? Psychol Med 2018;48:1787-94.
52. Hartman CA, Luteijn E, Serra M et al. Refinement of the Children's Social Behavior Questionnaire (CSBQ): an instrument that describes the diverse problems seen in milder forms of PDD. J Autism Dev Disord 2006;36:325-42.
53. Stanton K, DeLucia EA, Brown MFD et al. Advancing understanding of the classification of broad autism phenotype and attention-deficit/hyperactivity disorder symptom dimensions within the Hierarchical Taxonomy of Psychopathology. Personal Ment Health 2021;15:113-23.
54. Stanton K, Khoo S, McDonnell CG et al. An initial investigation of the joint classification of hypomania- and neurodevelopmental disorder-relevant dimensions within the Hierarchical Taxonomy of Psychopathology. Assessment 2023;30:414-32.
55. Slobodskaya HR. The hierarchical structure of personality and common psychopathology in childhood. J Res Pers 2014;53:36-46.
56. Carragher N, Krueger RF, Eaton NR et al. ADHD and the externalizing spectrum: direct comparison of categorical, continuous, and hybrid models of liability in a nationally representative sample. Soc Psychiatry Psychiatr Epidemiol 2014;49:1307-17.
57. Carragher N, Teesson M, Sunderland M et al. The structure of adolescent psychopathology: a symptom-level analysis. Psychol Med 2016;46:981-94.
58. Hewitt JK, Rutter M, Simonoff E et al. Genetics and developmental psychopathology: 1. Phenotypic assessment in the Virginia Twin Study of Adolescent Behavioral Development. J Child Psychol Psychiatry 1997;38:943-63.
59. Laceulle OM, Vollebergh WAM, Ormel J. The structure of psychopathology in adolescence: replication of a general psychopathology factor in the TRAILS Study. Clin Psychol Sci 2015;3:850-60.
60. Lahey BB, Zald DH, Perkins SF et al. Measuring the hierarchical general factor model of psychopathology in young adults. Int J Methods Psychiatr Res 2018;27:e1593.
61. Martel MM, Pan PM, Hoffmann MS et al. A general psychopathology factor (p factor) in children: structural model analysis and external validation through familial risk and child global executive function. J Abnorm Psychol 2017;126:137-48.

62. Snyder HR, Young JF, Hankin BL. Strong homotypic continuity in common psychopathology-, internalizing-, and externalizing-specific factors over time in adolescents. Clin Psychol Sci 2017;5:98-110.
63. Schweizer TH, Snyder HR, Young JF et al. The breadth and potency of transdiagnostic cognitive risks for psychopathology in youth. J Consult Clin Psychol 2020;88:196-211.
64. Afzali MH, Sunderland M, Carragher N et al. The structure of psychopathology in early adolescence: study of a Canadian sample. Can J Psychiatry 2018;63:223-30.
65. Achenbach TM. The classification of children's psychiatric symptoms: a factor-analytic study. Psychol Monogr 1966;80:1-37.
66. Ivanova MY, Achenbach TM, Dumenci L et al. Testing the 8-syndrome structure of the Child Behavior Checklist in 30 societies. J Clin Child Adolesc Psychol 2007;36:405-17.
67. Ivanova MY, Achenbach TM, Rescorla LA et al. Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the Child Behavior Checklist for ages 1.5-5. J Am Acad Child Adolesc Psychiatry 2010;49:1215-24.
68. Ivanova MY, Achenbach TM, Rescorla LA et al. Syndromes of self-reported psychopathology for ages 18-59 in 29 societies. J Psychopathol Behav Assess 2015;37:171-83.
69. Ivanova MY, Achenbach TM, Rescorla LA et al. Testing syndromes of psychopathology in parent and youth ratings across societies. J Clin Child Adolesc Psychol 2019;48:596-609.
70. McElroy E, Belsky J, Carragher N et al. Developmental stability of general and specific factors of psychopathology from early childhood to adolescence: dynamic mutualism or p-differentiation? J Child Psychol Psychiatry 2018;59:667-75.
71. Haltigan JD, Aitken M, Skilling T et al. "P" and "DP": examining symptom-level bifactor models of psychopathology and dysregulation in clinically referred children and adolescents. J Am Acad Child Adolesc Psychiatry 2018;57:384-96.
72. Hartman CA, Hox J, Mellenbergh GJ et al. DSM-IV internal construct validity: when a taxonomy meets data. J Child Psychol Psychiatry 2001;42:817-36.
73. Murray AL, Eisner M, Ribeaud D. The development of the general factor of psychopathology 'p factor' through childhood and adolescence. J Abnorm Child Psychol 2016;44:1573-86.
74. Niarchou M, Moore TM, Tang SX et al. The dimensional structure of psychopathology in 22q11.2 deletion syndrome. J Psychiatr Res 2017;92:124-31.
75. Pettersson E, Lahey BB, Larsson H et al. Criterion validity and utility of the general factor of psychopathology in childhood: predictive associations with independently measured severe adverse mental health outcomes in adolescence. J Am Acad Child Adolesc Psychiatry 2018;57:372-83.
76. Moore TM, Kaczkurkin AN, Durham EL et al. Criterion validity and relationships between alternative hierarchical dimensional models of general and specific psychopathology. J Abnorm Psychol 2020;129:677-88.
77. Miller M, Iosif AM, Young GS et al. The dysregulation profile in preschoolers with and without a family history of autism spectrum disorder. J Child Psychol Psychiatry 2019;60:516-23.
78. Clark DA, Hicks BM, Angstadt M et al. The general factor of psychopathology in the Adolescent Brain Cognitive Development (ABCD) study: a comparison of alternative modeling approaches. Clin Psychol Sci 2021;9:169-82.
79. Lahey BB, Applegate B, Waldman ID et al. The structure of child and adolescent psychopathology: generating new hypotheses. J Abnorm Psychol 2004;113:358-85.
80. Farmer RF, Seeley JR, Kosty DB et al. Hierarchical organization of axis I psychiatric disorder comorbidity through age 30. Compr Psychiatry 2013;54:523-32.
81. Ameringer KJ, Chou CP, Sussman S et al. Identifying shared latent dimensions of psychological symptoms: implications for the psychological correlates of smoking. J Psychopathol Behav Assess 2015;37:454-68.
82. Blanco C, Wall MM, He JP et al. The space of common psychiatric disorders in adolescents: comorbidity structure and individual latent liabilities. J Am Acad Child Adolesc Psychiatry 2015;54:45-52.
83. Caspi A, Houts RM, Ambler A et al. Longitudinal assessment of mental health disorders and comorbidities across 4 decades among participants in the Dunedin Birth Cohort Study. JAMA Netw Open 2020;3:e203221.
84. Cosgrove VE, Rhee SH, Gelhorn HL et al. Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. J Abnorm Child Psychol 2011;39:109-23.
85. Doyle MM, Murphy J, Shevlin M. Competing factor models of child and adolescent psychopathology. J Abnorm Child Psychol 2016;44:1559-71.
86. Forbush KT, Watson D. The structure of common and uncommon mental disorders. Psychol Med 2013;43:97-108.
87. Lahey BB, Rathouz PJ, Keenan K et al. Criterion validity of the general factor of psychopathology in a prospective study of girls. J Child Psychol Psychiatry 2015;56:415-22.
88. Tackett JL, Lahey BB, van Hulle C et al. Common genetic influences on negative emotionality and a general psychopathology factor in childhood and adolescence. J Abnorm Psychol 2013;122:1142-53.
89. Witkiewitz K, King K, McMahon RJ et al. Evidence for a multi-dimensional latent structural model of externalizing disorders. J Abnorm Child Psychol 2013;41:223-37.
90. Asherson P, Akehurst R, Kooij JJS et al. Under diagnosis of adult ADHD: cultural influences and societal burden. J Atten Disord 2012;16(Suppl. 5):20S-38S.
91. Antshel KM, Zhang-James Y, Wagner KE et al. An update on the comorbidity of ADHD and ASD: a focus on clinical management. Expert Rev Neurother 2016;16:279-93.
92. Gidziela A, Ahmadzadeh YI, Michelini G et al. Genetic influences on neurodevelopmental disorders and their overlap with co-occurring conditions in childhood and adolescence: a meta-analysis. medRxiv 2022;2022.02.17.22271089.
93. Imamura A, Morimoto Y, Ono S et al. Genetic and environmental factors of schizophrenia and autism spectrum disorder: insights from twin studies. J Neural Transm 2020;127:1501-15.
94. Taylor MJ, Robinson EB, Happé F et al. A longitudinal twin study of the association between childhood autistic traits and psychotic experiences in adolescence. Mol Autism 2015;6:44.
95. Tistarelli N, Fagnani C, Troianiello M et al. The nature and nurture of ADHD and its comorbidities: a narrative review on twin studies. Neurosci Biobehav Rev 2020;109:63-77.
96. Michelini G, Eley TC, Gregory AM et al. Aetiological overlap between anxiety and attention deficit hyperactivity symptom dimensions in adolescence. J Child Psychol Psychiatry 2015;56:423-31.
97. Arnett AB, Cairney BE, Wallace AS et al. Comorbid symptoms of inattention, autism, and executive cognition in youth with putative genetic risk. J Child Psychol Psychiatry 2018;59:268-76.
98. Faraone SV, Ghirardi L, Kuja-Halkola R et al. The familial co-aggregation of attention-deficit/hyperactivity disorder and intellectual disability: a register-based family study. J Am Acad Child Adolesc Psychiatry 2017;56:167-74.
99. Ghirardi L, Brikell I, Kuja-Halkola R et al. The familial co-aggregation of ASD and ADHD: a register-based cohort study. Mol Psychiatry 2018;23:257-62.
100. Ghirardi L, Pettersson E, Taylor MJ et al. Genetic and environmental contribution to the overlap between ADHD and ASD trait dimensions in young adults: a twin study. Psychol Med 2019;49:1713-21.
101. Ghirardi L, Kuja-Halkola R, Butwicka A et al. Familial and genetic associations between autism spectrum disorder and other neurodevelopmental and psychiatric disorders. J Child Psychol Psychiatry 2021;62:1274-84.
102. Moruzzi S, Pesenti-Gritti P, Brescianini S et al. Clumsiness and psychopathology: causation or shared etiology? A twin study with the CBCL 6-18 questionnaire in a general school-age population sample. Hum Mov Sci 2010;29:326-38.
103. Ronald A, Larsson H, Anckarsäter H et al. Symptoms of autism and ADHD: a Swedish twin study examining their overlap. J Abnorm Psychol 2014;123:440-51.
104. Stergiakouli E, Davey Smith G, Martin J et al. Shared genetic influences between dimensional ASD and ADHD symptoms during child and adolescent development. Mol Autism 2017;8:18.
105. Pettersson E, Anckarsäter H, Gillberg C et al. Different neurodevelopmental symptoms have a common genetic etiology. J Child Psychol Psychiatry 2013;54:1356-65.
106. Posthuma D, Polderman TJC. What have we learned from recent twin studies about the etiology of neurodevelopmental disorders? Curr Opin Neurol 2013;26:111-21.
107. Demontis D, Walters GB, Athanasiadis G et al. Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. Nat Genet 2023;55:198-208.
108. Grove J, Ripke S, Als TD et al. Identification of common genetic risk variants for autism spectrum disorder. Nat Genet 2019;51:431-44.
109. Peyre H, Schoeler T, Liu C et al. Combining multivariate genomic approaches to elucidate the comorbidity between autism spectrum disorder and attention deficit hyperactivity disorder. J Child Psychol Psychiatry 2021;62:1285-96.
110. Wu Y, Cao H, Baranova A et al. Multi-trait analysis for genome-wide association study of five psychiatric disorders. Transl Psychiatry 2020;10:209.
111. Yang Z, Wu H, Lee PH et al. Investigating shared genetic basis across Tourette syndrome and comorbid neurodevelopmental disorders along the impulsivity-compulsivity spectrum. Biol Psychiatry 2021;90:317-27.
112. Grotzinger AD, Rhemtulla M, de Vlaming R et al. Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. Nat Hum Behav 2019;3:513-25.

113. Grotzinger AD, Mallard TT, Akingbuwa WA et al. Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic and molecular genetic levels of analysis. Nat Genet 2022;54:548-59.
114. Li JJ, He Q, Wang Z et al. Enhancing the discriminatory power of ADHD and autism spectrum disorder polygenic scores in clinical and non-clinical samples. medRxiv 2022;2022.02.09.22270697.
115. Waldman ID, Poore HE, Luningham JM et al. Testing structural models of psychopathology at the genomic level. World Psychiatry 2020;19:350-9.
116. Schreiweis C, Bornschein U, Burguière E et al. Humanized Foxp2 accelerates learning by enhancing transitions from declarative to procedural performance. Proc Natl Acad Sci USA 2014;111:14253-8.
117. Sia GM, Clem RL, Huganir RL. The human language-associated gene SRPX2 regulates synapse formation and vocalization in mice. Science 2013;342:987-91.
118. Tsui D, Vessey JP, Tomita H. FoxP2 regulates neurogenesis during embryonic cortical development. J Neurosci 2013;33:244-58.
119. Breiderhoff T, Christiansen GB, Pallesen LT et al. Sortilin-related receptor SORCS3 is a postsynaptic modulator of synaptic depression and fear extinction. PLoS One 2013;8:e75006.
120. Demontis D, Walters RK, Martin J et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet 2019;51:63-75.
121. Qu X, Wei H, Zhai Y et al. Identification, characterization, and functional study of the two novel human members of the semaphorin gene family. J Biol Chem 2002;277:35574-85.
122. Le Meur N, Holder-Espinasse M, Jaillard S et al. MEF2C haploinsufficiency caused by either microdeletion of the 5q14.3 region or mutation is responsible for severe mental retardation with stereotypic movements, epilepsy and/or cerebral malformations. J Med Genet 2010;47:22-9.
123. Novara F, Beri S, Giorda R et al. Refining the phenotype associated with MEF2C haploinsufficiency. Clin Genet 2010;78:471-7.
124. Sobreira N, Walsh MF, Batista D et al. Interstitial deletion 5q14.3-q21 associated with iris coloboma, hearing loss, dental anomaly, moderate intellectual disability, and attention deficit and hyperactivity disorder. Am J Med Genet 2009;149A:2581-3.
125. Zoghbi HY, Bear MF. Synaptic dysfunction in neurodevelopmental disorders associated with autism and intellectual disabilities. Cold Spring Harb Perspect Biol 2012;4:a009886.
126. Martin J, Hamshere ML, Stergiakouli E et al. Genetic risk for attention-deficit/hyperactivity disorder contributes to neurodevelopmental traits in the general population. Biol Psychiatry 2014;76:664-71.
127. Stergiakouli E, Martin J, Hamshere ML et al. Association between polygenic risk scores for attention-deficit hyperactivity disorder and educational and cognitive outcomes in the general population. Int J Epidemiol 2017;46:421-8.
128. Askeland RB, Hannigan LJ, Ask H et al. Early manifestations of genetic risk for neurodevelopmental disorders. J Child Psychol Psychiatry 2022;63:810-9.
129. Waszczuk MA, Miao J, Docherty AR et al. General v. specific vulnerabilities: polygenic risk scores and higher-order psychopathology dimensions in the Adolescent Brain Cognitive Development (ABCD) study. Psychol Med 2023;53:1937-46.
130. Carlsson T, Molander F, Taylor MJ et al. Early environmental risk factors for neurodevelopmental disorders – a systematic review of twin and sibling studies. Dev Psychopathol 2021;33:1448-95.
131. Kim JH, Kim JY, Lee J et al. Environmental risk factors, protective factors, and peripheral biomarkers for ADHD: an umbrella review. Lancet Psychiatry 2020;7:955-70.
132. Lund JI, Boles K, Radford A et al. A systematic review of childhood adversity and executive functions outcomes among adults. Arch Clin Neuropsychol 2022;37:1118-32.
133. Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology 2011;214:55-70.
134. van Hoorn JF, Schoemaker MM, Stuive I et al. Risk factors in early life for developmental coordination disorder: a scoping review. Dev Med Child Neurol 2021;63:511-9.
135. Crump C, Sundquist J, Sundquist K. Preterm or early term birth and risk of autism. Pediatrics 2021;148:e2020032300.
136. James SN, Rommel AS, Cheung C et al. Association of preterm birth with ADHD-like cognitive impairments and additional subtle impairments in attention and arousal malleability. Psychol Med 2018;48:1484-93.
137. Albores-Garcia D, McGlothan JL, Guilarte TR. Early-life lead exposure and neurodevelopmental disorders. Curr Opin Toxicol 2021;26:22-7.
138. Delgado CF, Ullery MA, Jordan M et al. Lead exposure and developmental disabilities in preschool-aged children. J Public Health Manag Pract 2018;24:e10-7.
139. He J, Ning H, Huang R. Low blood lead levels and attention-deficit hyperactivity disorder in children: a systematic review and meta-analysis. Environ Sci Pollut Res Int 2019;26:17875-84.
140. Imbriani G, Panico A, Grassi T et al. Early-life exposure to environmental air pollution and autism spectrum disorder: a review of available evidence. Int J Environ Res Public Health 2021;18:1204.
141. Saghazadeh A, Rezaei N. Systematic review and meta-analysis links autism and toxic metals and highlights the impact of country development status: higher blood and erythrocyte levels for mercury and lead, and higher hair antimony, cadmium, lead, and mercury. Prog Neuropsychopharmacol Biol Psychiatry 2017;79:340-68.
142. Alameda L, Christy A, Rodriguez V et al. Association between specific childhood adversities and symptom dimensions in people with psychosis: systematic review and meta-analysis. Schizophr Bull 2021;47:975-85.
143. James SN, Rommel AS, Rijsdijk F et al. Is association of preterm birth with cognitive-neurophysiological impairments and ADHD symptoms consistent with a causal inference or due to familial confounds? Psychol Med 2020;50:1278-84.
144. Nelson HD, Nygren P, Walker M et al. Screening for speech and language delay in preschool children: systematic evidence review for the US Preventive Services Task Force. Pediatrics 2006;117:e298-319.
145. Johnson MH, Gliga T, Jones E et al. Annual Research Review: Infant development, autism, and ADHD – early pathways to emerging disorders. J Child Psychol Psychiatry 2015;56:228-47.
146. Thapar A, Cooper M, Rutter M. Neurodevelopmental disorders. Lancet Psychiatry 2017;4:339-46.
147. Ozonoff S, Gangi D, Hanzel EP et al. Onset patterns in autism: variation across informants, methods, and timing. Autism Res 2018;11:788-97.
148. Lee EJ, Zwicker JG. Early identification of children with/at risk of developmental coordination disorder: a scoping review. Dev Med Child Neurol 2021;63:649-58.
149. Sansavini A, Favilla ME, Guasti MT et al. Developmental language disorder: early predictors, age for the diagnosis, and diagnostic tools. a scoping review. Brain Sci 2021;11:654.
150. Cervin M. Developmental signs of ADHD and autism: a prospective investigation in 3623 children. Eur Child Adolesc Psychiatry 2023;32:1969-78.
151. Lohvansuu K, Torppa M, Ahonen T et al. Unveiling the mysteries of dyslexia – lessons learned from the prospective Jyväskylä longitudinal study of dyslexia. Brain Sci 2021;11:427.
152. Solmi M, Radua J, Olivola M et al. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol Psychiatry 2022;27:281-95.
153. Hassan N, Cavanna AE. The prognosis of Tourette syndrome: implications for clinical practice. Funct Neurol 2012;27:23-7.
154. Mason D, Capp SJ, Stewart GR et al. A meta-analysis of outcome studies of autistic adults: quantifying effect size, quality, and meta-regression. J Autism Dev Disord 2021;51:3165-79.
155. Agnew-Blais JC, Polanczyk GV, Danese A et al. Evaluation of the persistence, remission, and emergence of attention-deficit/hyperactivity disorder in young adulthood. JAMA Psychiatry 2016;73:713-20.
156. Asherson P, Buitelaar J, Faraone SV et al. Adult attention-deficit hyperactivity disorder: key conceptual issues. Lancet Psychiatry 2016;3:568-78.
157. Caye A, Rocha TB, Anselmi L et al. Attention-deficit/hyperactivity disorder trajectories from childhood to young adulthood: evidence from a birth cohort supporting a late-onset syndrome. JAMA Psychiatry 2016;73:705-12.
158. Goulardins JB, Rigoli D, Licari M et al. Attention deficit hyperactivity disorder and developmental coordination disorder: two separate disorders or do they share a common etiology. Behav Brain Res 2015;292:484-92.
159. May T, Brignell A, Williams K. Parent-reported autism diagnostic stability and trajectories in the longitudinal study of Australian children. Autism Res 2021;14:773-86.
160. Breda V, Rohde LA, Menezes AMB et al. The neurodevelopmental nature of attention-deficit hyperactivity disorder in adults. Br J Psychiatry 2021;218:43-50.
161. Sibley MH, Mitchell JT, Becker SP. Method of adult diagnosis influences estimated persistence of childhood ADHD: a systematic review of longitudinal studies. Lancet Psychiatry 2016;3:1157-65.
162. Dubois P, St-Pierre MC, Desmarais C et al. Young adults with developmental language disorder: a systematic review of education, employment, and independent living outcomes. J Speech Lang Hear Res 2020;63:3786-800.
163. Riglin L, Leppert B, Langley K et al. Investigating attention-deficit hyperactivity

disorder and autism spectrum disorder traits in the general population: what happens in adult life? Child Psychol Psychiatry 2021;62:449-57.
164. Pingault JB, Viding E, Galera C et al. Genetic and environmental influences on the developmental course of attention-deficit/hyperactivity disorder symptoms from childhood to adolescence. JAMA Psychiatry 2015;72:651-8.
165. Nigg JT, Sibley MH, Thapar A et al. Development of ADHD: etiology, heterogeneity, and early life course. Annu Rev Dev Psychol 2020;2:559-83.
166. Riglin L, Wootton RE, Thapar AK et al. Variable emergence of autism spectrum disorder symptoms from childhood to early adulthood. Am J Psychiatry 2021; 178:752-60.
167. Bathelt J, Vignoles A, Astle DE. Just a phase? Mapping the transition of behavioural problems from childhood to adolescence. Soc Psychiatry Psychiatr Epidemiol 2021;56:821-36.
168. Cheung CH, Rijsdijk F, McLoughlin G et al. Childhood predictors of adolescent and young adult outcome in ADHD. J Psychiatr Res 2015;62:92-100.
169. Boström P, Broberg M, Hwang CP. Different, difficult or distinct? Mothers' and fathers' perceptions of temperament in children with and without intellectual disabilities. J Intellect Disabil Res 2010;54:806-19.
170. Chetcuti L, Uljarević M, Varcin KJ et al. Caregiver psychological distress predicts temperament and social-emotional outcomes in infants with autism traits. Res Child Adolesc Psychopathol 2021;49:1669-81.
171. Conture EG, Kelly EM, Walden TA. Temperament, speech and language: an overview. J Commun Disord 2013;46:125-42.
172. Foley M, McClowry SG, Castellanos FX. The relationship between attention deficit hyperactivity disorder and child temperament. J Appl Dev Psychol 2008; 29:157-69.
173. Gomez R, Corr PJ. ADHD and personality: a meta-analytic review. Clin Psychol Rev 2014;34:376-88.
174. Jacobsson P, Hopwood CJ, Söderpalm B et al. Adult ADHD and emerging models of maladaptive personality: a meta-analytic review. BMC Psychiatry 2021; 21:282.
175. Mousavi F, Rozsa S, Nilsson T et al. Personality and intelligence: persistence, not self-directedness, cooperativeness or self-transcendence, is related to twins' cognitive abilities. PeerJ 2015;3:e1195.
176. Nakagawa A, Sukigara M, Miyachi T et al. Relations between temperament, sensory processing, and motor coordination in 3-year-old children. Front Psychol 2016;7:623.
177. Nigg JT, Goldsmith HH, Sachek J. Temperament and attention deficit hyperactivity disorder: the development of a multiple pathway model. J Clin Child Adolesc Psychol 2004;33:42-53.
178. Sung S, Fenoglio A, Wolff JJ et al. Examining the factor structure and discriminative utility of the Infant Behavior Questionnaire-Revised in infant siblings of autistic children. Child Dev 2022;93:1398-413.
179. Visser JC, Rommelse NNJ, Greven CU et al. Autism spectrum disorder and attention-deficit/hyperactivity disorder in early childhood: a review of unique and shared characteristics and developmental antecedents. Neurosci Biobehav Rev 2016;65:229-63.
180. Anckarsater H, Stahlberg O, Larson T et al. The impact of ADHD and autism spectrum disorders on temperament, character, and personality development. Am J Psychiatry 2006;163:1239-44.
181. Strunz S, Westphal L, Ritter K et al. Personality pathology of adults with autism spectrum disorder without accompanying intellectual impairment in comparison to adults with personality disorders. J Autism Dev Disord 2015;45:4026-38.
182. Forbes MK, Rapee RM, Camberis AL et al. Unique associations between childhood temperament characteristics and subsequent psychopathology symptom trajectories from childhood to early adolescence. J Abnorm Child Psychol 2017;45:1221-33.
183. Garon N, Zwaigenbaum L, Bryson S et al. Temperament and its association with autism symptoms in a high-risk population. J Abnorm Child Psychol 2016; 44:757-69.
184. Olino TM, Finsaas MC, Dyson MW et al. A multimethod, multiinformant study of early childhood temperament and depression and anxiety symptoms in adolescence. J Psychopathol Clin Sci 2022;131:741-53.
185. Mouga S, Café C, Almeida J et al. Intellectual profiles in the autism spectrum and other neurodevelopmental disorders. J Autism Dev Disord 2016;46:2940-55.
186. Debes NMMM, Lange T, Jessen TL et al. Performance on Wechsler intelligence scales in children with Tourette syndrome. Eur J Paediatr Neurol 2011;15:146-54.
187. Kuntsi J, Eley TC, Taylor A et al. Co-occurrence of ADHD and low IQ has genetic origins. Am J Med Genet Neuropsychiatr Genet 2004;124B:41-7.
188. Cheung CH, Frazier-Wood AC, Asherson P et al. Shared cognitive impairments and aetiology in ADHD symptoms and reading difficulties. PLoS One 2014;9: e98590.
189. Gonzalez-Gadea ML, Baez S, Torralva T et al. Cognitive variability in adults with ADHD and AS: disentangling the roles of executive functions and social cognition. Res Dev Disabil 2013;34:817-30.
190. Romer AL, Pizzagalli DA. Is executive dysfunction a risk marker or consequence of psychopathology? A test of executive function as a prospective predictor and outcome of general psychopathology in the Adolescent Brain Cognitive Development study. Dev Cogn Neurosci 2021;51:100994.
191. Karalunas SL, Hawkey E, Gustafsson H et al. Overlapping and distinct cognitive impairments in attention-deficit/hyperactivity and autism spectrum disorder without intellectual disability. J Abnorm Child Psychol 2018;46:1705-16.
192. van der Meer JMJ, Oerlemans AM, van Steijn DJ et al. Are autism spectrum disorder and attention-deficit/hyperactivity disorder different manifestations of one overarching disorder? Cognitive and symptom evidence from a clinical and population-based sample. J Am Acad Child Adolesc Psychiatry 2012;51: 1160-72.
193. Cavanna AE, Ganos C, Hartmann A et al. The cognitive neuropsychiatry of Tourette syndrome. Cogn Neuropsychiatry 2020;25:254-68.
194. Lachambre C, Proteau-Lemieux M, Lepage JF et al. Attentional and executive functions in children and adolescents with developmental coordination disorder and the influence of comorbid disorders: a systematic review of the literature. PLoS One 2021;16:e0252043.
195. Ullman MT, Earle FS, Walenski M et al. The neurocognition of developmental disorders of language. Annu Rev Psychol 2020;71:389-417.
196. Baron-Cohen S, Ashwin E, Ashwin C et al. Talent in autism: hyper-systemizing, hyper-attention to detail and sensory hypersensitivity. Philos Trans R Soc Lond B Biol Sci 2009;364:1377-83.
197. Ward J. Individual differences in sensory sensitivity: a synthesizing framework and evidence from normal variation and developmental conditions. Cogn Neurosci 2019;10:139-57.
198. Shephard E, Zuccolo PF, Idrees I et al. Systematic review and meta-analysis: the science of early-life precursors and interventions for attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2022;61:187-226.
199. Huisman-van Dijk HM, van de Schoot R, Rijkeboer MM. The relationship between tics, OC, ADHD and autism symptoms: a cross-disorder symptom analysis in Gilles de la Tourette syndrome patients and family-members. Psychiatry Res 2016;237:138-46.
200. Korrel H, Mueller KL, Silk T et al. Research Review: Language problems in children with attention-deficit hyperactivity disorder – a systematic meta-analytic review. J Child Psychol Psychiatry 2017;58:640-54.
201. Mikami AY, Miller M, Lerner MD. Social functioning in youth with attention-deficit/hyperactivity disorder and autism spectrum disorder: transdiagnostic commonalities and differences. Clin Psychol Rev 2019;68:54-70.
202. Parhiala P, Torppa M, Eklund K et al. Psychosocial functioning of children with and without dyslexia: a follow-up study from ages four to nine. Dyslexia 2015; 21:197-211.
203. Leekam S. Social cognitive impairment and autism: what are we trying to explain? Philos Trans R Soc Lond B Biol Sci 2016;371:20150082.
204. Thye MD, Bednarz HM, Herringshaw AJ et al. The impact of atypical sensory processing on social impairments in autism spectrum disorder. Dev Cogn Neurosci 2018;29:151-67.
205. Cervantes PE, Matson JL, Adams HL et al. Comparing social skill profiles of children with autism spectrum disorders versus children with attention deficit hyperactivity disorder: where the deficits lie. Res Autism Spectr Disord 2013;7: 1104-10.
206. Ros R, Graziano PA. A transdiagnostic examination of self-regulation: comparisons across preschoolers with ASD, ADHD, and typically developing children. J Clin Child Adolesc Psychol 2020;49:493-508.
207. Berkovits L, Eisenhower A, Blacher J. Emotion regulation in young children with autism spectrum disorders. J Autism Dev Disord 2017;47:68-79.
208. Banaschewski T, Jennen-Steinmetz C, Brandeis D et al. Neuropsychological correlates of emotional lability in children with ADHD. J Child Psychol Psychiatry 2012;53:1139-48.
209. Waldman ID. Aggressive boys' hostile perceptual and response biases: the role of attention and impulsivity. Child Dev 1996;67:1015-33.
210. Harden KP, Engelhardt LE, Mann FD et al. Genetic associations between executive functions and a general factor of psychopathology. J Am Acad Child Adolesc Psychiatry 2020;59:749-58.
211. Ogilvie JM, Stewart AL, Chan RC et al. Neuropsychological measures of executive function and antisocial behavior: a meta-analysis. Criminology 2011;49: 1063-107.
212. Schoemaker K, Mulder H, Deković M et al. Executive functions in preschool children with externalizing behavior problems: a meta-analysis. J Abnorm

Child Psychol 2013;41:457-71.
213. Aoki Y, Yoncheva YN, Chen B et al. Association of white matter structure with autism spectrum disorder and attention-deficit/hyperactivity disorder. JAMA Psychiatry 2017;74:1120-8.
214. Lake EMR, Finn ES, Noble SM et al. The functional brain organization of an individual allows prediction of measures of social abilities transdiagnostically in autism and attention-deficit/hyperactivity disorder. Biol Psychiatry 2019;86:315-26.
215. Hettwer MD, Larivière S, Park BY et al. Coordinated cortical thickness alterations across six neurodevelopmental and psychiatric disorders. Nat Commun 2022;13:6851.
216. McCutcheon RA, Pillinger T, Guo X et al. Shared and separate patterns in brain morphometry across transdiagnostic dimensions. Nat Mental Health 2023;1:55-65.
217. Cortese S, Solmi M, Michelini G et al. Candidate diagnostic biomarkers for neurodevelopmental disorders in children and adolescents: a systematic review. World Psychiatry 2023;22:129-49.
218. Carlisi CO, Norman LJ, Lukito SS et al. Comparative multimodal meta-analysis of structural and functional brain abnormalities in autism spectrum disorder and obsessive-compulsive disorder. Biol Psychiatry 2017;82:83-102.
219. Ecker C, Suckling J, Deoni SC et al. Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: a multicenter magnetic resonance imaging study. Arch Gen Psychiatry 2012;69:195-209.
220. Hoogman M, Bralten J, Hibar DP et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. Lancet Psychiatry 2017;4:310-9.
221. Lukito S, Norman L, Carlisi C et al. Comparative meta-analyses of brain structural and functional abnormalities during cognitive control in attention-deficit/hyperactivity disorder and autism spectrum disorder. Psychol Med 2020;50:894-919.
222. Norman LJ, Carlisi C, Lukito S et al. Structural and functional brain abnormalities in attention-deficit/hyperactivity disorder and obsessive-compulsive disorder: a comparative meta-analysis. JAMA Psychiatry 2016;73:815-25.
223. Shaw P, Eckstrand K, Sharp W et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci USA 2007;104:19649-54.
224. Dougherty CC, Evans DW, Myers SM et al. A comparison of structural brain imaging findings in autism spectrum disorder and attention-deficit hyperactivity disorder. Neuropsychol Rev 2016;26:25-43.
225. Cauda F, Geda E, Sacco K et al. Grey matter abnormality in autism spectrum disorder: an activation likelihood estimation meta-analysis study. J Neurol Neurosurg Psychiatry 2011;82:1304-13.
226. DeRamus TP, Kana RK. Anatomical likelihood estimation meta-analysis of grey and white matter anomalies in autism spectrum disorders. Neuroimage Clin 2015;7:525-36.
227. Frodl T, Skokauskas N. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatr Scand 2012;125:114-26.
228. Hoogman M, Muetzel R, Guimaraes JP et al. Brain imaging of the cortex in ADHD: a coordinated analysis of large-scale clinical and population-based samples. Am J Psychiatry 2019;176:531-42.
229. Nakao T, Radua J, Rubia K et al. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. Am J Psychiatry 2011;168:1154-63.
230. Nickl-Jockschat T, Habel U, Michel TM et al. Brain structure anomalies in autism spectrum disorder – a meta-analysis of VBM studies using anatomic likelihood estimation. Hum Brain Mapp 2012;33:1470-89.
231. van Rooij D, Anagnostou E, Arango C et al. Cortical and subcortical brain morphometry differences between patients with autism spectrum disorder and healthy individuals across the lifespan: results from the ENIGMA ASD Working Group. Am J Psychiatry 2018;175:359-69.
232. Via E, Radua J, Cardoner N et al. Meta-analysis of gray matter abnormalities in autism spectrum disorder: should Asperger disorder be subsumed under a broader umbrella of autistic spectrum disorder? Arch Gen Psychiatry 2011;68:409-18.
233. Kushki A, Anagnostou E, Hammill C et al. Examining overlap and homogeneity in ASD, ADHD, and OCD: a data-driven, diagnosis-agnostic approach. Transl Psychiatry 2019;9:318.
234. Boedhoe PSW, van Rooij D, Hoogman M et al. Subcortical brain volume, regional cortical thickness, and cortical surface area across disorders: findings from the ENIGMA ADHD, ASD, and OCD Working Groups. Am J Psychiatry 2020;177:834-43.
235. Opel N, Goltermann J, Hermesdorf M et al. Cross-disorder analysis of brain structural abnormalities in six major psychiatric disorders: a secondary analysis of mega- and meta-analytical findings from the ENIGMA Consortium. Biol Psychiatry 2020;88:678-86.
236. Radonjić NV, Hess JL, Rovira P et al. Structural brain imaging studies offer clues about the effects of the shared genetic etiology among neuropsychiatric disorders. Mol Psychiatry 2021;26:2101-10.
237. Badcock NA, Bishop DVM, Hardiman MJ et al. Co-localisation of abnormal brain structure and function in specific language impairment. Brain Lang 2012;120:310-20.
238. Lee JC, Nopoulos PC, Bruce Tomblin J. Abnormal subcortical components of the corticostriatal system in young adults with DLI: a combined structural MRI and DTI study. Neuropsychologia 2013;51:2154-61.
239. Liu Y, Miao W, Wang J et al. Structural abnormalities in early Tourette syndrome children: a combined voxel-based morphometry and tract-based spatial statistics study. PLoS One 2013;8:e76105.
240. Soriano-Mas C, Pujol J, Ortiz H et al. Age-related brain structural alterations in children with specific language impairment. Hum Brain Mapp 2009;30:1626-36.
241. Verhoeven JS, Rommel N, Prodi E et al. Is there a common neuroanatomical substrate of language deficit between autism spectrum disorder and specific language impairment? Cereb Cortex 2012;22:2263-71.
242. Wen F, Yan J, Yu L et al. Grey matter abnormalities in Tourette syndrome: an activation likelihood estimation meta-analysis. BMC Psychiatry 2021;21:184.
243. Hart H, Radua J, Nakao T et al. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA Psychiatry 2013;70:185-98.
244. McCarthy H, Skokauskas N, Frodl T. Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: a meta-analysis. Psychol Med 2014;44:869-80.
245. Chantiluke K, Barrett N, Giampietro V et al. Inverse effect of fluoxetine on medial prefrontal cortex activation during reward reversal in ADHD and autism. Cereb Cortex 2014;25:1757-70.
246. Chantiluke K, Barrett N, Giampietro V et al. Disorder-dissociated effects of fluoxetine on brain function of working memory in attention deficit hyperactivity disorder and autism spectrum disorder. Psychol Med 2014;45:1195-205.
247. Christakou A, Murphy CM, Chantiluke K et al. Disorder-specific functional abnormalities during sustained attention in youth with attention deficit hyperactivity disorder (ADHD) and with autism. Mol Psychiatry 2013;18:236-44.
248. Di Martino A, Zuo XN, Kelly C et al. Shared and distinct intrinsic functional network centrality in autism and attention-deficit/hyperactivity disorder. Biol Psychiatry 2013;74:623-32.
249. Maisog JM, Einbinder ER, Flowers DL et al. A meta-analysis of functional neuroimaging studies of dyslexia. Ann N Y Acad Sci 2008;1145:237-59.
250. Prasad S, Sagar R, Kumaran SS et al. Study of functional magnetic resonance imaging (fMRI) in children and adolescents with specific learning disorder (dyslexia). Asian J Psychiatry 2020;50:101945.
251. Richlan F, Sturm D, Schurz M et al. A common left occipito-temporal dysfunction in developmental dyslexia and acquired letter-by-letter reading? PLoS One 2010;5:e12073.
252. Kaufmann L, Wood G, Rubinsten O et al. Meta-analyses of developmental fMRI studies investigating typical and atypical trajectories of number processing and calculation. Dev Neuropsychol 2011;36:763-87.
253. Bohlhalter S, Goldfine A, Matteson S et al. Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. Brain 2006;129(Pt. 8):2029-37.
254. Tung YH, Lin HY, Chen CL et al. Whole brain white matter tract deviation and idiosyncrasy from normative development in autism and ADHD and unaffected siblings link with dimensions of psychopathology and cognition. Am J Psychiatry 2021;178:730-43.
255. Zhang M, Huang Y, Jiao J et al. Transdiagnostic symptom subtypes across autism spectrum disorders and attention deficit hyperactivity disorder: validated by measures of neurocognition and structural connectivity. BMC Psychiatry 2022;22:102.
256. Bathelt J, Caan M, Geurts H. More similarities than differences between ADHD and ASD in functional brain connectivity. https://osf.io/preprints/psyarxiv/4tfmn.
257. Kernbach JM, Satterthwaite TD, Bassett DS et al. Shared endo-phenotypes of default mode dysfunction in attention deficit/hyperactivity disorder and autism spectrum disorder. Transl Psychiatry 2018;8:133.
258. Konrad K, Eickhoff SB. Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. Hum Brain Mapp 2010;31:904-16.

259. Müller RA, Shih P, Keehn B et al. Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. Cereb Cortex 2011;21:2233-43.
260. Wang K, Xu M, Ji Y et al. Altered social cognition and connectivity of default mode networks in the co-occurrence of autistic spectrum disorder and attention deficit hyperactivity disorder. Aust N Z J Psychiatry 2019;53:760-71.
261. Yerys BE, Tunç B, Satterthwaite TD et al. Functional connectivity of frontoparietal and salience/ventral attention networks have independent associations with co-occurring attention-deficit/hyperactivity disorder symptoms in children with autism. Biol Psychiatry Cogn Neurosci Neuroimaging 2019;4:343-51.
262. Karcher NR, Michelini G, Kotov R et al. Associations between resting-state functional connectivity and a hierarchical dimensional structure of psychopathology in middle childhood. Biol Psychiatry Cogn Neurosci Neuroimaging 2021;6:508-17.
263. McLeod KR, Langevin LM, Goodyear BG et al. Functional connectivity of neural motor networks is disrupted in children with developmental coordination disorder and attention-deficit/hyperactivity disorder. Neuroimage Clin 2014;4:566-75.
264. Querne L, Berquin P, Vernier-Hauvette MP et al. Dysfunction of the attentional brain network in children with developmental coordination disorder: a fMRI study. Brain Res 2008;1244:89-102.
265. Cheng CH, Chan PYS, Hsieh YW et al. A meta-analysis of mismatch negativity in children with attention deficit-hyperactivity disorders. Neurosci Lett 2016;612:132-7.
266. Williams ZJ, Abdelmessih PG, Key AP et al. Cortical auditory processing of simple stimuli is altered in autism: a meta-analysis of auditory evoked responses. Biol Psychiatry Cogn Neurosci Neuroimaging 2021;6:767-81.
267. Menashe S. Audiovisual processing and selective attention in adult dyslexic readers: an event-related potential study. Dyslexia 2021;27:245-64.
268. Schaadt G, van der Meer E, Pannekamp A et al. Children with dyslexia show a reduced processing benefit from bimodal speech information compared to their typically developing peers. Neuropsychologia 2019;126:147-58.
269. Holeckova I, Cepicka L, Mautner P et al. Auditory ERPs in children with developmental coordination disorder. Act Nerv Super 2014;56:37-44.
270. Carruthers S, Michelini G, Kitsune V et al. Early neurophysiological stimulus processing during a performance-monitoring task differentiates women with bipolar disorder from women with ADHD. Psychiatry Res 2021;303:114088.
271. Kang E, Keifer CM, Levy EJ et al. Atypicality of the N170 event-related potential in autism spectrum disorder: a meta-analysis. Biol Psychiatry Cogn Neurosci Neuroimaging 2018;3:657-66.
272. Tye C, Battaglia M, Bertoletti E et al. Altered neurophysiological responses to emotional faces discriminate children with ASD, ADHD and ASD+ADHD. Biol Psychol 2014;103:125-34.
273. Bellato A, Norman L, Idrees I et al. A systematic review and meta-analysis of altered electrophysiological markers of performance monitoring in obsessive-compulsive disorder (OCD), Gilles de la Tourette syndrome (GTS), attention-deficit/hyperactivity disorder (ADHD) and autism. Neurosci Biobehav Rev 2021;131:964-87.
274. Michelini G, Kitsune GL, Cheung CH et al. Attention-deficit/hyperactivity disorder remission is linked to better neurophysiological error detection and attention-vigilance processes. Biol Psychiatry 2016;80:923-32.
275. Cunha P, Monteiro de Castro Silva I, Neiva ER et al. Auditory processing disorder evaluations and cognitive profiles of children with specific learning disorder. Clin Neurophysiol Pract 2019;4:119-27.
276. Frizzo ACF. Auditory evoked potential: a proposal for further evaluation in children with learning disabilities. Front Psychol 2015;6:788.
277. Tsai CL, Pan CY, Chang YK et al. Deficits of visuospatial attention with reflexive orienting induced by eye-gazed cues in children with developmental coordination disorder in the lower extremities: an event-related potential study. Res Dev Disabil 2010;31:642-55.
278. Cui T, Wang PP, Liu S et al. P300 amplitude and latency in autism spectrum disorder: a meta-analysis. Eur Child Adolesc Psychiatry 2017;26:177-90.
279. Kamita MK, Silva LAF, Matas CG. Cortical auditory evoked potentials in autism spectrum disorder: a systematic review. Codas 2021;33:e20190207.
280. Kaiser A, Aggensteiner PM, Baumeister S et al. Earlier versus later cognitive event-related potentials (ERPs) in attention-deficit/hyperactivity disorder (ADHD): a meta-analysis. Neurosci Biobehav Rev 2020;112:117-34.
281. Szuromi B, Czobor P, Komlósi S et al. P300 deficits in adults with attention deficit hyperactivity disorder: a meta-analysis. Psychol Med 2011;41:1529-38.
282. Brandt VC, Stock AK, Münchau A et al. Evidence for enhanced multi-component behaviour in Tourette syndrome – an EEG study. Sci Rep 2017;7:7722.
283. Suzuki K, Kita Y, Shirakawa Y et al. Reduced Nogo-P3 in adults with developmental coordination disorder (DCD). Int J Psychophysiol 2020;153:37-44.
284. Tsai CL, Chang YK, Chen FC et al. Effects of cardiorespiratory fitness enhancement on deficits in visuospatial working memory in children with developmental coordination disorder: a cognitive electrophysiological study. Arch Clin Neuropsychol 2014;29:173-85.
285. Wang J, Barstein J, Ethridge LE et al. Resting state EEG abnormalities in autism spectrum disorders. J Neurodevelop Disord 2013;5:24.
286. Clarke AR, Barry RJ, Johnstone S. Resting state EEG power research in attention-deficit/hyperactivity disorder: a review update. Clin Neurophysiol 2020;131:1463-79.
287. Rudo-Hutt AS. Electroencephalography and externalizing behavior: a meta-analysis. Biol Psychol 2015;105:1-19.
288. Chiarenza GA. Quantitative EEG in childhood attention deficit hyperactivity disorder and learning disabilities. Clin EEG Neurosci 2021;52:144-55.
289. Jäncke L, Saka MY, Badawood O et al. Resting-state electroencephalogram in learning-disabled children: power and connectivity analyses. Neuroreport 2019;30:95-101.
290. Gurau O, Bosl WJ, Newton CR. How useful is electroencephalography in the diagnosis of autism spectrum disorders and the delineation of subtypes: a systematic review. Front Psychiatry 2017;8:121.
291. Neuhaus E, Lowry SJ, Santhosh M et al. Resting state EEG in youth with ASD: age, sex, and relation to phenotype. J Neurodev Disord 2021;13:33.
292. Babiloni C, Stella G, Buffo P et al. Cortical sources of resting state EEG rhythms are abnormal in dyslexic children. Clin Neurophysiol 2012;123:2384-91.
293. Lenartowicz A, Mazaheri A, Jensen O et al. Aberrant modulation of brain oscillatory activity and attentional impairment in attention-deficit/hyperactivity disorder. Biol Psychiatry Cogn Neurosci Neuroimaging 2018;3:19-29.
294. David N, Schneider TR, Peiker I et al. Variability of cortical oscillation patterns: a possible endophenotype in autism spectrum disorders? Neurosci Biobehav Rev 2016;71:590-600.
295. Vainieri I, Michelini G, Adamo N et al. Event-related brain-oscillatory and ex-Gaussian markers of remission and persistence of ADHD. Psychol Med 2022;52:352-61.
296. Coben R, Mohammad-Rezazadeh I, Frohlich J et al. Imaging brain connectivity in autism spectrum disorder. In: Casanova MF, El-Baz A, Suri JS (eds). Autism imaging and devices. Boca Raton: CRC Press, 2017:246-77.
297. Michelini G, Jurgiel J, Bakolis I et al. Atypical functional connectivity in adolescents and adults with persistent and remitted ADHD during a cognitive control task. Transl Psychiatry 2019;9:137.
298. Shephard E, Tye C, Ashwood KL et al. Oscillatory neural networks underlying resting-state, attentional control and social cognition task conditions in children with ASD, ADHD and ASD+ADHD. Cortex 2019;117:96-110.
299. Safar K, Vandewouw MM, Pang EW et al. Shared and distinct patterns of functional connectivity to emotional faces in autism spectrum disorder and attention-deficit/hyperactivity disorder children. Front Psychol 2022;13:826527.
300. Grant WB, Wimalawansa SJ, Holick MF et al. Emphasizing the health benefits of vitamin D for those with neurodevelopmental disorders and intellectual disabilities. Nutrients 2015;7:1538-64.
301. Khoshbakht Y, Bidaki R, Salehi-Abargouei A. Vitamin D status and attention deficit hyperactivity disorder: a systematic review and meta-analysis of observational studies. Adv Nutr 2018;9:9-20.
302. Walton C, Isaac A, Kerr M. Prevalence of vitamin D deficiency in people with learning disability: a systematic review. Br J Learn Disabil 2019;47:279-88.
303. Wang T, Shan L, Du L et al. Serum concentration of 25-hydroxyvitamin D in autism spectrum disorder: a systematic review and meta-analysis. Eur Child Adolesc Psychiatry 2016;25:341-50.
304. Babaknejad N, Sayehmiri F, Sayehmiri K et al. The relationship between zinc levels and autism: a systematic review and meta-analysis. Iran J Child Neurol 2016;10:1-9.
305. Saghazadeh A, Mahmoudi M, Dehghani Ashkezari A et al. Systematic review and meta-analysis shows a specific micronutrient profile in people with Down syndrome: lower blood calcium, selenium and zinc, higher red blood cell copper and zinc, and higher salivary calcium and sodium. PLoS One 2017;12:e0175437.
306. Sun GX, Wang BH, Zhang YF. Relationship between serum zinc levels and attention deficit hyperactivity disorder in children. Zhongguo Dang Dai Er Ke Za Zhi 2015;17:980-3.
307. Warthon-Medina M, Moran VH, Stammers AL et al. Zinc intake, status and indices of cognitive function in adults and children: a systematic review and meta-analysis. Eur J Clin Nutr 2015;69:649-61.
308. Zhang J, Luo W, Li Q et al. Peripheral brain-derived neurotrophic factor in

attention-deficit/hyperactivity disorder: a comprehensive systematic review and meta-analysis. J Affect Disord 2018;227:298-304.
309. Zheng Z, Zhang L, Zhu T et al. Peripheral brain-derived neurotrophic factor in autism spectrum disorder: a systematic review and meta-analysis. Sci Rep 2016;6:31241.
310. Gyllenberg D, Gissler M, Malm H et al. Specialized service use for psychiatric and neurodevelopmental disorders by age 14 in Finland. Psychiatr Serv 2014;65: 367-73.
311. Valentine AZ, Brown BJ, Groom MJ et al. A systematic review evaluating the implementation of technologies to assess, monitor and treat neurodevelopmental disorders: a map of the current evidence. Clin Psychol Rev 2020;80: 101870.
312. Davis E, Barnhill LJ, Saeed SA. Treatment models for treating patients with combined mental illness and developmental disability. Psychiatr Q 2008;79: 205-23.
313. Embracing Complexity. Briefing on transdiagnostic approaches to mental health and neurodevelopment. https://embracingcomplexity.org.uk.
314. Cortese S, Adamo N, Del Giovane C et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 2018;5:727-38.
315. Kortekaas-Rijlaarsdam AF, Luman M, Sonuga-Barke E et al. Does methylphenidate improve academic performance? A systematic review and meta-analysis. Eur Child Adolesc Psychiatry 2019;28:155-64.
316. Faraone SV, Banaschewski T, Coghill D et al. The World Federation of ADHD International Consensus Statement: 208 evidence-based conclusions about the disorder. Neurosci Biobehav Rev 2021;128:789-818.
317. Pearson DA, Santos CW, Aman MG et al. Effects of extended-release methylphenidate treatment on cognitive task performance in children with autism spectrum disorder and attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2020;30:414-26.
318. Sturman N, Deckx L, van Driel ML. Methylphenidate for children and adolescents with autism spectrum disorder. Cochrane Database Syst Rev 2017;11: CD011144.
319. Cicchetti D, Rogosch FA. Equifinality and multifinality in developmental psychopathology. Dev Psychopathol 1996;8:597-600.
320. Happé F, Frith U. Annual Research Review: Looking back to look forward – changes in the concept of autism and implications for future research. J Child Psychol Psychiatry 2020;61:218-32.
321. Larson T, Anckarsäter H, Gillberg C et al. The autism-tics, AD/HD and other Comorbidities inventory (A-TAC): further validation of a telephone interview for epidemiological research. BMC Psychiatry 2010;10:1.
322. Falkmer T, Anderson K, Falkmer M et al. Diagnostic procedures in autism spectrum disorders: a systematic literature review. Eur Child Adolesc Psychiatry 2013;22:329-40.
323. Zander E, Willfors C, Berggren S et al. The interrater reliability of the Autism Diagnostic Interview-Revised (ADI-R) in clinical settings. Psychopathology 2017; 50:219-27.
324. Hill A, Bölte S, Petrova G et al. Stability and interpersonal agreement of the interview-based diagnosis of autism. Psychopathology 2001;34:187-91.
325. Taylor LJ, Eapen V, Maybery M et al. Brief Report: An exploratory study of the diagnostic reliability for autism spectrum disorder. J Autism Dev Disord 2017; 47:1551-8.
326. Regier DA, Narrow WE, Clarke DE et al. DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. Am J Psychiatry 2013;170:59-70.
327. Chamorro Y, Bolaños L, Trejo S et al. Do teachers confirm parent's ratings of ADHD DSM-IV criteria? A study of a Mexican population. Neuropsychiatr Dis Treat 2021;17:1965-75.
328. Mitsis EM, McKay KE, Schulz KP et al. Parent-teacher concordance for DSM-IV attention-deficit/hyperactivity disorder in a clinic-referred sample. J Am Acad Child Adolesc Psychiatry 2000;39:308-13.
329. Willcutt EG, Nigg JT, Pennington BF et al. Validity of DSM-IV attention deficit/ hyperactivity disorder symptom dimensions and subtypes. J Abnorm Psychol 2012;121:991-1010.
330. Lobbestael J, Leurgans M, Arntz A. Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). Clin Psychol Psychother 2011;18:75-9.
331. Rice CE, Carpenter LA, Morrier MJ et al. Defining in detail and evaluating reliability of DSM-5 criteria for autism spectrum disorder (ASD) among children. J Autism Dev Disord 2022;52:5308-20.
332. De Los Reyes A, Augenstein TM, Wang M et al. The validity of the multi-informant approach to assessing child and adolescent mental health. Psychol Bull 2015;141:858-900.
333. Woolfenden S, Sarkozy V, Ridley G et al. A systematic review of the diagnostic stability of autism spectrum disorder. Research in Autism Spectrum Disorders 2012;6:345-54.
334. Duncan L, Comeau J, Wang L et al. Research Review: Test-retest reliability of standardized diagnostic interviews to assess child and adolescent psychiatric disorders: a systematic review and meta-analysis. J Child Psychol Psychiatry 2019;60:16-29.
335. Sprafkin J, Gadow KD, Salisbury H et al. Further evidence of reliability and validity of the Child Symptom Inventory-4: parent checklist in clinically referred boys. J Clin Child Adolesc Psychol 2002;31:513-24.
336. Osório FL, Loureiro SR, Hallak JEC et al. Clinical validity and intrarater and test-retest reliability of the Structured Clinical Interview for DSM-5 - Clinician Version (SCID-5-CV). Psychiatry Clin Neurosci 2019;73:754-60.
337. Leopold DR, Christopher ME, Burns GL et al. Attention-deficit/hyperactivity disorder and sluggish cognitive tempo throughout childhood: temporal invariance and stability from preschool through ninth grade. J Child Psychol Psychiatry 2016;57:1066-74.
338. Benedetto L, Cucinotta F, Maggio R et al. One-year follow-up diagnostic stability of autism spectrum disorder diagnosis in a clinical sample of children and toddlers. Brain Sci 2021;11:37.
339. Bhat A. Multidimensional motor performance in children with autism mostly remains stable with age and predicts social communication delay, language delay, functional delay, and repetitive behavior severity after accounting for intellectual disability or cognitive delay: a SPARK dataset analysis. Autism Res 2023;16:208-29.
340. Robinson EB, Munir K, Munafò MR et al. Stability of autistic traits in the general population: further evidence for a continuum of impairment. J Am Acad Child Adolesc Psychiatry 2011;50:376-84.
341. Baranek GT, Carlson M, Sideris J et al. Longitudinal assessment of stability of sensory features in children with autism spectrum disorder or other developmental disabilities. Autism Res 2019;12:100-11.
342. Overgaard KR, Oerbeck B, Friis S et al. Attention-deficit/hyperactivity disorder from preschool to school age: change and stability of parent and teacher reports. Eur Child Adolesc Psychiatry 2023;32:1947-55.
343. Schmiedeler S, Schneider W. Attention-deficit hyperactivity disorder (ADHD) in the early years: diagnostic issues and educational relevance. Clin Child Psychol Psychiatry 2014;19:460-75.
344. Lilienfeld SO, Landfield K. Issues in diagnosis: categorical vs. dimensional. In: Craighead WE, Miklowitz DJ, Craighead LW (eds). Psychopathology: history, diagnosis, and empirical foundations. Chichester: Wiley, 2008:1-31.
345. Klin A, Lang J, Cicchetti DV et al. Brief Report: Interrater reliability of clinical diagnosis and DSM-IV criteria for autistic disorder: results of the DSM-IV autism field trial. J Autism Dev Disord 2000;30:163-7.
346. McDonnell CG, Bradley CC, Kanne SM et al. When are we sure? Predictors of clinician certainty in the diagnosis of autism spectrum disorder. J Autism Dev Disord 2019;49:1391-401.
347. Keller AS, Leikauf JE, Holt-Gosselin B et al. Paying attention to attention in depression. Transl Psychiatry 2019;9:279.
348. Reich W. Diagnostic Interview for Children and Adolescents (DICA). J Am Acad Child Adolesc Psychiatry 2000;39:59-66.
349. First MB, Williams JBW, Karg RS et al. Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV). Arlington: American Psychiatric Publishing, 2016.
350. Huerta M, Bishop SL, Duncan A et al. Application of DSM-5 criteria for autism spectrum disorder to three samples of children with DSM-IV diagnoses of pervasive developmental disorders. Am J Psychiatry 2012;169:1056-64.
351. Kulage KM, Smaldone AM, Cohn EG. How will DSM-5 affect autism diagnosis? A systematic literature review and meta-analysis. J Autism Dev Disord 2014;44: 1918-32.
352. Shekim WO, Cantwell DP, Kashani J et al. Dimensional and categorical approaches to the diagnosis of attention deficit disorder in children. J Am Acad Child Psychiatry 1986;25:653-8.
353. Swanson JM, Schuck S, Porter MM et al. Categorical and dimensional definitions and evaluations of symptoms of ADHD: history of the SNAP and the SWAN rating scales. Int J Educ Psychol Assess 2012;10:51-70.
354. Heidbreder R. ADHD symptomatology is best conceptualized as a spectrum: a dimensional versus unitary approach to diagnosis. ADHD Atten Def Hyp Disord 2015;7:249-69.
355. Kessler RC, Adler L, Ames M et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychol Med 2005;35:245-56.
356. Collett BR, Ohan JL, Myers KM. Ten-year review of rating scales. V: Scales as-

sessing attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2003;42:1015-37.

357. Foss-Feig JH, McPartland JC, Anticevic A et al. Re-conceptualizing ASD within a dimensional framework: positive, negative, and cognitive feature clusters. J Autism Dev Disord 2016;46:342-51.
358. Constantino JN, Gruber CP. Social Responsiveness Scale: SRS-2. Torrance: Western Psychological Services, 2012.
359. Frazier TW, Dimitropoulos A, Abbeduto L et al. The Autism Symptom Dimensions Questionnaire: development and psychometric evaluation of a new, open-source measure of autism symptomatology. Dev Med Child Neurol 2023; 65:1081-92.
360. Lam KSL, Aman MG. The Repetitive Behavior Scale-Revised: independent validation in individuals with autism spectrum disorders. J Autism Dev Disord 2007;37:855-66.
361. Constantino JN, Davis SA, Todd RD et al. Validation of a brief quantitative measure of autistic traits: comparison of the Social Responsiveness Scale with the Autism Diagnostic Interview-Revised. J Autism Dev Disord 2003;33:427-33.
362. Murray MJ, Mayes SD, Smith LA. Brief Report: Excellent agreement between two brief autism scales (Checklist for Autism Spectrum Disorder and Social Responsiveness Scale) completed independently by parents and the Autism Diagnostic Interview-Revised. J Autism Dev Disord 2011;41:1586-90.
363. Lemay KR, Kogan CS, Rebello TJ et al. An international field study of the ICD-11 behavioural indicators for disorders of intellectual development. J Intellect Disabil Res 2022;66:376-91.
364. McGuire JF, Piacentini J, Storch EA et al. Defining tic severity and tic impairment in Tourette Disorder. J Psychiatr Res 2021;133:93-100.
365. Burrows CA, Grzadzinski RL, Donovan K et al. A data-driven approach in an unbiased sample reveals equivalent sex ratio of autism spectrum disorder-associated impairment in early childhood. Biol Psychiatry 2022;92:654-62.
366. Markon KE, Chmielewski M, Miller CJ. The reliability and validity of discrete and continuous measures of psychopathology: a quantitative review. Psychol Bull 2011;137:856-79.
367. Abi-Dargham A, Moeller SJ, Ali F et al. Candidate biomarkers in psychiatric disorders: state of the field. World Psychiatry 2023;22:236-62.
368. Loth E, Evans DW. Converting tests of fundamental social, cognitive, and affective processes into clinically useful bio-behavioral markers for neurodevelopmental conditions. Wiley Interdiscip Rev Cogn Sci 2019;10:e1499.
369. Michelini G, Norman LJ, Shaw P et al. Treatment biomarkers for ADHD: taking stock and moving forward. Transl Psychiatry 2022;12:444.
370. Waterhouse L. Heterogeneity thwarts autism explanatory power: a proposal for endophenotypes. Front Psychiatry 2022;13:947653.
371. Jacob S, Wolff JJ, Steinbach MS et al. Neurodevelopmental heterogeneity and computational approaches for understanding autism. Transl Psychiatry 2019;9: 63.
372. Miller A, Shen J, Mâsse LC. Child functional characteristics explain child and family outcomes better than diagnosis: population-based study of children with autism or other neurodevelopmental disorders/disabilities. Health Rep 2016;27:9-18.
373. Michelini G, Gair K, Tian Y et al. Do general and specific factors of preschool psychopathology predict preadolescent outcomes? A transdiagnostic hierarchical approach. Psychol Med 2023;53:5405-14.
374. Lahey BB, Pelham WE, Loney J et al. Instability of the DSM-IV subtypes of ADHD from preschool through elementary school. Arch Gen Psychiatry 2005; 62:896-902.
375. Lahey BB, Willcutt EG. Predictive validity of a continuous alternative to nominal subtypes of attention-deficit/hyperactivity disorder for DSM-V. J Clin Child Adolesc Psychol 2010;39:761-75.
376. Martel MM, Roberts B, Gremillion M et al. External validation of bifactor model of ADHD: explaining heterogeneity in psychiatric comorbidity, cognitive control, and personality trait profiles within DSM-IV ADHD. J Abnorm Child Psychol 2011;39:1111-23.
377. Shemmassian SK, Lee SS. Comparative validity of DSM-IV and alternative empirically derived approaches for the assessment of ADHD. J Atten Disord 2017; 21:405-15.
378. Astle DE, Bathelt J, CALM Team et al. Remapping the cognitive and neural profiles of children who struggle at school. Dev Sci 2019;22:e12747.
379. Reed GM, Keeley JW, Rebello TJ et al. Clinical utility of ICD-11 diagnostic guidelines for high-burden mental disorders: results from mental health settings in 13 countries. World Psychiatry 2018;17:306-15.
380. Gadow KD, Garman HD. Social anhedonia in children and adolescents with autism spectrum disorder and psychiatry referrals. J Clin Child Adolesc Psychol 2020;49:239-50.
381. Waszczuk MA, Zimmerman M, Ruggero C et al. What do clinicians treat: diagnoses or symptoms? The incremental validity of a symptom-based, dimensional characterization of emotional disorders in predicting medication prescription patterns. Compr Psychiatry 2017;79:80-8.
382. Embracing Complexity. Embracing complexity in diagnosis: multi-diagnostic pathways for neurodevelopmental conditions. https://embracingcomplexity.org.uk.
383. Conners CK, Sitarenios G, Parker JD et al. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol 1998;26:257-68.
384. Katzman MA, Bilkey TS, Chokka PR et al. Adult ADHD and comorbid disorders: clinical implications of a dimensional approach. BMC Psychiatry 2017;17:302.
385. Skuse D, Warrington R, Bishop D et al. The developmental, dimensional and diagnostic interview (3di): a novel computerized assessment for autism spectrum disorders. J Am Acad Child Adolesc Psychiatry 2004;43:548-58.
386. Tassé MJ, Balboni G, Navas P et al. Developing behavioural indicators for intellectual functioning and adaptive behaviour for ICD-11 disorders of intellectual development. J Intellect Disabil Res 2019;63:386-407.
387. Driscoll H, Kimberg AD, Chung RJ. Caring for adolescents and young adults with attention-deficit/hyperactivity disorder in primary care: seizing opportunities to address youth mental health needs. Curr Opin Pediatr 2022;34:306-12.
388. Brian JA, Zwaigenbaum L, Ip A. Standards of diagnostic assessment for autism spectrum disorder. Paediatr Child Health 2019;24:444-60.
389. Hyman SL, Levy SE, Myers SM et al. Identification, evaluation, and management of children with autism spectrum disorder. Pediatrics 2020;145: e20193447.
390. Lord C, Charman T, Havdahl A et al. The Lancet Commission on the future of care and clinical research in autism. Lancet 2022;399:271-334.
391. Talbott MR, Miller MR. Future directions for infant identification and intervention for autism spectrum disorder from a transdiagnostic perspective. J Clin Child Adolesc Psychol 2020;49:688-700.
392. Mattingly GW, Anderson RH. Optimizing outcomes in ADHD treatment: from clinical targets to novel delivery systems. CNS Spectr 2016;21(Suppl. 1):45-59.
393. Evans K, Whitehouse AJO, D'Arcy E et al. Perceived support needs of school-aged young people on the autism spectrum and their caregivers. Int J Environ Res Public Health 2022;19:15605.
394. Boulton KA, Coghill D, Silove N et al. A national harmonised data collection network for neurodevelopmental disorders: a transdiagnostic assessment protocol for neurodevelopment, mental health, functioning and well-being. JCPP Adv 2021;1:e12048.
395. Thapar A, Livingston LA, Eyre O et al. Practitioner Review: Attention-deficit hyperactivity disorder and autism spectrum disorder – the importance of depression. J Child Psychol Psychiatry 2023;64:4-15.
396. Underwood JFG, DelPozo-Banos M, Frizzati A et al. Neurological and psychiatric disorders among autistic adults: a population healthcare record study. Psychol Med 2023;53:5663-73.
397. Hansen BH, Oerbeck B, Skirbekk B et al. Neurodevelopmental disorders: prevalence and comorbidity in children referred to mental health services. Nord J Psychiatry 2018;72:285-91.
398. Ahmedani BK, Hock RM. Health care access and treatment for children with co-morbid autism and psychiatric conditions. Soc Psychiatry Psychiatr Epidemiol 2012;47:1807-14.
399. Coller RJ, Berry JG, Kuo DZ et al. Health system research priorities for children and youth with special health care needs. Pediatrics 2020;145:e20190673.
400. Agnew-Blais J, Michelini G. Taking stock of the present and looking to the future of ADHD research: a commentary on Sonuga-Barke et al. (2023). J Child Psychol Psychiatry 2023;64:533-6.
401. Bölte S, Lawson WB, Marschik PB et al. Reconciling the seemingly irreconcilable: the WHO's ICF system integrates biological and psychosocial environmental determinants of autism and ADHD: the International Classification of Functioning (ICF) allows to model opposed biomedical and neurodiverse views of autism and ADHD within one framework. Bioessays 2021;43:e2000254.
402. Tregnago MK, Cheak-Zamora NC. Systematic review of disparities in health care for individuals with autism spectrum disorders in the United States. Research in Autism Spectrum Disorders 2012;6:1023-31.
403. Sapiets SJ, Totsika V, Hastings RP. Factors influencing access to early intervention for families of children with developmental disabilities: a narrative review. J Appl Res Intellect Disabil 2021;34:695-711.
404. Karpur A, Lello A, Frazier T et al. Health disparities among children with autism spectrum disorders: analysis of the National Survey of Children's Health 2016. J Autism Dev Disord 2019;49:1652-64.
405. Ben-Zeev D, Young MA, Corrigan PW. DSM-V and the stigma of mental illness. J Ment Health 2010;19:318-27.
406. Parke EM, Mayfield AR, Barchard KA et al. Factor structure of symptom dimen-

sions in attention-deficit/hyperactivity disorder (ADHD). Psychol Assess 2015; 27:1427-37.
407. Kim H, Keifer CM, Rodriguez-Seijas C et al. Structural hierarchy of autism spectrum disorder symptoms: an integrative framework. J Child Psychol Psychiatry 2018;59:30-8.
408. Kim H, Keifer C, Rodriguez-Seijas C et al. Quantifying the optimal structure of the autism phenotype: a comprehensive comparison of dimensional, categorical, and hybrid models. J Am Acad Child Adolesc Psychiatry 2019;58:876-86.e2.
409. Baron-Cohen S, Wheelwright S, Skinner R et al. The Autism-Spectrum Quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J Autism Dev Disord 2001;31:5-17.
410. Gomez R, Stavropoulos V, Vance A. Psychometric properties of the Autism Spectrum Quotient: Children's Version (AQ-Child). J Autism Dev Disord 2019; 49:468-80.
411. Hoekstra RA, Vinkhuyzen AAE, Wheelwright S et al. The construction and validation of an abridged version of the Autism-Spectrum Quotient (AQ-Short). J Autism Dev Disord 2011;41:589-96.
412. Frazier TW, Ratliff KR, Gruber C et al. Confirmatory factor analytic structure and measurement invariance of quantitative autistic traits measured by the Social Responsiveness Scale-2. Autism 2014;18:31-44.
413. Farmer RF, Seeley JR, Kosty DB et al. Refinements in the hierarchical structure of externalizing psychiatric disorders: patterns of lifetime liability from mid-adolescence through early adulthood. J Abnorm Psychol 2009;118:699-710.

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Scientific validation of the ICD-11 CDDR

The process of scientific validation of the ICD-11 Clinical Descriptions and Diagnostic Requirements (CDDR) for Mental Disorders has spanned more than 10 years, being remarkably comprehensive and inclusive as well as truly international, with the involvement of many hundreds of clinicians and researchers from all regions of the world.

The field trials of the ICD-11 CDDR – contrary to those of the ICD-10 Clinical Descriptions and Diagnostic Guidelines (CDDG) and the DSM-5 diagnostic criteria – have been genuinely "developmental" (as opposed to "summative" or "evaluative") in their nature[1]. That is, they have been conducted *before* the finalization of the relevant sets of criteria or guidelines – thus allowing the identification of conceptual or terminological problems in the proposed texts, the correction of those texts, and the further testing of the revised versions – rather than being conducted or concluded *after* the finalization of the relevant sets of criteria or guidelines, thus just providing information to clinicians about what they could expect from those products. As we will see, several amendments to the CDDR were actually implemented as a consequence of this design.

The CDDR field trials can be subdivided into two main groups: a) Internet-based trials, implemented through the Global Clinical Practice Network (involving, at the time when the trials were conducted, more than 15,000 mental health and primary health care professionals from more than 150 countries), which used a case vignette methodology to assess the effects of specific differences between the CDDR and the ICD-10 CDDG on the participants' clinical decision making; b) clinic-based (or ecological) trials, assessing the reliability and clinical utility of the CDDR in real clinical contexts. The clinic-based trials differed from the DSM-5 field trials in that they used a joint-rater design (with two clinicians jointly interviewing each patient) rather than a test-retest design (with two clinicians separately interviewing each patient at different time points), thus controlling for information variance and more specifically testing the reliability of the proposed guidelines (rather than testing more generally the reliability of the relevant psychiatric diagnoses)[2].

Among the Internet-based CDDR field trials, of special interest have been those focusing on disorders specifically associated with stress[3], and on feeding and eating disorders[4]. A case-control field trial on the former grouping of disorders[3], conducted with 1,738 mental health professionals from 76 countries, found that several changes introduced in the ICD-11 – including the addition of complex post-traumatic stress disorder (complex PTSD) and prolonged grief disorder – resulted in significantly improved diagnostic decisions. However, the trial also identified some problems with the proposed CDDR text (including difficulties with interpretation of the "re-experiencing" criterion for the PTSD diagnosis, and in differentiating prolonged grief disorder from normal bereavement), which led to a revision and further validation of the text.

Similarly, a case-control field trial on feeding and eating disorders[4], conducted with 2,288 mental health professionals representing all world regions, found that the changes introduced in the ICD-11 CDDR improved the diagnostic accuracy and clinical utility compared to the ICD-10 CDDG. However, the trial also identified difficulties in determining whether a person with a diagnosis of anorexia nervosa was recovered, as well as problems in the identification of binge eating episodes, which led to a refinement of the definition of recovery for anorexia nervosa and to the specification that the subjective experience of loss of control over eating and related distress is a pathognomonic feature of binge eating even when the amount of food consumed is not objectively large.

Among the clinic-based CDDR field trials, the largest one – conducted among 1,806 patients in 13 countries and focusing on mental disorders which account for the greatest proportion of global disease burden (schizophrenia and other primary psychotic disorders, mood disorders, anxiety and fear-related disorders, and disorders specifically associated with stress) found that intraclass kappa coefficients for diagnoses ranged from 0.45 (for dysthymic disorder) to 0.88 (for social anxiety disorder), and could be considered moderate to almost perfect for all diagnoses, with an overall reliability superior for the CDDR compared to the ICD-10 CDDG[2]. The same trial also found that the CDDR were perceived as easy to use, corresponding accurately to patients' presentations, clear and understandable, providing an appropriate level of detail, taking about the same or less time than clinicians' usual practice, and providing useful guidance about the distinction of each disorder from normality and from other disorders[5].

The somewhat long period of time elapsed between the production of the first draft and the finalization of the CDDR has also allowed an extensive and detailed validation of some of the categories newly introduced in the ICD-11. Emblematic in this respect has been the validation of the new categories of prolonged grief disorder and complex PTSD.

According to a PubMed search performed on February 8, 2024, the papers with original data published since 2013 on prolonged grief disorder have been 57. Overall, they documented the construct validity of the new category, its differentiation from other disorders (e.g., depression and PTSD); its association with marked functional impairment (beyond the effects of concomitant disorders); and its higher consistency with patterns of prolonged grief in longitudinal studies compared to DSM-5 persistent complex bereavement disorder. This evidence has led to the inclusion of prolonged grief disorder in the DSM-5-TR[6].

A PubMed search performed on the same date detected 199 papers with original data published since 2013 on complex PTSD. Overall, they documented the validity of the new category, and its differentiation from PTSD in a wide range of cultures, in children and adolescents as well as in adults, and across several traumatized populations[7]. This research has been facilitated by the development and validation – prompted by the circulation of the CDDR drafts – of a new specific assessment instrument, the International Trauma Questionnaire.

A further significant difference between the ICD-11 CDDR and the DSM-5 diagnostic criteria which has been tested internationally is that concerning the classification of severe irritability in children and adolescents. A study conducted with 196 clinicians from 48 countries[8] found that the formulation proposed in the CDDR (using chronic irritability-anger as a specifier for the diagnosis of oppositional defiant disorder) led to a more accurate identification of severe irritability and a better differentiation from boundary presentations compared to both the DSM-5 solution (introducing the new category of disruptive mood dysregulation disorder) and the ICD-10 classification (listing oppositional defiant disorder as one of several conduct disorders without attention to irritability). Participants using the DSM-5 often failed to apply the diagnosis of disruptive mood dysregulation disorder when it was required, whereas they more often applied a psychiatric diagnosis to irritability that was normative in relation to the developmental stage.

One more innovative aspect of the process of validation of the ICD-11 CDDR has been the systematic involvement of experts by experience, through an international study (INCLUDE) conducted in India, the UK and the US[9]. This study collected users' input on five diagnoses: depressive episode, generalized anxiety disorder, schizophrenia, bipolar I disorder, and personality disorder. Overall, the CDDR were in many cases perceived as useful and relevant to lived experience.

Of course, a currently missing key element in the scientific validation of the CDDR is their performance in ordinary clinical practice. The ongoing efforts to translate them in as many languages as possible, to widely disseminate them, and to accelerate their endorsement and implementation by national governments, will be crucial in this respect, and a regular update of the text (every two years)[7], to be performed on this basis, is already being planned.

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1. First M. Lancet Psychiatry 2016;3:579-84.
2. Reed GM, Sharan P, Rebello TJ et al. World Psychiatry 2018;17:174-86.
3. Keeley JW, Reed GM, Roberts MC et al. Int J Clin Health Psychol 2016;16:109-27.
4. Claudino AM, Pike KM, Hay P et al. BMC Med 2019;17:93-109.
5. Reed GM, Keeley JW, Rebello TJ et al. World Psychiatry 2018;17:306-15.
6. Prigerson HG, Boelen PA, Xu J et al. World Psychiatry 2021;20:96-106.
7. Reed GM, First MB, Billieux J et al. World Psychiatry 2022;21:189-213.
8. Evans SC, Roberts MC, Keeley JW et al. J Child Psychol Psychiatry 2021;62:303-12.
9. Hackmann C, Balhara YPS, Clayman K et al. Lancet Psychiatry 2019;6:778-85.

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The WHO Flexible Interview for ICD-11 (FLII-11)

The movement to a descriptive, symptom-based diagnostic system that started with the DSM-III was in part a response to widespread concerns and criticisms regarding the reliability of psychiatric diagnoses. This fueled an emphasis on increasingly precise operationalization of diagnostic constructs and criteria, based on the assumption that this would produce successive improvements in reliability.

Clinician-administered structured diagnostic interviews were subsequently developed. For example, the Research Diagnostic Criteria were used to develop a Schedule for Affective Disorders and Schizophrenia[1], while the DSM-III criteria were incorporated into the Structured Clinical Interview for DSM (SCID)[2]. In addition, the Diagnostic Interview Schedule[3] was developed for use by non-clinician interviewers in epidemiological surveys of mental disorders. These instruments have been widely used in research on mental disorders.

Structured diagnostic interviews have subsequently been developed or adapted for successive revisions of the DSM and the ICD. The SCID, a semi-structured interview – meaning that the interviewer probes unclear responses and makes certain clinical judgments – has been updated with each edition of the DSM[4]. The briefer and fully structured Mini International Neuropsychiatric Interview (MINI)[5] has also been widely employed. The Composite International Diagnostic Interview (CIDI)[6] incorporated both DSM and ICD diagnostic requirements and was used in the National Comorbidity Survey and the World Mental Health Surveys. Similarly, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), based on the Present State Examination, assessed for both DSM and ICD requirements[7]. Structured diagnostic interviews for children have also been developed, as have a range of more focused interviews that cover specific conditions or diagnostic groupings.

Based on an extensive program of field testing, the reliability of the diagnostic guidance provided in the Clinical Descriptions and Diagnostic Requirements for ICD-11 Mental, Behavioural and Neurodevelopmental Disorders (CDDR)[8] was found to be higher than that of other mental disorder classification systems, ranging from moderate to almost perfect according to the specific category. This finding was perhaps counterintuitive, insofar as the CDDR avoid highly prescriptive symptom counts and duration requirements, unless these are specifically supported scientifically, in order to facilitate clinical use.

These results, therefore, challenge the assumed relationship between operational precision and diagnostic reliability. They also suggest that the diagnoses based on the CDDR would be sufficiently reliable for certain types of research projects (e.g., studies focusing on diagnostic groups in health care settings). However, in other types of research, standardized diagnostic assessments are desirable to control clinician-level variability associated with different skill levels, interviewing styles, and clinical judgment. For example, in pharmacological trials that select participants based on certain diagnostic requirements, the ability to document specific symptom patterns reliably and reproducibly is often important. Epidemiological or other population-based surveys involving lay (i.e., not clinically trained) interviewers also require prescripted questions and strict decision rules, because they cannot rely on the interviewer's clinical knowledge to determine whether specific features are present.

Diagnostic interviews have therefore been a part of the work plan related to the CDDR nearly from the beginning. The relevant work has employed a rigorous development process and included international experts in the fields of nosology and diagnostic interviews. Work on the Structured Clinical Interview for ICD-11 (SCII-11) has been ongoing since 2014. This is a semi-structured diagnostic interview – designed to be administered by a trained clinician – that provides a standardized set of questions, each assessing a specific diagnostic requirement for the purpose of formulating a differential diagnosis. Though developed for research applications, the SCII-11 will also be useful for training purposes and in clinical settings.

Due to the CDDR's more clinically-oriented framing of diagnostic requirements, additional operationalization has been necessary in developing the SCII-11. Specifically, the SCII-11 substitutes more precise diagnostic thresholds for less prescriptive terms in the CDDR (e.g., at least three rather than "several" symptoms; at least three months rather than "persistent"). In addition, specific questions have been developed for elements of the CDDR that may manifest in a variety of different ways (e.g., "persistent delusions" in schizophrenia).

The World Health Organization (WHO) Flexible Interview for ICD-11 (FLII-11) is being developed as an open-access tool to support national epidemiological investigations and other population-based and clinical studies of mental disorders. It is a fully structured diagnostic interview that can be administered by trained lay interviewers and assesses mental disorders associated with the greatest global disease burden. It builds on the operationalization work completed for the SCII-11. Like the SCII-11, the FLII-11 is modular and customizable to assess a subset of disorders, and can evaluate current and lifetime diagnostic status. Available modules include psychotic, mood, anxiety, obsessive-compulsive and related, post-traumatic, eating, addictive behaviour, and substance use disorders, and attention deficit hyperactivity disorder. An adaptation for adolescents aged 13-17 has also been developed.

There has been a high level of interest in the FLII-11, due to the increasing global importance given to mental disorders, and the desire of WHO member states to use an open-access measure that is consistent with the current official global diagnostic system. The FLII-11 is being prepared for feasibility testing, including review by people with lived experience, as a part of an international collaboration that involves Brazil, China, India, Liberia, Mexico, South Africa, Sri Lanka, Tunisia and Uganda. This is occurring in tandem with its use in national mental health surveys in several of these countries.

The FLII-11 is being translated into multiple languages and employed in a broad range of settings around the globe. It is therefore critical that complex concepts be phrased in readily understandable and culturally appropriate ways. This has necessitated the development of a standardized cultural adaptation and translation process. The WHO aims to develop an online platform that will facilitate the collection, analysis and sharing of international data and become a resource for international mental health epidemiology.

Diagnostic interviews based on the ICD-11 CDDR promise to be useful for both clinicians and researchers. At the same time, several concerns should be borne in mind as this work proceeds. A first concern relates to the limitations of an approach to diagnostic assessment of mental disorders that relies primarily on direct self-report of their essential features. There are also concerns about areas in which interviewees may have an incentive to minimize or deny their symptoms (e.g., when they relate to illegal or highly stigmatized behaviours), or when an aspect of the presentation is poor or absent insight or a distorted view of their own behaviour and functioning. Validation of diagnostic interviews in these areas requires particular attention.

Another ongoing question is how best to validate an interview undertaken by an experienced clinician. Spitzer proposed using a "longitudinal expert all data (LEAD) standard"[9], which is difficult and burdensome to do and still subject to clinician bias. New diagnostic measures are more commonly validated against other measures; for example, results of the lay-administered FLII-11 could be compared to those of the clinician-administered SCII-11, rather than against a measure not based on the ICD-11. The issue of false positives in epidemiological research remains a concern and must be evaluated, but may be ameliorated by training.

Establishing the cross-cultural feasibility and validity of structured diagnostic interviews for the ICD-11 will provide an important foundation for international mental health research.

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1. Endicott J, Spitzer RL. Acta Psychiatr Belg 1987;87:361-516.
2. Spitzer RL, Williams JBW, Gibbon M et al. Arch Gen Psychiatry 1992;49:624-9.
3. Robins LN, Helzer JE, Croughan J et al. Arch Gen Psychiatry 1981;38:381-9.
4. First MB. Structured Clinical Interview for the DSM (SCID). In: Cautin RL, Lilienfeld SO (eds). The encyclopedia of clinical psychology. Hoboken: Wiley, 2015:1-6.
5. Sheehan DV, Lecrubier Y, Sheehan KH et al. J Clin Psychiatry 1998;59:22-33.
6. Janca A, Ustün TB, Sartorius N. Acta Psychiatr Scand 1994;90:73-83.
7. Wing JK, Babor T, Brugha T et al. Arch Gen Psychiatry 1990;47:589-93.
8. World Health Organization. Clinical descriptions and diagnostic requirements for ICD-11 mental, behavioural and neurodevelopmental disorders. https://www.who.int/publications/i/item/9789240077263.
9. Spitzer RL. Compr Psychiatry 1983;24:399-411.

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Prolonged grief disorder: detection, diagnosis, and approaches to intervention

The recent addition of prolonged grief disorder (PGD) to the ICD-11 and the DSM-5-TR has brought changes in what many mental health experts consider to be best practice in bereavement care. Because PGD is newly recognized as an official mental disorder, clinicians may be unfamiliar with current approaches to its detection, diagnosis and treatment. Here we provide answers to common questions that have arisen regarding: a) the settings in which clinicians are likely to encounter a person meeting criteria for PGD; b) who typically initiates help-seeking and the receptivity of those with PGD to treatment from mental health professionals; c) how to distinguish PGD from typical grief as well as from major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) secondary to bereavement; d) implications of diagnostic criteria for treatment; and e) how to apply criteria to ensure their cross-cultural sensitivity and validity.

Where might clinicians encounter someone who might be diagnosed with PGD? Although the age of the mourner has proven inversely associated with PGD risk, older adults are more likely to experience the death of a spouse or partner – a kinship relationship to the deceased person posing elevated PGD risk[1]. Therefore, geriatricians serve populations at high risk for PGD. Moreover, due to a high concentration of deaths, nursing homes, assisted living facilities, cancer clinics, hospices and palliative care services, hospitals (particularly intensive care units), war zones, and places where natural or man-made disasters occur, are settings in which clinicians are likely to encounter persons – surviving family and friends – at elevated risk of PGD.

Counter to the claim that those who meet criteria for PGD are uninterested in treatment, our research revealed that 100% of the bereaved respondents who met criteria for PGD indicated that they would be interested in receiving treatment for it[2]. However, though they might be interested in treatment, few bereaved individuals with PGD actually seek help[3]. In a study of bereaved caregivers of patients who died of cancer, we found that, despite 71% of caregivers with PGD reporting increased suicidality, only 43% reported accessing mental health services following the patient's death – a rate significantly below those for bereaved study participants diagnosed with MDD or PTSD[3].

Anecdotally, our Cornell Center for Research on End-of-Life Care is frequently contacted by concerned family members seeking treatment for someone whom they believe has PGD. These people typically describe a situation in which their bereaved family member has struggled with grief for many years, been diagnosed with MDD or PTSD, and received treatment for those disorders to no avail. Such experiences are consistent with results which prompted our initial interest in grief – findings from a randomized controlled trial demonstrating that an antidepressant (i.e., nortriptyline) alone and together with psychotherapy addressing role transitions (i.e., interpersonal psychotherapy), while effective for symptoms of late-life bereavement-related depression, did not prove effective for the resolution of grief symptoms[4]. These findings highlight the need to distinguish PGD from MDD among mourners, and to identify effective treatments for the reduction of symptoms of distressing and disabling grief. Currently, many psychotherapeutic interventions, particularly cognitive behavioral therapies (CBTs)[5], have proven efficacious for reducing PGD symptoms.

How can a clinician determine whether a bereaved person's grief response is ordinary or pathological? Diagnostic criteria for PGD found in the ICD-11 or DSM-5-TR require responses that, while seemingly normal, at severe levels and after six or twelve months from the loss (depending on whether ICD-11 or DSM-5-TR criteria are applied), identify mourners at risk of enduring distress and dysfunction. Missing the deceased person and loss of interest in socializing and concentration at work are not abnormal in the initial months following a significant interpersonal loss. Beyond the first anniversary of the death, however, it is surprisingly rare (4-15%[6]) for bereaved individuals to yearn intensely for the deceased person throughout the day (a preoccupation with thoughts of the deceased making it difficult to focus and engage in usual activities); feel disturbingly detached from others; be agonizingly alone; and lack a sense of meaning, purpose and identity without the deceased person. Individuals who survive a significant other's death from natural causes who exhibit these thoughts and feelings beyond the first anniversary of the death should be evaluated for PGD.

Differences between PGD and MDD focus on the distinction between the deceased person-specific trigger in PGD versus a generalized sense of sadness and pessimism about present and future outcomes in MDD. Yearning for the deceased person is specific to PGD and is not present in MDD (nor PTSD). In PTSD, avoidance is focused on fear of a life-threatening event either to oneself or a significant other and helplessness to prevent harm. In PGD, avoidance is focused on disbelief and lack of emotional and cognitive acceptance of the fact that the loved one has died.

Because the core symptom in PGD is yearning, there are similarities with diagnostic criteria for addictive disorders. For example, PGD symptoms of yearning, anger, and protest of separation from the source of reward resemble the craving and withdrawal symptoms of substance use disorder. These similarities suggest that persons at risk of PGD are those for whom the deceased person was a primary source of love, support, security, identity and validation; that is, a source of psychological reward. They also suggest that interventions – both psychosocial and pharmacological – which blunt reward derived from the deceased person (e.g., naltrexone) might reduce yearning and promote an openness to interacting with living others who might fill social voids, thereby reducing symptoms of PGD and promoting bereavement adjustment more broadly[7].

Lastly, while we consider grief a universal human (but not uniquely human, given evidence of its presence in other mammalian species – e.g., elephants, monkeys, voles) response to separation from a significant other, we also acknowledge important cultural influences on the form that grief responses take. What may be considered normal or expected in one culture (e.g., prohibitions on dating or dress) may be regarded as abnormal in another. Linguistic differences may affect the ability to assess symptoms (e.g., if a language has no words or imperfect synonyms for the PGD criteria). The ICD-11 and DSM-5-TR note a "cultural caveat" whereby judgments about normal versus pathological grief reactions are considered within the mourner's cultural context[8].

The Grief and Bereavement Cultural interview[9] has been developed to assist clinicians in factoring in the role of culture in making a PGD diagnosis. Statistical techniques such as item response theory can be used to determine which items provide the most unbiased information with respect to an underlying grief "attribute" within a specific culture or language. Both clinical and data analytic techniques should be employed to ensure cross-cultural reliability and precision in the application of the PGD criteria.

In conclusion, PGD is a new mental disorder that clinicians may not know how to detect, diagnose or treat. We have briefly addressed some of the most common questions asked by clinicians about assessing PGD, and offered guidelines for intervening to ensure consistency with current best practices in bereavement care.

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1. Maciejewski PK, Prigerson HG. In: Reynolds CF (ed). Grief and prolonged grief disorder. Washington: American Psychiatric Association, 2024:151-2.
2. Johnson JG, First MB, Block S et al. Death Stud 2009;33:691-711.
3. Lichtenthal WG, Nilsson M, Kissane DW et al. Psychiatr Serv 2011;62:1225-9.
4. Reynolds CF 3rd, Miller MD, Pasternak RE et al. Am J Psychiatry 1999;156:202-8.
5. Komischke-Konnerup KB, Zachariae R, Boelen PA et al. J Consult Clin Psychol 2024;92:236-48.
6. Prigerson HG, Boelen PA, Xu J et al. World Psychiatry 2021;20:96-106.
7. Prigerson HG, Singer J, Killikelly C. Am J Geriatr Psychiatry 2024;32:634.
8. Reed GM, First MB, Billieux J et al. World Psychiatry 2022;21:189-213.
9. Smid GE, Groen S, de la Rie SM et al. Psychiatr Serv 2018;69:1050-2.

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Suicide crisis syndrome: a specific diagnosis to aid suicide prevention

Suicide is a global public health issue, claiming over 700,000 lives annually worldwide. Opportunities for intervention are ample, as half of suicide decedents contacted a health care provider within a month of their deaths. In these encounters, suicide risk assessments are based on patients' self-report of suicidal intent and chronic risk factors, such as past attempts and prior psychiatric diagnoses. Yet, up to 75% of those dying by suicide explicitly denied suicidal intent at their last meeting with a health professional[1], and almost 20% of suicide attempters do not have a diagnosable mental disorder[2]. Moreover, traditional risk factors, such as previous suicide attempts and history of mental illness, do not reliably predict short-term suicide risk[3].

Over the last decade, several independent research teams have documented the existence of specific acute mental states associated with emergence of suicidal behavior. However, neither the DSM nor the ICD ever carried a diagnosis referring to these states. The suicide crisis syndrome (SCS) aims to fill this gap in psychiatric nosology and is under review for inclusion in the DSM. This diagnosis provides a systematic tool for recognizing and treating a mental disorder presenting imminent suicide risk without relying on self-reported suicidal intent[4].

SCS is the last and most acute stage of the Narrative Crisis Model of suicide (NCM), which reflects the progression of suicidal risk from chronic risk factors to imminent suicidal risk, and provides a comprehensive framework for the design and implementation of treatments that specifically target each of the four stages in the suicidal process[5].

The empirically-driven SCS criteria have evolved iteratively over a period of 15 years. They incorporate five empirically validated domains, which together constitute a unidimensional syndrome. Suicidal ideation is not included, due to its demonstrated unreliability as an indicator of imminent suicidal behavior. The first SCS domain, criterion A, features a persistent and intense feeling of frantic hopelessness, in which the individual feels trapped in a situation experienced both as intolerable and inescapable. Criterion B includes four distinct symptom dimensions: B1 Affective disturbance, B2 Loss of cognitive control, B3 Hyperarousal, and B4 Social withdrawal.

B1 Affective disturbance may manifest itself through: 1) emotional pain, 2) depressive turmoil; 3) extreme anxiety with unusual physical sensations; and 4) acute anhedonia. B2 Loss of cognitive control involves: 1) ruminations; 2) cognitive rigidity; 3) failed thought suppression; and 4) ruminative flooding – loss of control over thoughts accompanied by headaches or head pressure. B3 Hyperarousal involves: 1) agitation/restlessness; 2) hypervigilance, i.e. an intense and exaggerated responsiveness to sensory inputs; 3) irritability; and 4) insomnia. Finally, B4 Social withdrawal involves avoidance of social engagements and evasive communication with others.

To be diagnosed with SCS, patients must meet criterion A and have at least one symptom from each of criteria B1-B4.

Several SCS assessment instruments have been developed for use among diverse populations. The latest validated self-report measures are the Revised Suicide Crisis Inventory (SCI-2) and the Suicide Crisis Inventory - Short Form (SCI-SF). The full 61-item SCI-2 reflects the five dimensions of SCS, with items rated on a 5-point Likert scale. Clinician-rated measures include the proxy-validated 14-item SCS Checklist (SCS-C)[6], and the clinically implemented Abbreviated SCS Checklist (A-SCS-C), a 5-item checklist reflecting the five symptom domains[7]. Both checklists give a dichotomous present or absent SCS diagnosis.

SCS demonstrated excellent internal consistency within and across the five symptom dimensions in US and international samples. Several US studies – as well as those conducted in India, Korea, Taiwan, Russia and Brazil – further supported the unidimensionality and 5-factor structure of SCS. Both SCI and SCI-2 scores were associated with concurrent (past month) and lifetime suicidal ideation and behaviors, and showed discriminant validity for symptoms of depression, anxiety and psychosis[8].

To date, over fifteen studies have demonstrated the predictive validity of SCS for imminent suicidal ideation, preparatory actions and suicidal attempts. Furthermore, when compared to concurrent and past suicidal ideation or attempts, SCS – as measured by the SCI and SCI-2 – was either the only significant predictor of suicide attempt, or showed incremental predictive validity for suicidal thoughts and behaviors at one-month follow-up[9]. The best prediction of suicidal behaviors was achieved when all five components of SCS were considered.

As a categorical objective diagnosis, SCS provides actionable information for front-line clinicians, potentially simplifying clinical decision-making when working with high-risk patients in emergency rooms, inpatient units, and outpatient offices. Most importantly, clinical use of SCS has resulted in high perceived clinical utility by clinicians as well as actual clinical utility in admit/discharge clinical decisions (91% concordance with SCS present/absent diagnosis). Moreover, patients with SCS had a 75% lower post-discharge general and suicide-specific emergency room readmission rate vs. those without this diagnosis.

In light of the psychometric strength and clinical utility of SCS, an increasing number of clinical settings around the world are integrating SCS diagnostic tools into their routine workflow (specifically, in Israel, Hungary, Norway, Taiwan, Chile, Turkey and Spain). To that end, the SCI-2 and SCS-C have been translated into 14 different languages across 16 countries and four continents. An ongoing study using the data from the International Suicide Prevention Assessment Research Collaboration suggests that SCS is an excellent cross-cultural predictor of concurrent suicidal behaviors, with an area under the curve ranging from 0.83 to 0.95.

The rapid dissemination of SCS assessment as a clinical tool, and its proposal for inclusion in the DSM as a suicide-specific diagnosis, have opened the door to important research questions. First, the evidence about the discriminative validity of SCS vs. other DSM conditions needs to be enhanced. While SCS has divergent validity with regard to dimensional measures of depression, hostility, phobic anxiety and interpersonal problems, discriminant validity with several diagnoses – such as major depression, panic disorder and post-traumatic stress disorder – is under investigation. Second, the duration of SCS requires clarification, as well as the relationship between repeated SCS episodes and risk for suicidal behaviors. Third, further validation is needed of the clinical utility of SCS assessment as a clinical decision tool across diverse outpatient, inpatient and emergency settings globally. Lastly, clinical trials are needed to assess the effectiveness of pharmacological and psychotherapy treatments for SCS. All of these questions are currently being investigated by our group and dozens of other researchers around the world.

A DSM (and possibly ICD) diagnosis of SCS with an assigned diagnostic code would provide clinicians with a systematic means for assessing and reducing imminent suicide risk, even in high-risk individuals denying suicidal ideation and intent, while distinguishing patients with self-reported suicidal ideation at little risk of suicidal behavior. Furthermore, the conceptual and operational clarity of SCS would likely decrease clinicians' anxiety about working with suicidal patients, in turn promoting the development of an effective therapeutic alliance. Lastly, we believe that the increased clarity of suicide risk assessment using a DSM-based SCS diagnosis would reduce legal challenges, promote education, and stimulate research for new treatments, all necessary to enhance and maximize suicide prevention.

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1. Berman AL, Silverman MM. Arch Suicide Res 2020;24(Suppl. 2):S370-80.
2. Oquendo MA, Wall M, Wang S et al. JAMA Psychiatry 2024;81:572-8.
3. Cohen LJ, Ardalan F, Yaseen Z et al. Suicide Life Threat Behav 2018;48:613-23.
4. Galynker I, Yaseen ZS, Cohen A et al. Depress Anxiety 2017;34:147-58.
5. Galynker I. The suicidal crisis: clinical guide to the assessment of imminent suicide risk. Oxford: Oxford University Press, 2023.
6. Bafna A, Rogers ML, Galynker II. J Psychiatr Res 2022;156:228-35.
7. Karsen E, Cohen LJ, White B et al. J Clin Psychiatry 2023;84:22m14655.
8. Melzer L, Forkmann T, Teismann T. Suicide Life Threat Behav 2024;54:556-74.
9. Bloch-Elkouby S, Barzilay S, Gorman BS et al. J Affect Disord 2021;295:1280-91.

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Ethical challenges in contemporary psychiatry: an overview and an appraisal of possible strategies and research needs

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Psychiatry shares most ethical issues with other branches of medicine, but also faces special challenges. The Code of Ethics of the World Psychiatric Association offers guidance, but many mental health care professionals are unaware of it and the principles it supports. Furthermore, following codes of ethics is not always sufficient to address ethical dilemmas arising from possible clashes among their principles, and from continuing changes in knowledge, culture, attitudes, and socio-economic context. In this paper, we identify topics that pose difficult ethical challenges in contemporary psychiatry; that may have a significant impact on clinical practice, education and research activities; and that may require revision of the profession's codes of ethics. These include: the relationships between human rights and mental health care, research and training; human rights and mental health legislation; digital psychiatry; early intervention in psychiatry; end-of-life decisions by people with mental health conditions; conflicts of interests in clinical practice, training and research; and the role of people with lived experience and family/informal supporters in shaping the agenda of mental health care, policy, research and training. For each topic, we highlight the ethical concerns, suggest strategies to address them, call attention to the risks that these strategies entail, and highlight the gaps to be narrowed by further research. We conclude that, in order to effectively address current ethical challenges in psychiatry, we need to rethink policies, services, training, attitudes, research methods and codes of ethics, with the concurrent input of a range of stakeholders, open minded discussions, new models of care, and an adequate organizational capacity to roll-out the implementation across routine clinical care contexts, training and research.

Key words: Ethics of psychiatry, human rights, coercive practices, mental health legislation, digital psychiatry, early intervention, conflicts of interests, end-of-life decisions, shared decision-making, experts by experience, family supporters

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Psychiatry shares most ethical issues with other branches of medicine. However, it also has to confront special ethical challenges. Psychiatrists are often called to face responsibilities that extend beyond health care *stricto sensu*: for instance, they may be expected to predict risky behaviors of the people they serve, and to somehow protect them and the public from these behaviors. Moreover, the power differential that exists in all medical specialties between users and physicians tends to be more pronounced in the mental health field, and this has contributed to generate, in some contexts, various forms of abuse that have raised widespread ethical concerns[1-3].

Although psychiatry faces unique ethical challenges, the profession has had no code of ethics until the 1970s. In 1977, after alarming reports of political abuse of the profession in some countries, the World Psychiatric Association (WPA) officially adopted the Declaration of Hawaii (the first of several international declarations dealing with the ethics of psychiatry), which was followed in 2020 by a Code of Ethics for Psychiatry[4,5].

The WPA Code of Ethics outlines the ethical principles for clinical practice of psychiatry; psychiatric education, research and publications; and public mental health. Five principles are identified which should guide the actions of all psychiatrists: beneficence, respect for users' autonomy, non-maleficence (i.e., avoiding harm), improving standards in practice, and applying expertise to the service of society (i.e., using psychiatric knowledge and skills to promote mental health).

However, ethical dilemmas may arise when the above principles seem to clash. Furthermore, ethical issues associated with psychiatry evolve as the professional and socio-cultural contexts change and new sensitivities emerge. Recent examples are the development of digital psychiatry, and the increasing awareness of the need to actively involve people with lived experience of mental health conditions (PWLE) and their family/informal supporters in clinical decision-making and service planning.

This paper identifies several current ethical challenges for the psychiatric profession, suggests possible strategies to address them, calls attention to risks entailed by the proposed strategies, and highlights the gaps to be narrowed by further research.

There is a focus on human rights throughout the paper. We cannot ignore that these rights, to which everyone is entitled by virtue of being human, have been sometimes denied – and continue to be denied in some contexts – to PWLE, nor the growing evidence that the quality of care, research and training in psychiatry crucially depends on respecting these rights[6-9].

The United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD)[10] has been an important step forward in this respect. It has represented a paradigm shift in viewing persons with disability, including disability related to a mental health condition, no longer as just "objects" of charity, medical treatment and social protection, but rather as "subjects" with rights, capable of claiming these rights and making choices. The CRPD, as interpreted by some experts and stakeholders (though contested by others), has also raised concerns about some psychiatric practices, in particular those pertaining to treatment of persons against their will, and about conventional mental health laws. These concerns are currently a lively matter of debate.

The focus on human rights is highly relevant to the ongoing changes in mental health care provision, especially in those countries that have downscaled or are downscaling large psychiatric institutions and replacing them with community-based care. The implementation and sustainability of these changes differ significantly across countries, and even across regions within the same country. Their outcome crucially depends upon a socio-economic-political landscape that discourages discrimination and supports social inclusion and equitable access to health care, including mental health care.

The development of digital tools and interventions in psychiatry can be seen as a promising way to promote equity in the access to mental health care. However, it is also generating a wide range of ethical issues, that are being actively discussed. Similar considerations apply to the area of early intervention in psychiatry. While consistent with important ethical and health care principles, and a feasible and promising way to reduce the disability burden related to mental disorders, early intervention is raising ethical concerns due to the risk of overmedicalization of transitory conditions, and the possibility of unwanted consequences of risk/vulnerability labels.

Difficult-to-solve ethical challenges also apply to another important contemporary topic: end-of-life decisions. This issue is currently debated in general medicine, but is much more controversial in psychiatry, where certain symptoms may interfere with competent decision-making.

Psychiatrists also face ethical challenges when, in line with the principle of contributing to improved standards of care, they interact with the pharmaceutical and medical device industry; when clinical activities aiming to benefit people are influenced by intellectual allegiance to a particular school of thought[11,12]; or when the pursuit of people's well-being and autonomy clashes with the psychiatrist's interest in preventing perceived or actual risks related to legal responsibility.

All the above emerging ethical challenges and conundrums are addressed in the various sections of this paper. A final section focuses on the role of PWLE and family/informal supporters in shaping the agendas concerning mental health care, research and training, and in framing mental health policies that are ethically and legally sound and are at the same time tailored to their needs. No real progress of psychiatry is likely to occur without a strong collaboration among professionals, PWLE, family/informal supporters, and policy makers[13]. While this is largely acknowledged, such a collaboration is not yet implemented at a global level.

HUMAN RIGHTS AND MENTAL HEALTH CARE, RESEARCH AND TRAINING

The modern human rights framework is based on the concept of respect for the inherent dignity of all humans[14]. It was crystallized by the UN in the Universal Declaration of Human Rights (1948)[15], which – along with the 1966 International Covenant on Civil and Political Rights[16] and International Covenant on Economic, Social and Cultural Rights[17] – forms the so-called International Bill of Human Rights[14,18]. The subject of human rights has since expanded greatly, and is now a fundamental part of our legal, political and moral landscape.

Economic, social and cultural rights (often characterized as "positive rights") include the rights to housing, food, education, employment, health, social inclusion, and cultural participation. Civil and political rights (sometimes referred to as "negative rights") include the rights to liberty; freedom from torture, cruel or degrading treatment, exploitation, violence and abuse; and equal recognition before the law. The above dichotomy has some conceptual basis: the former rights involve the obligation by the State to ensure that fundamental entitlements are provided; the latter refer to the duty by the State not to intrude into the lives of persons without a clear and defensible justification. However, it is well recognized that all human rights are interdependent, interrelated and indivisible[14,18,19].

Both mental health and human rights are concerned with social justice and social responsibility[18], and they are inextricably related in three ways[20,21]: mental health policy and practice can either protect or violate human rights; conversely, human rights violations adversely impact mental health; and finally, the promotion of mental health and human rights mutually reinforce each other.

Despite the central importance of the relationship between human rights and mental health, it was more than 40 years after the Universal Declaration of Human Rights that the rights of persons with a mental health condition received international acknowledgement. This was through the Principles for the Protection of Persons with Mental Illness and the Improvement of Mental Health Care (the Mental Illness Principles or MI Principles), adopted by the UN General Assembly in 1991[22,23].

The MI Principles included promotion of mental health and prevention of mental disorders; access to basic mental health care; provision of the least restrictive type of mental health care; self-determination; and automatic periodic review mechanisms. However, these Principles did not have legally binding status in terms of international law[24]. Moreover, they were criticized on several grounds, including failing to include organizations representing PWLE in their development, and appearing to offer weaker protection than other pre-existing human rights instruments, particularly on matters of consent to treatment[25,26].

Although the International Bill of Human Rights protected the rights of all persons, in practice several particularly vulnerable groups were neglected. This has led to the development, in the past four decades, of treaties concerning particular groups, with children (Convention on the Rights of the Child), women (Convention on Elimination of All Forms of Discrimination Against Women) and racial minorities (International Convention on the Elimination of All Forms of Racial Discrimination) being prominent examples. These specific conventions do not create new rights, but elaborate and expand on the realization of rights included in the International Bill, focusing on the special needs of these groups.

In the last three decades, advocacy by persons with disabilities and their representative organizations has led to the recognition that these persons were another special group and to the acknowledgement that a specific convention was required to protect their rights. The CRPD was adopted by the UN in 2006, after five years of negotiations between various stakeholders, including government delegations, UN representatives, human rights agencies and organizations working in the field, and, uniquely, PWLE and family supporter bodies[10]. The Convention entered into force in 2008.

The CRPD emphasizes economic, social and cultural rights, including the right to life (Article 10), and rights concerning independent living and inclusion/participation in the community (Article 19), home and family (Article 23), education (Article 24), health (Article 25), habilitation and rehabilitation (Article 26), work and employment (Article 27), adequate standard of living and social protection (Article 28), and participation in cultural life (Article 30). Civil and political rights are also stressed in the CRPD, including equal recognition before the law (Article 12); freedom from torture or cruel, inhuman or degrading treatment or punishment (Article 15); and freedom from exploitation, violence and abuse[27,28].

The human rights framework adopted by the CRPD requires a renewed focus on respect for the dignity and autonomy of PWLE. The Convention states that "persons with disabilities have the right to 'legal capacity' – that is the right to legal standing as well as legal agency – on an equal basis with others" (Article 12); "the existence of a disability shall in no case justify a deprivation of liberty" (Article 14); and "every person with disability has a right to respect for his or her physical and mental integrity on an equal basis with others" (Article 17).

Some scholars and organizations, as well as the UN Committee set up to monitor the implementation of the Convention (CRPD Committee), interpret these articles as prohibiting involuntary psychiatric hospitalization and treatment, as well as the appointment of substitute decision makers, in any circumstances[29,30]. They claim that the "rights, will and preferences" of the person must always be respected, and the State is obliged to ensure that support is provided to persons to allow them to express their "will and preferences". However, other commentators regard this interpretation as "absolutist" or "radical" and unrealistic. They have argued that, despite support, it may be sometimes difficult to determine what are the will and preferences of the individual concerned.

In such circumstances, the CRPD Committee states that the "best interpretation of the will and preferences of the individual" should be considered. In practice, this principle may be very close to "substitute decision-making". Medical professionals contend that there are occasions when substitute decision-making is required to protect other key rights, including the right to health or the right to life[31-33]. Accordingly, the WPA Code of Ethics calls for respecting the autonomy and dignity of persons with mental health conditions, but recognizes that involuntary psychiatric interventions may be required, as a last resort, when less restrictive interventions have failed, to protect safety and to restore the person's autonomy[4].

Attention is also drawn to CRPD Article 12.4, which states that any measure affecting the exercise of "legal capacity" must apply for the shortest period, be free from conflicts of interests, and have strong safeguards in place. Coercive and restrictive interventions continue to be over-used in psychiatry. Hence, the WPA has issued a position statement and set up a task force to implement alternatives to coercion in mental health care[34,35].

The age-old principles of beneficence and non-maleficence must be respected, but the human rights framework encourages the profession of psychiatry to emancipate itself from a paternalistic and institutional mentality, and shift the pendulum towards respecting the autonomy and dignity of PWLE, while also advocating for necessary supports to be available[36].

While it can be argued that coercive interventions may sometimes be required as a life-saving measure or to restore autonomy, the widespread over-use of these interventions in psychiatry is a function and reflection of risk aversion in society. Therefore, any attempts to shift the pendulum in clinical practice towards greater respect for people's autonomy must be accompanied by a societal level discussion on human rights promotion, stigma, media sensationalism, and risk appetite (i.e., the level of risk that can be accepted) within political circles and society at large.

Overt paternalism cannot be replaced by neglect and abandonment of PWLE. The CRPD does not advocate for such a move either. A human rights-based focus on alternatives to coercion is required, along with a recognition that risks and mistakes are part of the human endeavor, including for people with a psychosocial disability. This focus can be implemented in locally adapted ways through evidence-based, recovery-oriented, and trauma-informed practices in services that are community-based, and work within a system of collaborative care. This approach, whether implemented at national, regional or service levels, can shift the focus of psychiatric ethics towards greater respect for persons' autonomy and dignity.

One commonly cited obstacle to the above approach is a lack of adequate resources, which then forces clinicians to rely on coercive measures. However, over-use of coercion is not restricted to scarce resource settings[37]. In order to implement a human rights-based approach, psychiatrists and other mental health professionals must advocate for and lobby to secure the necessary resources. Continuing to use coercion where there are scarce resources generates a vicious cycle, and allows the system to keep on underfunding services[38].

The WPA Code of Ethics encompasses public mental health, including mental health promotion. Human rights and social justice are complementary to promotion of mental health at a population level[39,40]. Social justice requires equal rights through equitable access to resources and opportunities, especially for people living in poverty or with disability, or who are marginalized in various ways[41,42].

We have the knowledge and means to deal with the social determinants of health, including mental health[43,44]. Equitable access to affordable housing, education and jobs, and social participation and inclusion in the community, are core responsibilities of governments. Political work is needed to ensure that knowledge is translated into action and mental health is the focus of policy makers in every sector of governments, including the health sector. The profession of psychiatry needs to embrace the human rights framework and champion the promotion of mental health and prevention of mental disorders[45], as well as the acceptance and application of the recovery paradigm in mental health care[46].

A pertinent ethical dilemma for many psychiatrists is the opportunity cost of dedicating time to public mental health promotion and prevention when they have heavy service commitments requiring their time. However, the example of cardiology is relevant here: just as cardiologists continue to focus on clinical work, while advising public health departments about the preventive role of healthy diet and exercise, psychiatrists should fulfil their clinical obligations, while advising public health departments – but also other departments, including social security, housing and criminal justice – about public mental health principles and strategies. Psychiatrists need to take every opportunity to ensure that public health departments see mental health promotion within their role, with input and guidance from mental health professionals, PWLE and family/informal supporters[39,47].

Psychiatry training needs to embrace the human rights framework, and include macro-level skills of leadership, collaborative work with PWLE and their family/informal supporters, public advocacy, and positive use of the media[48]. Psychiatric research needs to focus on social and public health aspects of mental health, as well as neuroscience and biomedicine[39].

NON-DISCRIMINATORY MENTAL HEALTH LAW

As previously discussed, the focus on human rights requires a shift in the pendulum of ethics in psychiatry from paternalism to a greater emphasis on respecting the autonomy and dignity of all people. This raises concerns about the principles governing the usual forms of mental health law and the treatment of persons against their will[49-52]. The principles commonly governing involuntary treatment in mental health law have remained fundamentally unchanged for around two centuries. They reflect deeply rooted prejudicial stereotypes of people with mental illness, i.e., that they are necessarily incapable of making sound judgments and intrinsically dangerous to others.

The conventional criteria for compulsion are the presence of a "mental disorder", usually vaguely defined, and a risk of harm to the person or to others. Such a "disorder + risk" schema can be seen as discriminating against people with a mental health condition, depriving them of rights enjoyed by those without a mental disorder diagnosis. In jurisdictions with well-developed laws governing non-consensual treatment in general medicine, it is only when a person lacks the decision-making capacity to consent to a treatment that the possibility of non-consensual treatment enters the frame. There is usually a further requirement: treatment must be in the person's "best interests". It is accepted that patients with "physical" disorders, if they have decision-making capacity, can make treatment refusals even when this may carry grave consequences.

For a person with a "mental disorder" who rejects treatment, conventional mental health law does not demand that special regard be given to the person's decision-making ability, as it is usually done for people with "physical" diseases – for example, the ability to understand important information about the illness and reasons for the proposed treatment; to appreciate the relevance of that information to one's predicament; and to use or reason with that information in the light of one's values or personal life goals[53]. Nor does the question arise of how the proposed treatment is purported to be in the person's "best interests". The perspective is essentially the clinician's, not the service user's one. The unfair discrimination towards those with a "mental disorder" is thus clear.

There is a second form of possible discrimination: the liability to preventive detention. People with mental disorders may be detained because they are deemed to present a risk of harm to others, without – like everyone else – having committed an offence (or being strongly suspected of having committed one). The overwhelming majority of people in the population presenting a risk to others do not have a mental disorder. People with a mental disorder account for only a very low proportion of cases of serious violence[54,55]. Nevertheless, civil commitment law often permits detention on the basis of risk alone for those with a mental disorder. One can argue that equals are being treated unequally. If preventive detention is to be allowed for those with a mental disorder solely on account of the risk posed to others, the same criteria should apply to everyone.

To eliminate the above forms of discrimination, a single law – covering all medical settings, including psychiatry – has been proposed. This would be applicable when a person has a difficulty in making a serious treatment decision[50,51,56]. In this proposal, involuntary treatment would only be permitted when the objecting person has an impairment of decision-making ability – from any cause – and if treatment is in the person's best interests.

There is no reason to believe that a mental capacity-based law cannot be applied in mental health care. Indeed, such a legislation has been drafted and enacted[57,58]. Measures – for example, the involvement of those who know the person well, independent advocacy, second opinions, appeals to a tribunal when there is disagreement – can be devised to ensure that PWLE are not regarded as lacking decision-making ability simply because they disagree with their doctors.

The concepts of "capacity" and "best interests" have advanced over the years, particularly in relation to the assessment of the "use" and "weigh" (or "appreciation" and "reasoning") elements of the former, and the special regard to be given to the person's beliefs and values in the assessment of the latter.

There may also be here an avenue for engagement with the CRPD[10]. As previously noted, the CRPD Committee insists that involuntary treatment of people with mental health (or "psychosocial") disabilities is prohibited[29]. The Committee argues that Article 12 of the Convention entails that all persons, regardless of their decision-making ability, must enjoy "legal capacity" on an "equal basis with others"[29]. Legal capacity involves the right to be recognized as a person before the law, as well as the right to legal agency, that is, to have one's decisions legally recognized. A distinction is maintained between "legal capacity" and "mental" or decision-making capacity, and it is argued that the latter cannot provide a justification for a deprivation of the former.

This interpretation has stirred much controversy[59]. Actually, the understanding of the implications of an advance statement or directive becomes problematic in this Committee's interpretation, throwing up a significant inconsistency[60,61].

Advance directives are a valuable tool to support persons' autonomy in a decision-making capacity-based regime. They are also endorsed as a measure to support a person's legal capacity by the CRPD Committee: "For many persons with disabilities, the ability to plan in advance is an important form of support, whereby they can state their will and preferences which should be followed at a time when they may not be in a position to communicate their wishes to others".

In an advance directive, a person, when having clear decision-making ability (Time 1), states that, if a future episode of illness should occur (Time 2), he/she – on the basis of past experience – will likely express a preference (e.g., refusal of treatment) that is not to be regarded as what he/she truly or "autonomously" desires, and thus should not be respected. If the illness episode occurs, which preference (Time 1 or 2) should be respected? The CRPD Committee provides no guidance on the question. Is it the Time 2 preference (refusal of treatment), disavowed at Time 1, that is to be followed, or that at Time 1? If it is the one expressed at Time 2, what is the point of such an advance statement?

Reference to the CRPD's expression "will and preferences" is now common, yet no authority, including the CRPD Committee, has provided a definition. What could these words mean? "Preference" has a relatively straightforward meaning: a greater liking for one alternative over another. The meaning of "will" is less clear. In ordinary language, "will" has a sense of strong resolve to act in a particular way. The "will" also has a long history in the philosophy of mind and action, where it has contested meanings. However, reasonably common is the concept of the "will" as a kind of higher-order motivating or self-governing mental structure that determines which desires, wishes or "preferences" should be translated into acts, and in which the person's "values" play a key role[60,62].

Thus, a distinction may be drawn between "the will" and "a preference". "The will" can be taken to be a manifestation of a person's deeply held, reasonably stable and coherent personal beliefs, values, commitments and conception of the good. In this sense, it is not the same as a desire, inclination, or "a preference", held in the present, even a strongly expressed one. Normally, "will" and "preferences", by and large, run together. It is when "the will" and "a preference" diverge or are contradictory, and a person needs to make a serious decision, that a problem may arise.

In this view, an advance directive is based on the difference between "the will" of a person (and its associated preferences) expressed at Time 1, and the "preferences" that the person anticipates will be expressed at Time 2 and which the person asks to be ignored as they are not what he/she "truly wills". We generally honor the person's Time 1 "will", when the instruction reflects the person's deeply held beliefs and values. The person might specify the psychological or behavioral indicators that his/her decision-making ability is sufficiently impaired to trigger the advance directive. This is especially important in the case of "self-binding" directives, in which the person may specify in substantial detail the conditions to be met for treatment to be given despite his/her objection, essentially giving an advance consent to that treatment.

To honor the Time 2 preference where a disjunction exists with that at Time 1 is to undermine the "will" or, in essence, the "autonomy" of the person and would not be consistent with the first General Principle of the CRPD ("respect for [the] inherent dignity, individual autonomy, including the freedom to make one's own choices, and independence of persons").

If this analysis is accepted, it would follow that we should give similar consideration to the person's "will" and its bearing on a decision ("preference") even if the person had not made a written advance directive, but had expressed that "will" through various statements and life choices, evidenced by people who know him/her well – for example, close relatives and friends.

This analysis of "will and preferences" adds a further dimension to the meanings of "decision-making capacity" and "best interests", which may warrant a significant reformulation. Treatment decision-making ability is undermined when there is a serious divergence, or incoherence, between the person's "will" and a currently expressed treatment "preference". A person's best interest is served primarily by acting to give effect, as far as possible, to the person's "will". The stronger is the case for an involuntary intervention, the greater is the threat to the person's "will" – that is, to his/her deeply held beliefs and values, commitments and life projects – that would result from the person enacting a contradicting "preference".

This approach has some similarity to the position taken by the German Federal Constitutional Court, based on a distinction in German Law between a person's *natürlicher Wille* ("natural will") and *freier Wille* ("free will")[63], akin to the distinction between "a preference" and "the will", respectively. The court ruled that the State's obligation to provide protection to a person who faces serious harm, and who is unable to form a "free will", permits the person's "natural will" – if impaired in its formation by the effects of an illness – to be overridden. The person's "original free will" – a competent "will" formed in the past – is to be given precedence. Support may be needed to enable the person to express that "free will".

There are situations where it may be impossible to know what the person's "will" might be – for example, where no one is available who knows the person, or the person has a severe intellectual disability and has not been able to clearly express a coherent "will". In such cases, it has been proposed that the default position would be to consider the human rights relevant to the situation as the guide for the decision to be made[64,65].

ETHICS IN GLOBAL DIGITAL PSYCHIATRY

The focus on human rights is also relevant to the digital turn in psychiatry. This turn promises improved equity and accessibility of care, thus meeting some key principles of global codes of ethics. However, digital psychiatry has given rise to a wide range of ethical and, in some cases, legal issues that warrant urgent attention.

Clear potential benefits heralded by digital developments in psychiatry include web-based and other information communication technology (ICT)-based forms of support, helping to break down geographical barriers[66-68], and facilitate confidential and anonymous help-seeking. This may provide opportunities to engage hard-to-reach populations. Those in low- and middle-resource settings may especially benefit from accessible digitally facilitated support[69]. Digital technology can also improve the availability of quality information to increase awareness of relevant forms of support, promote early identification and treatment, and help in monitoring and coordinating service provision.

However, there is potential for digital approaches to undermine face-to-face support; degrade trust between people and their mental health practitioners; threaten privacy, safety and security; undermine accountability and professional responsibility when things go wrong; and amplify discrimination and inequity along lines of race, language, gender, disability and poverty.

Artificial intelligence (AI) algorithms, for example, can be susceptible to biases arising from the data they are trained on, thus exacerbating existing disparities, because AI learns from humans and society. We must understand how AI makes decisions in various critical settings[70]. Implicit and explicit biases that can be captured by AI algorithms have been well-documented[71]. In the US, which appear to have applied automated decision-making most extensively, there is even evidence that AI has been responsible for reducing access of African-American PWLE to adequate mental health care[72].

Privacy and confidentiality can be undermined in the context of a lucrative market for people's health data, including highly sensitive data on individuals' mental health conditions[73]. In March 2023, for example, the US Federal Trade Commission filed a complaint against the online therapy company BetterHelp[74], which was fined US$ 7.8 million for allegedly revealing consumers' data to Facebook, TikTok and other technology firms. The data were used for targeted advertising, despite the company promising to keep personal data confidential. In other cases, hacking of personal records from online therapy services have also brought issues of safety and security into sharp relief[75-77].

AI chatbots have also raised safety concerns, including where they have reportedly offered harmful advice to people seeking mental health support[78-80]. These chatbots may also undermine service user autonomy when they are deployed in online mental health services without informed consent or traditional research approval[80].

Given the lack of any unified governance for digital mental health technologies, ethical principles offer the clearest guidance. But one problem with navigating the ethical issues is the great diversity of activities that fall under the banner of telepsychiatry. The World Health Organization (WHO) has defined telepsychiatry broadly, as "using information and communication technologies to provide mental health services"[81]. Accepting this broad definition poses an immediate challenge. Diverse technological practices often bring an equally diverse set of ethical and legal issues.

The range of uses for contemporary ICT in mental health is striking, including communication, information sharing (such as the sharing of electronic health records), professional decision support (including presenting data to aid professionals with decision-making), digital therapies (where technologies are used as a treatment, such as mobile apps prescribed by doctors)[82], "personalized medicine" (involving generation and analysis of "big data" concerning a person's genes, environment and behaviors to guide treatment), patient and/or population monitoring and surveillance (involving the "tracking" of individual or population health information over time, such as identifying people or communities at risk of suicide or psychosis[83,84], monitoring medication compliance by use of "digital pills"[85], or global positioning system surveillance of forensic psychiatry patients)[86], and service user informatics (e.g., supporting service users and their navigation in health systems, including personal health records, service user decision aids, and even regulatory reporting)[87].

Some of these practices appear in diverse settings, not merely in health care but also in contexts involving education (student support and monitoring tools), criminal justice (risk assessment and remote monitoring), workplaces (employment assistance programs), and the sale of direct-to-consumer products, such as the 10,000+ mental health apps on the market[88]. In this latter respect, the scale of private investment is notable: in 2021, according to one market report, digital startups focusing on mental health secured more than five billion dollars in venture capital – more than double that for any other medical issue[89], and investment further increased in 2023[90].

It is often unclear whether, and to what extent, such initiatives have been subject to scientific or ethical scrutiny. Recent reports suggest that even digital health devices cleared by the US Food and Drug Administration (FDA) lack rigor. Across all approved devices, just two had been evaluated in at least one study that was randomized and blinded and that used other rigorous standards of evidence[91]. Another study of digital health startups found no correlation between clinical robustness and the number of clinical claims, total funding, or company age[92].

There is also evidence that ethical scrutiny seldom forms a substantial part of applied research in the field[93]. Regulators are also seeking clarity as they try to move from a reactive to a proactive approach, yet questions remain as to what makes for an ideal regulatory scheme, and gaps in ethical and regulatory frameworks remain[94].

Ethical schemes continue to offer value in the evolving digital mental health environment described above. Acknowledging the frequent tension between clinical practice and the consumer-driven mobile industry has generated a plethora of ethical safeguards, focused on managing risk to the therapeutic relationship, informed consent, confidentiality, and mutual alignment of treatment goals and expectations[88]. Efforts have been made to identify ethical principles, themes and issues that cut across diverse practices[87,95-98]. Broad themes and issues include safety and security; autonomy; partnership and active involvement of PWLE impacted by new technologies; privacy; accountability; transparency; equity, non-discrimination and fairness; professional responsibility, scientific integrity, and evidence-based practice.

These general concepts may be helpful for broad discussions, but specific technological practices in specific settings will typically require closer consideration. This is occurring, for example, with the rise of digital phenotyping[99-102], electronic health records[103,104], and smartphone apps[105]. As the scientific evidence has evolved, so have the ethical concerns. For example, it is clear that digital mental health studies should include digital control groups[106], but ethical issues around blinding and control conditions remain largely unexplored.

Taking mental health apps as one example, they have not succeeded in "transforming care" as so many had hoped, despite billions of dollars of public and private investment[107]. This failure can no longer be attributed to a "digital divide" concerning access to technology, although equitable access to ICTs by PWLE remains an issue[108,109].

A first problem is digital self-determination, which remains "underdeveloped in populations with the greatest mental health needs"[107]. This is partly due to inequalities in digital literacy which are rooted in deeper inequalities in educational skills. For example, a study of UK people with serious mental illness found that, while only 12% did not own a smartphone, nearly 42% lacked the fundamental digital literacy skills necessary to use a device to advance their recovery[110].

A second problem involves concerns about efficacy and privacy. While people are interested in using mental health apps, most do not believe that these apps work and actually protect their privacy[94,107]. Most people report that they "don't think it will be helpful" when surveyed on reasons for non-use[111]. National studies in the UK and the US suggest that less than 15% of people are willing to share anonymized personal health information with a company for the purposes of improving health care[112]. Concerns about lack of efficacy and privacy are not isolated, and have been identified as barriers to uptake in low- and middle-income countries as well[113].

The third problem relates to social connections. Low engagement has quickly emerged as a leading cause of digital mental health abandonment and non-efficacy[114]. While efforts at better design, gamification and incentives may be productive, technology alone is unlikely to solve the fundamental issue. Since isolation and loneliness are public health threats, digital mental health tools will work best "when they help people form strong social connections instead of motivating them to continue focusing inward"[107]. This means that digital tools must be integrated into fuller care and treatment plans. Yet, only 25% of apps today have that capability[107]. Moreover, adding more human support comes at a cost and reduces the unlimited scalability of digital health tools. It also introduces new foci for quality control, given the variation inherent to unlicensed clinical support in the form of new app coaches, or digital navigators, who will likely drive the next generation of these tools[115].

Efforts to support digital self-determination, efficacy and privacy, and social connections can be implemented today[116]. Improving digital literacy is feasible, as demonstrated by programs such as the Digital Opportunities for Obtaining Resources and Skills (DOORS), which offers education, resources, and skills training so that participants can become comfortable and engaged using apps. App selection and verification methods have also been proposed. An example is the M-Health Index and Navigation Database (MIND), which uses the American Psychiatric Association's evaluation framework to allow clinicians to make a more informed choice between apps in a particular case[116].

Social connection and engagement can be fueled by peer supporters, who could participate in the development of a digital health literacy curriculum, but also have a crucial role to play in leading and participating in responsible governance through regulation and oversight[117]. This latter role may be particularly important to ensure opportunities to interrogate the objectives, outcomes and potential trade-offs of introducing digital approaches to psychiatric services.

The European AI Act recognizes the potential for disparities and discrimination that AI tools present. Proposals include recognition of a principle of respect for "diversity, non-discrimination and fairness", requiring AI systems to be "developed and used in a way that includes diverse actors and promotes equal access, gender equality and cultural diversity, while avoiding discriminatory impacts and unfair biases that are prohibited"[118].

Despite both hype and panic, the actual development of technology will continue at a steady pace, that necessitates reasoned, not rushed, and rational, not reactive, approaches to ensure that the next generation of digital mental health tools are more "proportionate, prudent, and person-centred"[119]. Such practices should be guided by ethical principles, professional codes of conduct, and established norms of law. They should include PWLE and family/informal supporters in their development and impact monitoring.

ETHICS OF EARLY INTERVENTION IN PSYCHIATRY

Prevention has become a social and ethical imperative in psychiatry[4,66,120], especially because the onset of most mental disorders occurs at a young age, and access to appropriate care is significantly delayed. These two elements contribute to poor clinical and functional outcomes[121,122]. Not surprisingly, mental disorders represent the 7th cause of disability-adjusted life years (DALYs) – accounting for 4.9% of the global DALYs – and the 2nd leading cause of years lived with disability (YLDs) – being responsible for 14.6% of global YLDs[123]. These figures may even be an underestimate[124].

In the last decades there has been an increasing investment in early intervention approaches. The focus has been on identifying subjects in the early stages of, or at risk for, developing a mental disorder, along with strategies favoring early access to care, early monitoring of clinical course, and implementation of early intervention. The aim is to delay or prevent the onset of disorder or improve its longitudinal trajectory[125-127], as is common for cardiovascular diseases, cancer and several other physical conditions.

One approach to early intervention is built on the clinical high-risk for psychosis (CHR-P) paradigm[125]. This paradigm identifies individuals who are at risk of developing a psychotic disorder as they show attenuated psychotic symptoms, brief and limited intermittent psychotic symptoms, or genetic risk and functional decline[127,128]. More recently, following the example of the CHR-P paradigm, researchers have developed constructs identifying risk states for other mental disorders, such as bipolar, major depressive and anxiety disorders[125,129].

Recent evidence, however, has shown that at-risk conditions have a low positive predictive value, as the majority of individuals identified as at risk for a mental disorder will never develop it[130,131]. Moreover, no tested intervention has proved effective in preventing the transition to a mental disorder[132,133]. Limitations of research paradigms, screening and recruitment methods[126,134], and concerns about cost-effectiveness[135-138] and prognostic validity[139], have fueled the debate on the usefulness of current models of early intervention[140], and have cast doubts on the possibility to implement an indicated prevention in line with the ethical principles of beneficence and non-maleficence and the pursuit of people's autonomy.

PWLE suffer from stigma (including self-stigma) and discrimination. Particularly motivated by the inclusion of the attenuated psychosis syndrome among "conditions for further study" in the DSM-5[141-145], several scholars and advocacy associations have noted that risk/vulnerability labels may carry similar risks. In fact, without appropriate public education, risk/vulnerability conditions may be confounded with the full-blown mental disorders[143,146].

Many studies reported that at-risk labelling may cause stigmatizing and self-stigmatizing attitudes[147] and called for the development of stigma-related interventions[148]. Stigma-related stress and fear of developing a serious mental illness may lead to decreased quality of life, hopelessness, anxiety and depression, and actually increase the likelihood of psychosis onset and suicidality[149]. In addition, scholars highlighted that stigma, including self-stigma, may be particularly harmful during adolescence and early adulthood, as it might interfere with normal identity development and the achievement of educational/occupational competences and social milestones[143].

However, before being formally labelled as "at-risk", individuals may already suffer from stigma and discrimination due to their behaviors and symptoms, and may internalize stereotypes and feelings of shame which may lead to social isolation[150,151]. In this case, the identification of the at-risk condition could provide an acceptable explanation of the distressing experiences, avoiding the use of negative and untrue stereotypes[152]. In fact, there is evidence that the discussion with a clinician is beneficial, as it can provide understanding and recognition, and facilitate coping and hope[153].

The unwanted consequences of risk/vulnerability labels, in addition to the uncertainty about their prognostic value and the lack of treatment options, cast doubts on the opportunity of informing patients about the risk, and on the best way to do it[154]. From an ethical point of view, the information about the presence of an at-risk condition may have a negative psychological impact, thus contradicting the principle of non-maleficence. However, choosing not to disclose the presence of an at-risk condition would violate the principle of respect for autonomy, which states that people have the right to make autonomous choices and that the duty of psychiatrists is to make them aware of the potential consequences of their choices. Being informed about one's vulnerability may help to make decisions about one's life and, in particular, clinically relevant lifestyles, such as substance use[154-156].

Surveys investigating the attitudes towards receiving information on at-risk conditions revealed a variety of perspectives and highlighted the complexity of the subject[157-160]. Attitudes about risk disclosure may vary depending on individual-related factors – such as, for instance, the diagnosis, degree of certainty[158], or current psychological condition[159] – but may also depend on cultural factors[160]. The "right not to know" has been frequently discussed as an important aspect of individual autonomy, particularly in relation to genetic diagnosis[161,162], while – for those who want to know – the quality and quantity of information to provide is difficult to define[161,163].

The ethical issue is further complicated by the differences across countries in regard to informed consent rules, by the complexity and uncertainty of the available knowledge, by the nosological status of risk/vulnerability conditions, and by the legal status of help-seeking individuals who, in many cases, are minors.

The best solution is likely to be a person-tailored approach[154,164], which takes into account a variety of factors such as age, cognitive abilities, education, comorbidity and suicide risk, while being empathetic and acknowledging the distress that even low-risk estimates may cause[165,166]. Current research gaps should be accurately explained, as well as the uncertain prognostic implications of risk conditions. For instance, the use of absolute risk (e.g., ten percent risk) instead of relative risk (ten-fold increased risk) measures, and the avoidance of terms such as "early detection" and "prodromes", in favor of a more hope-oriented terminology, have been suggested as appropriate[167,168].

In the light of the above ethical concerns, current international guidelines and empirical evidence advise against the use of risk screening tools in the general population, and emphasize the need to restrict assessment and referral to help-seeking individuals[125,127]. Several studies document that CHR-P individuals suffer from and seek help for a variety of distressing conditions, including anxiety, depression, substance abuse, cognitive impairment, social isolation, and impaired social and vocational functioning[169-171]. In addition, while only a minority of subjects develop full-blown psychosis, most non-transitioning ones have poor clinical and functional long-term outcomes[172,173]. On these grounds, while the use of pharmacological interventions for preventive purposes is not recommended, need-based and low-risk psychosocial interventions (psychoeducation, substance abuse reduction programs, cognitive training, social/vocational functioning) may be clinically and ethically justified, as the majority of targeted individuals may benefit from them[167,174].

Early identification and intervention approaches may also raise concerns relevant to the principle of social justice[4,175]. In fact, resources invested in prevention services may not reach population segments with a high prevalence of risk factors but low access to mental health services, and in particular to the few services specialized in early intervention[121,135,176,177]. Indeed, early help-seeking behavior is associated with potentially beneficial social determinants, such as higher education and stronger social support[178-181], while migrants and individuals belonging to ethnic minorities are more likely to access mental health services only when the severity of their condition requires more intense and urgent care[182,183].

There is evidence that minorities are under-represented in risk/vulnerable samples in comparison with clinical samples[184-187], though this has been questioned by proponents of the model, who in turn argue that ethnic minorities are still over-represented if compared to the general population[153].

Other approaches to early intervention in youth mental health care for people aged 12-25 years (or sometimes 15-30 years) have been developed and implemented in a number of countries, including Australia[188-190], Ireland[191,192], Canada[193,194] and the US[195]. These programs represent progress towards community engagement and stigma reduction, as well as empowerment and participation of youth and families, and service co-design[196,197]. They aim to allow "soft entry" (often through walk-in or self-referral options) to holistic assessment and care programs including brief psychosocial interventions and "supported transitioning" to secondary forms of care when engaging with individuals with more severe conditions[190,198]. They also provide digital mental health platforms as well as community awareness and prevention campaigns[199]. Many offer integrated, "one-stop-shop" care, including general health care and vocational, educational, housing and substance abuse assistance[197]. They characteristically take an approach tailored to the individual's needs and strengths[198].

Headspace in Australia is the most extensively developed of these programs to date. It has been used by youth and families across the country[200] and has received plaudits as well as critiques in regard to efficacy[201-205], cost-effectiveness[202,206], and suitability for individuals with different cultural backgrounds[207]. Evaluations of programs in other countries are underway[208-210]. Important questions remain on how to best facilitate coordination and collaboration with other institutions, including school systems and pre-existing mental health services[192,211,212]. Adaptation of these models to lower-resource settings needs to be explored.

Progress in early identification and intervention might provide convincing answers to the above ethical challenges. However, several of them – including stigma, discrimination, threats to the person's autonomy, and lack of social justice – are difficult to eliminate, and future scientific developments may even bring additional challenges. For instance, the implementation of biomarkers-based screening might increase the risk of stigma and discrimination[213], and genetic testing might require appropriate counselling to minimize the risk of misunderstanding the results[214].

The complex ethical challenges addressed above are not meant to fuel a pessimistic attitude towards the early identification of mental disorders. On the contrary, they aim to contribute to the development and dissemination of more ethically informed indicated prevention models, such as those developed for youth in the last two decades, co-designed with PWLE and characterized by a holistic and youth-friendly approach to promoting hope and resilience[190]. These programs need to be adapted to different cultural and socio-economic contexts, and financial and human resources should be found or redirected before they can be scaled up across countries.

END-OF-LIFE DECISIONS BY PEOPLE WITH MENTAL HEALTH CONDITIONS

The ethical and legal background of decisions about the end of life is complicated by some aspects of mental disorders, including symptoms that may interfere with competent decision-making. Here we discuss the ethical issues involved in the application to PWLE of some widely debated approaches in this area.

With the development of technologies that can prolong life for people with severe impairments, such as persistent vegetative states, pressure has grown for mechanisms that would allow people to decline life-sustaining interventions in situations in which they believe that their lives have lost meaning. Appeal in these discussions is typically made to the value of personal autonomy, that is, the right of a person to determine what happens to his/her body[215]. As the value of autonomy has come to predominate, countervailing considerations – such as the interests of family members in sustaining their loved ones, of the State in preserving the lives of its citizens, and of the medical profession in shaping its roles in end-of-life decisions – have been relegated to secondary concerns.

Supporting the change in attitudes regarding control over how one's life ends, the law has evolved to provide greater choice for individuals. The right of competent persons to refuse life-sustaining treatment has been widely recognized[216], along with their right in some countries to determine in advance which interventions will be applied (e.g., cardiopulmonary resuscitation, ventilators), and under what conditions[217]. These advance directives can also be used to designate a proxy decision-maker who can assume responsibility for choices about medical care, should the person become incompetent to make choices for him/herself. PWLE, as long as they are considered competent to make decisions about their treatment, can formulate advance directives in the same way as any other person.

Taking the rationale for individual autonomy in decisions about one's body a step further, a growing number of jurisdictions around the world have adopted statutes or simply implemented practices that allow physician assistance in bringing about one's death[218]. Initially, patients with untreatable conditions that were likely to result in death in the foreseeable future (e.g., within six months) were eligible to receive prescriptions from physicians for lethal doses of medication. Because of concern that some patients (for example, those with advanced amyotrophic lateral sclerosis) would be unable to take the medication themselves, this practice was extended in some jurisdictions to encompass physician administration of the medications, usually intravenously, a practice denoted by the term "euthanasia"[219].

However, people with disorders that were not likely to be rapidly fatal, but were associated with severe irremediable distress, soon argued that the restriction of physician-assisted death to terminal cases was irrational and discriminatory[220]. As a result, several countries expanded their laws to allow prescription and/or administration of fatal doses of medication in these cases as well[221]. It soon became evident that, once the principle was granted that an individual has the right to assistance in ending his/her life due to intolerable distress, it would be difficult to restrict this practice to cases involving physical illness. Thus, with similar arguments about discriminatory application of the law, several jurisdictions have extended physician-assisted death to include persons whose distress is the result of ostensibly untreatable mental disorders[222]. And, although prevailing laws still require some diagnosis that is said to be associated with intolerable and intractable distress, media reports indicate that social isolation, financial concerns, and interpersonal difficulties appear to be the motivation behind physician-assisted death in an indeterminate number of cases[223].

There has been considerable push-back against the extension of physician-assisted death to primary psychiatric indications. Among the concerns expressed are that a desire for death is frequently the manifestation of a mental disorder, especially but not exclusively depression[224]. Hence, psychiatrists who acquiesce to the desire of PWLE to end their lives, in contrast to the long-standing commitment of the profession to preventing suicide, are facilitating the worst possible outcome of a psychiatric condition.

In addition, although access to physician assistance is predicated, according to relevant national legislation, on a disorder being "unbearable and untreatable", the assessment of these criteria in psychiatry is highly fraught. How unbearable a condition is can only be judged by a person's self-report, rendering it entirely subjective and potentially derivative of the condition itself[225]. Since legislation generally provides that only treatments that patients are willing to accept can be used in determining treatability, this too resides in the hands of the patient, where the known association of hopeless/helpless attitudes with depression may play a role[226]. Assessment of decisional competence in these cases may be extraordinarily difficult, and some data suggest that it is not being done very carefully in any case. Finally, there is concern that the offer of physician assistance in dying will be used as a substitute for the provision of adequate psychiatric and psychosocial support[227], as already reported in Canada[228].

All the approaches to strengthening individual autonomy over end-of-life decisions are premised on the persons making the choices being legally competent to do so. Although the terms used to define legal competence vary across jurisdictions, they generally refer to four core concepts[229]. Competence consists in a person's abilities to understand the relevant information, appreciate its implications for his/her own situation, reason about the choice at hand, and express his/her desires with regard to the decision.

Regardless of the presence of a mental disorder, persons who manifest these four abilities to a reasonable degree are considered competent to make their own decisions. Although severe mental disorders can impair a person's ability to use his/her decisional abilities, as can the effects of other serious illnesses, most people with psychiatric diagnoses retain the power to choose for themselves. As a matter of law, people are presumed to have decisional capacity unless shown not to.

Although psychiatrists often have training in conducting assessments of decisional capacity, most physicians have little or no exposure to these concepts or their application. Even highly consequential decisions about terminating life-sustaining treatment or requesting physician-assisted death may proceed without any careful assessment of a patient's decisional abilities. Data from the Netherlands appear to indicate that, even when physician assistance or euthanasia is being sought for a psychiatric indication, non-psychiatric physicians may do the assessment, and global judgments of competence without detailed inquiry into the elements of decisional capacity may be the norm[230].

An approach to performing such assessments would take into account the importance of persons' understanding of the nature of their illness, whether psychiatric or non-psychiatric; their likely prognosis; the pain or discomfort that may be associated with their condition in the future; and possible interventions to reduce that discomfort and/or treat the underlying condition, including the option of palliative care. In addition, people should have a realistic appreciation of their condition and its prognosis, and the consequences of death, especially its irreversibility and the consequent cut-off of future possibilities of ongoing interactions with people with whom they may have meaningful relationships. They should be able to make a clear and stable choice about their preferred option (some jurisdictions have waiting periods for physician-assisted death to ensure this). Finally, they should be able to describe how they arrived at their decision, with consideration of consequences with and without treatment and/or interventions to end their lives, and some process of weighing one set of considerations against the other and arriving at a choice consistent with those considerations.

How does a physician know whether a person has performed sufficiently well on these dimensions to be competent to make the highly consequential decision of moving in a direction that would end his/her life? As noted, all persons are presumed competent in the absence of evidence to the contrary. However, high-stakes decisions such as death generally require more capacity than lower-stakes decisions. Unfortunately, there is no precise algorithm and, though instruments have been developed to assist with the assessment of capacity to make decisions about refusal of treatment or to complete an advance directive, no such tools yet exist for decisions about physician-assisted death. Significant impairment on any dimension of competence should probably be taken to indicate incapacity for a decision as consequential as death.

Many major medical associations oppose direct physician involvement in bringing about the death of patients. The American Medical Association, for example, has held that "physician-assisted suicide is fundamentally incompatible with the physician's role as healer, would be difficult or impossible to control, and would pose serious societal risks"[231]. In jurisdictions where physician-assisted death has been legalized, however, medical associations have tended to move toward neutral or favorable positions, perhaps in part to spare members who participate in these now-legal interventions from being labelled as unethical.

Psychiatric associations, however, have taken somewhat different stances. The American Psychiatric Association has rejected the practice holding that "a psychiatrist should not prescribe or administer any intervention to a non-terminally ill person for the purpose of causing death"[232]. Perhaps because of differences of opinion between jurisdictions where physician-assisted death has been legalized for mental disorders and those where it has not, the WPA Code of Ethics has a more limited proscription: "Psychiatrists avoid endorsing patients' requests for implementing termination of life-sustaining treatment or physician-assisted death, when they recognize that underlying psychopathology drives those requests"[4].

How do individual physician's ethics come into play in issues relating to end-of-life decisions? In general medical settings, psychiatrists' role will be limited to assessing patients' competence to make decisions about refusal of life-sustaining treatment, when that is in question. Given the general acceptance of the principle of patient autonomy as it applies to such choices, few psychiatrists are likely to have qualms about conducting such evaluations, and those who do should have no difficulty finding a colleague who is willing to perform them instead. The situation may be different, however, for cases in which patients are requesting physician-assisted death, since many physicians still believe that this practice conflicts with their role in sustaining life. Controversy erupted in Ontario when the College of Physicians indicated that physicians who declined to participate in such cases had an obligation to refer people to a physician who would be willing to implement their preferences. Even that degree of facilitating the process was unacceptable to some physicians, who saw the requirement as implicating them in a practice that they considered unethical[233].

Opposition among many psychiatrists to involvement in physician-assisted death for psychiatric indications is even stronger, given all the concerns mentioned above[223,234,235]. Understandably, they believe that referring a person whom they view as suicidal to a practitioner or facility that will help him/her die would be antithetical to their primary obligation to treat mental disorders and prevent suicide. Although some psychiatrists who work in jurisdictions where the practice has been legalized have accepted the legitimacy of their participation, others remain strongly opposed. Given the split in the profession and the strongly held views, it does seem reasonable to allow psychiatrists who oppose physician-assisted death to opt out of participation, including referral.

CONFLICTS OF INTERESTS IN MENTAL HEALTH CARE, RESEARCH AND TRAINING

Conflicts of interests (CoIs) are defined as a set of circumstances that may unduly interfere with physicians' professional obligations and primary interests in providing care, advancing research and scientific knowledge, and promoting public health. They can be financial, or related to professional achievements, or arising from allegiance to political/cultural beliefs or schools of thought[236,237]. The term CoI does not refer to ethical dilemmas arising from tensions between two physicians' primary interests (e.g., a conflict between the respect for a person's autonomy and the principle of non-maleficence).

CoIs can lead to misconduct and illegal or unprofessional behavior, but far more often can influence judgment in subtle ways, and most clinicians and researchers may be unaware of an existing bias in their decision-making[238]. CoIs may threaten the quality of clinical care as well as the integrity of research and education, and may jeopardize public trust in science and medicine, including psychiatry[236,239]. The issue of public trust may be particularly relevant for psychiatry, which, more often than other medical specialties, has to face a poor public image as both a profession and a scientific discipline[240-245].

Health care professionals, including psychiatrists, may benefit from relationships with pharmaceutical and biomedical manufacturers in ways that are consistent with their primary interests, as they can acquire information on new therapeutic options, have the opportunity to give their feedback to facilitate further development of industry products, and access resources to update their knowledge and continue their education. However, while both pharmaceutical companies and professionals share the goal of improving health care, important differences cannot be ignored, as companies remain profit-driven and have their primary interest in the promotion of their brand and products. In all countries, pharmaceutical companies target health care professionals through a series of marketing strategies, which may involve gifts, free meals and travels, and provision of drug samples[246,247].

Interactions between industry and professionals have raised concerns, as they can potentially influence physicians' clinical decision-making. Several studies have addressed the relationship between financial interactions and prescription patterns[248], and systematic reviews[249,250] have reported a correlation between the two, also suggesting a temporal and dose-dependent association. A study conducted in the US found that physicians were from 39% to 83% less likely to prescribe a new medication if they practiced in states with regulations against using pharmaceutical representatives to market products, in comparison with colleagues practicing in non-regulated states[251].

In the light of these concerns, attempts have been made to regulate the interactions of physicians with pharmaceutical company representatives. These have included specific restrictions on interactions or the disclosure of these interactions (either self-regulated or mandatory), especially when benefits are received by the physician. However, relevant policies and legislations show substantial heterogeneity across countries[252-255].

Both the WPA and the European Psychiatric Association (EPA) have developed sets of recommendations for psychiatrists in their relationships with the industry and in situations presenting potential CoIs[256,257]. The WPA warns psychiatrists to take with caution and critical review the information provided by industry representatives, and suggests that psychiatrists and health care organizations limit meetings and interactions with pharmaceutical company representatives, and forbid their access to patient care areas. Both the WPA and the EPA currently discourage psychiatrists from accepting meals and gifts, and the WPA additionally recommends accepting drug samples only to provide them to people who are otherwise unable to afford medications. In addition, both associations discourage psychiatrists from exposing items bearing companies' logos in the presence of service users, because these may influence the users' perceptions of the relationship between the industry and their doctors[258].

CoI concerns have led to the development of disclosure policies mandating transparent reporting of financial interactions, such as the Physician Payments Sunshine Act[259] in the US, and the Disclosure Code of the European Federation of Pharmaceutical Industries and Associations (EFPIA)[260] in Europe. Disclosure may motivate clinicians to avoid circumstances and behaviors representing potential CoIs[261,262], and aims to improve public trust in the health system through transparency. However, CoI disclosure may actually decrease trust, as it may make patients more aware of the relationships between their physicians and pharmaceutical companies[263,264].

By significantly increasing public access to data on the financial ties of the pharmaceutical and biomedical industries with health care systems, disclosure policies have allowed systematic tracking and better understanding of this complex phenomenon. In particular, recent data shed light on the existence of a complex network involving not only prescribers and industry representatives, but multiple other parties, such as regulators, supply chains, patient advocacy groups and foundations. For instance, patient advocacy groups have been the subject of increasing reports of funding from pharmaceutical companies[265-267], and may participate in drug advisory committees, drug reviews and public reimbursement decisions[268], thus indirectly influencing prescription patterns. Hence, a narrow focus on individual relationships, such as the direct ties between health care professionals and industry representatives, may overlook the role of the multiple pathways through which clinical decision-making may be indirectly influenced. These pathways, which may have cumulative effects, are far less documented, and may not be detected by policy makers [269].

CoI restriction policies have been implemented to reduce the probability of prescribing a newly marketed drug as a result of marketing activities[270,271], but their prevalence and strictness vary greatly, with North American medical schools having more frequent and stricter CoI policies as compared to European institutions[272,273].

Non-financial CoIs are also relevant to psychiatric practice, and clinical decision-making may be influenced in case of intellectual allegiance to a school of thought or to political ideas[12], or in relation to defensive practices[274]. In the case of the latter, the pursuit of the primary interest of the PWLE's well-being and autonomy may be attenuated by the physician's personal interest in preventing a perceived or actual risk of litigation or legal responsibility. For instance, the clinician may opt for overly cautious interventions – such as overmedication, hospitalization, delayed discharge from the hospital, and even coercive measures such as involuntary hospitalization – instead of less invasive ones. Although psychiatry is at low risk of malpractice claims in comparison to other specialties[275], surveys in different countries report that the majority of interviewed psychiatrists acknowledged having resorted to defensive practices, which, in their opinion, compromised the quality of the provided care[274,276,277].

CoIs may also be relevant to research activities, in which the pharmaceutical and medical device industries are often important partners[236]. Financial interactions may create secondary interests interfering with the primary goal, i.e., contributing to scientific progress through rigorous research[257]. Several studies indicate that industry funding can lead to bias in clinical trials, systematic reviews and clinical guidelines[278-281].

CoIs in research activities are currently regulated by a set of norms, policies and guidelines for researchers participating in scientific investigations, clinical trials, peer-review and publication processes, and guideline development[282-285]. However, financial CoIs do not only affect individual researchers, but also academic institutions and institutional leaders[286-289], and current policies tend to regulate even small benefits to individual researchers (e.g., free meals), while often failing to address appropriately the effects of large amount of funding for institutions[289,290]. In addition, while current policies identify different magnitudes and types of CoIs, the lack of a shared standardized taxonomy of CoIs and the dearth of studies testing the influence of different CoIs on research and publication activities limit the efficiency of restrictions[290].

Non-financial CoIs are less often acknowledged, although they may impact research as much as, or even more than, financial ones. Indeed, it has been stated that "the prospect of fame may be even more seductive than fortune"[291]. According to this perspective, non-financial CoIs should be disclosed, or even regulated, using similar policy frameworks as for financial CoIs[292]. In psychotherapy, for instance, an allegiance to a particular approach, due to personal training or involvement in previous research efforts, may significantly influence reported outcomes of results[293-296]. A systematic review of 30 meta-analyses found that researchers' allegiance to the tested psychotherapy inflated the reported effect sizes by almost 30%[297].

Concerns about non-financial CoI disclosure have included privacy violation (e.g., in the case of political or religious beliefs) and irrelevance, insofar as it duplicates publicly available information, such as intellectual positions and education, training, institutional and academic affiliations[298]. It has been argued that these CoIs may be better addressed through other approaches, such as ensuring a balance of opposing perspectives[299,300] and diversity of professional backgrounds in the involved researchers[301].

Psychiatrists often have roles as teachers, mentors and public speakers, and participate in the education of students and residents. As such, they have a professional obligation to share up-to-date, evidence-based and ethically informed knowledge[4]. In these roles, CoIs may arise when either financial or non-financial secondary interests influence the content, quality and objectivity of the teaching and training. For instance, as pharmaceutical companies aim to promote their brands, as well as new therapeutic options, they have an interest in sponsoring educational initiatives, materials and events. Education providers may receive promotional speaking fees, which may bias – or be perceived to bias – the information they provide[302]. Additionally, participants may receive gifts, reimbursements to participate in sponsored conferences, or scholarships[236,303], and the possibility that these marketing activities influence their prescription patterns cannot be ruled out. The WPA Code of Ethics indicates that psychiatrists should be presenting in sponsored educational activities only when they have control over the educational content[4].

Several regulators[304-308] have developed accreditation criteria limiting direct industry funding, as well as codes of conduct requiring management and transparent disclosure of CoIs. As noted, however, these regulations have limitations and may fail to address indirect financial ties and influences[309,310].

Recent research and policy efforts have improved transparency and thus increased our understanding of the complexity of the issue of CoIs, as well as of the relevant health care and scientific ecosystem. In this ecosystem, not only clinicians and researchers, but each individual player may have multiple financial and non-financial interactions with multiple entities[269], often in ways that are consistent with the primary interests of benefitting PWLE and society. However, all these interactions carry risks of undue influences, and growing evidence shows that commercial sponsors can influence these networks both at individual and institutional levels. Future policy and legislative efforts should not only aim to cut down such potential influences, but also promote a confluence of primary and secondary interests[291] and foster public trust through transparency and accountability.

THE ETHICAL DEMAND OF INVOLVING PEOPLE WITH LIVED EXPERIENCE AND FAMILY/INFORMAL SUPPORTERS IN ALL ASPECTS OF PSYCHIATRY

The ethical demand of involving PWLE and their family/informal supporters in all aspects of psychiatry – from clinical practice to policy development, research and training – is being increasingly acknowledged. The WPA endorsed these concepts in position statements in 2011[311] and 2023[312], and the WHO has developed a framework for meaningful engagement of PWLE[313].

A qualitative study found that PWLE often perceive the efforts of professionals to involve them in mental health care as tokenistic. They would like more information and ability to make decisions about their own care and treatment[314,315]. They feel that the relationship between the service user and the service deliverer is the most important factor in their care[315].

Much remains to be done to replace clinical practices based on the traditional therapeutic relationship – in which the roles are well defined and shaped by a thousand-year experience – by a new model of treatment that is still a work in progress. In fact, we need to consider the possible clash between the principles of autonomy and beneficence. By simply respecting people's autonomy and their decisions, physicians might betray their responsibilities and neglect the ethical principle of beneficence. In addition, other rights listed by the CRPD may not be enjoyed, including the right to the highest possible standard of health care.

Do all PWLE have sufficient knowledge and tools to take on the burden of the care decision responsibility? Would patient decision aids (PDA), i.e. tools designed by professionals to help PWLE understand treatment options and clarify their choices and preferences[316], represent a solution? Should all these tools be co-designed by professionals, PWLE and family/informal supporters together? May the responsibility of making decisions and choosing treatment options be distressing for some patients, and eventually worsen their mental conditions? Answers to these questions require further research – designed, conducted, analyzed and interpreted with the participation of PWLE and family/informal supporters.

Interest in peer support (i.e., involvement of PWLE in supporting other PWLE) has waxed and waned over the years, with a tremendous amount of activity at present[317]. PWLE perform as well as others when they are in licensed practitioner roles[317]. However, designated peer support roles are unique, with values and practices distinguishable from conventional roles[318]. In general, PWLE are particularly good at getting engagement of other PWLE, reducing the use of emergency rooms and hospitals, and reducing substance misuse[319]. Peer supporters increase users' sense of hope and control, self-care, sense of belonging to a community, life satisfaction, and the ability to change their lives[317].

However, randomized controlled trials and systematic reviews reporting on the different methodologies and effectiveness of the inclusion of peer supporters in specific contexts are greatly needed, and may aid in the identification of emerging ethical issues. For instance, it is important to ascertain that placement of peer supporters in mental health services is not exclusively driven by the need to lower the costs, and that the workload does not cause them any harm (e.g., burnout).

Concerns often voiced by family/informal supporters of PWLE include lack of information about a loved one's mental health status, difficult relationships with professionals, and limited to no familial involvement in their mental health treatment[320], as well as substantial personal burdens involved in providing care.

Training family/informal supporters is one of the suggested solutions to their burden[321,322]. With training, supporters' morbidities, perceived burden, and negative expressed emotion have been found to decrease[322]. People whose supporters received training tend to have fewer relapses than others[323]. Training supporters to identify and use their resources to make meaning from their situations, and giving them knowledge of recovery and treatment outcomes, can help them feel empowered[324].

In the last decades, evidence has accumulated about the inclusion of family members in the treatment and care of their relatives with a mental health condition[325]. Their perspectives are valuable to foster professionals' understanding of the problems related to those conditions, but also of the strengths associated with them. However, conflicts might arise between PWLE and relatives when they work together. In addition, the therapeutic relationship is based on respect for confidentiality, and there are instances in which PWLE oppose any involvement of their relatives in the process of care, or experience their involvement as creating high level of distress[326]. The psychiatrist may face pressure from both the PWLE and the family, and may need to consider the needs of both, while giving priority to the privacy and autonomy of the person for whose treatment he/she is responsible.

PWLE and caregivers have been involved as trainers of mental health professionals in the UK[327]. Topics covered in teaching ranged from communication to diagnostic skills, the experience of being a patient or caregiver, and involvement of PWLE in evaluation and research. Both medical students and their teachers found the experience to be valuable. Benefits to PWLE and supporters included feeling more confident and empowered, having their expertise valued, and improving their understanding of mental health professionals. Students developed increased empathy, greater awareness of stigma, and more positive views of the ability of PWLE to participate in their own care. Training of psychiatrists by PWLE often involves sharing narratives of recovery[328], but PWLE should not be pressured to disclose more than they are confident with, because they may find the process of revealing their past to be distressing[327].

Policy development should involve family/informal supporters and PWLE, and their inclusion is actually becoming common[329-332]. One important policy win for PWLE was that they were heavily involved in negotiating and drafting the CRPD. This treaty makes involvement of service users and family supporters a legal requirement. Therefore, no policy development, review or amendment of legislation or additions to regulations should be undertaken without including PWLE. Barriers to meaningful involvement in policy formulation include that patient organizations may not really be involved in decisions, but just be performative members of groups[333].

Most research in psychiatry is about PWLE and sometimes also about family supporters, but they are usually just the subjects of research, without direct involvement in either choosing the research directions or analyzing the results. Following from the idea of "Nothing about us without us", it is desirable in many situations for PWLE and family supporters to be part of the team that determines the goals of the research and its applications[312,334,335].

There have been attempts to assess the practice of including PWLE in research[336]. It has been found that collaboration helped both academic researchers and PWLE to develop skills, and increased the credibility of research in the broader PWLE base, resulting in more legitimacy and accountability. Later studies suggested that including PWLE also helped the production of higher-quality research, better implementation chances for chosen policies, and increased empowerment and hopes for those people who contributed to the research[333,337]. A quantitative review also found that studies with higher patient involvement achieved higher recruitment targets, and sometimes more success in funding[338].

Barriers to including PWLE in research were the challenge of an altered power structure, and the belief by some academics that psychiatric diagnoses preclude people from being able to conduct research, or concerns that they will not be objective[336]. Further concerns were lack of training for PWLE and, if they do have research expertise, the argument that they may not be representative of their wider community[336]. Also, there is not much training of researchers in how to effectively engage with PWLE[339].

The WHO framework for meaningful engagement of PWLE and family/informal supporters[313], designed for leaders of health organizations, included the following basic principles: dignity and respect, power and equity, inclusivity and intersectionality, commitment and transparency, and institutionalization (i.e., making sure that the approaches are brought into common use in all institutions) and contextualization. Enablers of engagement include: sustainable financing, redistributing power, elimination of stigmatization, integrated approaches, capacity-building, and institutionalizing engagement.

Further research should be designed and conducted together with PWLE and family/informal supporters to clarify the best strategies and practices to foster their involvement at the different levels of mental health care, training, policies and research.

DISCUSSION

We have identified several ethical challenges in contemporary psychiatry, with the aim of raising awareness, proposing possible solutions and noting the risks entailed by these, and highlighting gaps to be narrowed by further studies and critical reflection. These challenges arise, and the potential responses are considered, in the context of major social and political changes, including health policies and the need for care, across countries.

The WPA Code of Ethics offers guidance for our profession. However, many mental health professionals are unaware of its principles. While public and professional awareness of the links between human rights and mental health care has increased significantly in the last few decades, a recent review found that only 15 out of the 143 WPA Member Societies had formal ethical documents of their own, and that these were rarely reviewed and updated[340].

The paternalistic model, in which doctors decide and PWLE passively accept their decisions, is gradually being replaced by the shared decision-making model, in which PWLE are entitled to propose, discuss and make decisions, deserve trust and respect, and should be involved in all steps of health care provision, from service planning to care delivery[27]. While in theory everyone agrees with this transformation, in practice there is resistance. The new models are still to be scaled up and implemented across countries and diverse cultures, and several ethical challenges need to be addressed[341-343].

The ratification of the CRPD in most countries across the world has contributed to enhancing awareness that the human rights of people with disabilities, including those due to severe mental disorders, cannot be ignored any longer. In line with the WPA Code of Ethics, the CRPD, in whose drafting PWLE were significantly involved, requires respect for dignity and autonomy of these people in psychiatric practice. In addition, it provides a detailed articulation of these principles by referring to the right to legal capacity, to liberty, and to mental and physical integrity on an equal basis with other people.

Unfortunately, while the CRPD has provided a new and important focus on human rights for PWLE, the interpretation of some of its articles has raised concerns among psychiatrists and other stakeholders. In particular, "radical" interpretations of Articles 12 and 14 as prohibiting involuntary psychiatric treatment under any circumstances are very problematic, and raise important challenges due to the clash between different ethical principles (i.e., autonomy versus beneficence, or versus right to health and life).

Anyway, the overuse of coercive and restrictive interventions in psychiatry represents an important ethical issue and requires effective action[34,35]. Would adequate mental health laws provide an effective solution? This is difficult to say, and even more difficult in light of the argument that a law specific for mental health care may complicate, instead of solving, the relevant ethical challenges, as it would involve an additional discrimination between PWLE and people with other medical conditions. Hence, the proposal of a law applicable across all medical specialties, in all settings, when a person has a difficulty in making decisions about treatment. Whether such a proposal provides an acceptable solution for psychiatrists and colleagues in other medical branches remains to be clarified.

Adequate legislation may contribute to addressing the above-mentioned ethical challenges, provided that the right to autonomy and freedom for PWLE does not lead to their abandonment and consequent poor mental health, social isolation and socio-economic deprivation. Advances in legislation must be complemented by adequate financial and human resources, aimed at supporting the implementation of human rights-based, recovery-oriented and trauma-informed mental health care on a large scale. The participation of PWLE and family/informal supporters should be part of this transformative project, from legislative changes to service planning, organization and delivery.

How can we reconcile the costs of this transformation with constraints in resources which seem to affect most parts of the world? Should we fear a two-level mental health care system, in which human rights-based and recovery-oriented care is provided to those who can afford paying for it, while the others will be "assisted" in lower-cost services? These are further questions requiring reflection and action.

There is hope that digital solutions may contribute to addressing the described ethical challenges by breaking down geographical barriers, enabling confidential and anonymous help-seeking, providing a quick and inexpensive answer to treatment needs for those with access to the Internet, and thus freeing up resources elsewhere in mental health services. However, we should not underestimate the risk that existing inequalities in the access to and regulation of these technologies within and between countries may exacerbate health inequalities and thus raise further ethical issues.

Relevant research and policies should contribute to improve the capacity to bring digital technologies to those most in need of access to mental health care, and support the development and adequate regulation of digital solutions for culturally diverse and resource-constrained environments. Experts, including PWLE and family/informal supporters, should implement guidelines for a gradual and cautious uptake of innovative tools through a cyclic process of testing, and a constant evaluation of sustainability with respect to the local mental health system (in which each tool should be integrated), funding and government support.

All digital solutions should be designed with the participation of end-users and long-term implementers[117], and should be based on open standards, data and sources, to avoid the development of an unregulated and exploitive market. Unfortunately, this is not the most likely outcome currently. Joint coordinated initiatives involving policy makers and main stakeholders are urgently needed to design appropriate approval and regulatory procedures, including ethical, legal and context analyses.

The digital revolution might also have implications for another area affected by important ethical challenges, i.e. early intervention in psychiatry. At a first glance, this is an area in which the pros of intervention outweigh the cons: intuitively, the earlier we intervene to address a mental health condition, the more likely we are to spare suffering, avoid failures in achieving life's milestones, and prevent the onset or worsening of a mental disorder.

However, we still need to improve our ability to reach people in need of help, support and care at an early stage without causing stigmatization, stigma-related stress and fear of developing a serious mental illness, which are likely to lead to decreased quality of life, hopelessness, anxiety, depression, and even an increased risk of developing a serious mental disorder[143]. On one side, we run the risk of breaching the principle of non-maleficence by providing information and eventually intervention; on the other, we run the risk of failing to provide relevant information and intervention to persons who might otherwise, for example, persist in clinically and socially adverse lifestyles, such as substance use, social isolation, or unhealthy sleep patterns.

Currently, guidelines emphasize the need to restrict assessment and referral to help-seeking individuals (indicated prevention), and offer low-risk psychosocial interventions (psychoeducation, substance abuse reduction programs, cognitive training, social/vocational functioning). This may be clinically and ethically appropriate, when considering that the majority of targeted individuals may benefit from them and will not need a pharmacological treatment that, in turn, is likely to raise several complex ethical concerns. However, even the adoption of the above-mentioned constraints raises ethical challenges, especially relevant to the principle of social justice[4]. Help-seeking behavior is associated with beneficial social determinants, and resources invested in prevention services – especially the few providing specialized early intervention – may not reach population segments with a high prevalence of risk factors but low access to mental health care services[135,196].

There is hope that both financial and ethical issues (especially those relevant to social justice) could benefit from future implementation of biomarker-based screening, which might lead to more accurate identification of those in need of interventions, thus enabling the concentration of available resources on a limited number of people and avoiding unnecessary stigma. This apparently exciting perspective, however, also raises important ethical challenges, especially related to the potential misuse of information regarding biomarkers (including genetic variants) by insurance companies and employers who might acquire, request or use this information for their own interests. Thus, an opportunity for early mental health care could be transformed into another tool for discrimination and exclusion.

Highlighting the complex ethical challenges relevant to early intervention in psychiatry is not aimed to discourage such an important component of current models of care, but to contribute to the development and dissemination of more ethically informed prevention models, such as those co-designed with PWLE and characterized by a holistic and youth-friendly approach promoting hope and resilience[199].

Ethical challenges in contemporary psychiatry are also raised by the role of psychiatrists in end-of-life decisions for PWLE expressing a desire to die, which may be part of their mental condition. The WPA Code of Ethics states that "Psychiatrists avoid endorsing patients' requests for implementing termination of life-sustaining treatment or physician-assisted death, when they recognize that underlying psychopathology drives those requests"[4]. This is familiar to clinicians, because in our practice we often meet persons who, when suffering from depression or other severe mental disorders, express a strong desire to die and, when remitted, are thankful to those who helped them overcome their difficulties and are again happy to live their life.

However, this is not necessarily obvious to policy makers. In a context in which persons' autonomy is assigned a priority in decisions concerning health and control of their bodies, excluding PWLE from assisted life termination might be interpreted as discriminating them with respect to persons with severe physical illnesses who can freely choose to end their lives, provided that they are considered "competent to make decisions". As a matter of fact, the extension of physician-assisted death to persons with mental disorders considered untreatable has occurred already in some countries, raising at least two ethical concerns: a) in psychiatry, more than in other medical specialties, defining a condition as untreatable is a difficult task (e.g., it is not always possible to ascertain whether the lack of treatment response is real or due to poor adherence, or whether it will generalize to treatments not yet attempted); b) the disorder itself may drive the belief that the condition is untreatable, as hopelessness is part of the disorder. In any case, given the complexity of the relevant ethical challenges, psychiatrists who are strongly opposed to physician-assisted death for PWLE should be allowed to refuse both participation and referral to another psychiatrist.

The WPA Code of Ethics might also provide further recommendations relevant to CoIs in clinical care, research and training. When illustrating the "non-maleficence" principle, the Code recommends that "Psychiatrists avoid engaging in relationships with third parties, including but not limited to the pharmaceutical industry, that may compromise their primary focus on the interests of their patients. Financial relationships should always be disclosed"[4]. Does this mean that, in addition to following the existing rules which limit interactions with industry representatives, as well as their access to care facilities, a clinician should present his/her patients a CoI declaration? While such a declaration is largely used in scientific meetings and publications, and is often adopted in educational contexts, it is not part of routine clinical practice. However, many US academic medical centers post CoI disclosures on a public website, and the US Physician Payments Sunshine Act[259] established a federal website on which all payments by pharmaceutical companies to physicians are posted annually.

The available evidence shows a complex picture in which disclosure in clinical settings may lead to different outcomes. In fact, it might generate distrust, irrespective of the quality of the physician's advice and whether the disclosure is voluntary or mandatory. On the other hand, the disclosure might also produce increased trust, due to the enhanced perception of the physician's expertise.

Would the disclosure obligation also apply to non-financial CoIs? This appears even more complex, and would probably require different recommendations and procedures for different CoIs. Disclosing a CoI relevant to defensive practices is likely to have a negative impact on the therapeutic relationship, and to interfere with the person's willingness to accept the treatment.

As to research and publications, while there is no doubt that, when publishing the results of their research, psychiatrists must disclose the sources of their funding and other potential sources of bias, at the same time it is important to improve public understanding that the expression "CoI" refers to circumstances of factual or perceived risk of undue influence, and does not *per se* imply unethical behaviors. Relationships between physicians and other entities, including pharmaceutical companies, can lead to ethical problems, but it is equally true that sometimes such partnerships have led to new drug and medical device development.

Misbehaviors of some professionals should not translate into unjustified generalizations. Physicians should clearly state their relationships with all relevant individuals, companies or organizations, and in each action consider the ethical principles that should guide their behavior. However, at the same time, initiatives (e.g., debates, newspaper articles) should be implemented aimed at clarifying the correct interpretation of the term "CoI".

Further ethical questions, which are probably more relevant to psychiatry than to other medical disciplines, are those related to the involvement of PWLE and family/informal supporters. Certainly, this involvement can contribute to improving the quality of human-rights-based mental health care, research and training. However, different ethical questions may arise depending on the kind of involvement, and the involved stakeholders, as the specific concerns often differ for PWLE and family/informal supporters.

The involvement of PWLE in their own care is generally referred to as shared decision-making, a model of care apparently endorsed by all service providers but, according to service users, too often representing a merely tokenistic approach. Of course, tokenism is not in line with the main ethical principles of our practice, and especially with respect for patients' autonomy. However, much remains to be done to replace clinical practices based on the traditional therapeutic relationship with a new model of treatment that is still a work in progress.

PWLE in the role of caring for other PWLE could be an important resource in mental health care, given their ability to understand another's situation empathically through the shared experience of emotional distress. However, the evidence on the effectiveness of interventions provided by peer support workers is mixed. For patients with severe mental illnesses, for instance, there is some evidence of positive effects on measures of hope, recovery and empowerment, but there is no evidence of an impact on other important outcomes, such as hospitalization or overall symptoms. For patients with addiction issues, peer support can promote abstinence and result in increased involvement with Alcoholics Anonymous[319]. However, further better-designed research in this area is warranted.

The role of family and informal supporters in shaping the agenda of mental health care and research should not be undervalued any longer. They represent important stakeholders, especially in the context of community-based care for people with severe mental disorders. However, PWLE may be against the involvement of relatives in their own care, or experience their involvement as creating high level of distress. This represents a significant ethical challenge.

National recommendations should be developed in all countries – based on the WPA position paper on developing partnerships with PWLE and family/informal supporters[312], and on the WHO guidance for setting up new peer support mental health services[344] – in order to disseminate information on the principles that should guide this partnership. In addition, further research should be designed and conducted together with PWLE and family/informal supporters to clarify the best strategies and practices to foster their involvement at the different levels of care, training, research and policies.

In conclusion, this review of ethical challenges in contemporary psychiatry aims to stimulate critical reflection on our models of care, mental health policies, training and other educational activities, as well as research methods and products. We are confronted with radical and rapid social transformations; innovations whose consequences are difficult to predict; increased awareness of and, at the same time, obvious violations of human rights; increased focus on individual needs and autonomy that are likely to clash with decreasing societal resources; and increased demand for full participation in all aspects of mental health care, education, research and policy by PWLE and their family/informal supporters.

A rethinking is needed of policies, services, training, attitudes, research methods and codes of ethics in psychiatry. This work involves engaging with major stakeholders and open-minded discussions, as well as commitment to implementation and monitoring of locally agreed solutions across health and social policy, clinical care, training and research.

REFERENCES

1. Lopez-Munoz F, Alamo C, Dudley M et al. Psychiatry and political-institutional abuse from the historical perspective: the ethical lessons of the Nuremberg Trial on their 60th anniversary. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:791-806.
2. Buoli M, Giannuli AS. The political use of psychiatry: a comparison between totalitarian regimes. Int J Soc Psychiatry 2017;63:169-74.
3. van Voren R. Political abuse of psychiatry – an historical overview. Schizophr Bull 2010;36:33-5.
4. World Psychiatric Association. Code of Ethics for Psychiatry. www.wpanet.org/policies.
5. World Psychiatric Association. Declaration of Hawaii. J Med Ethics 1978;4:71-3.
6. Drew N, Funk M, Tang S et al. Human rights violations of people with mental and psychosocial disabilities: an unresolved global crisis. Lancet 2011;378:1664-75.
7. Drolet MJ, Rose-Derouin E, Leblanc JC et al. Ethical issues in research: perceptions of researchers, research ethics board members and research ethics experts. J Acad Ethics 2023;21:269-92.
8. Wisgalla A, Hasford J. Four reasons why too many informed consents to clinical research are invalid: a critical analysis of current practices. BMJ Open 2022;12:e050543.
9. Taljaard M, McRae AD, Weijer C et al. Inadequate reporting of research ethics review and informed consent in cluster randomised trials: review of random sample of published trials. BMJ 2011;342:d2496.
10. United Nations. Convention on the Rights of Persons with Disabilities. New York: United Nations, 2007.
11. Maj M. Financial and non-financial conflicts of interests in psychiatry. Eur Arch Psychiatry Clin Neurosci 2010;260(Suppl. 2):S147-51.
12. Maj M. Non-financial conflicts of interests in psychiatric research and practice. Br J Psychiatry 2008;193:91-2.
13. Thornicroft G, Sunkel C, Aliev AA et al. The Lancet Commission on ending stigma and discrimination in mental health. Lancet 2022;400:1438-80.
14. Donnelly J. Universal human rights in theory and practice. Ithaca and London: Cornell University Press, 2013.
15. United Nations. The Universal Declaration of Human Rights. New York: United Nations, 1948.
16. United Nations. International Covenant on Civil and Political Rights. New York: United Nations, 1966.
17. United Nations. International Covenant on Economic, Social and Cultural Rights. New York: United Nations, 1966.
18. Dudley M, Silove D, Gale F. Mental health, human rights, and their relationship: an introduction. In: Dudley M, Silove D, Gale F (eds). Mental health and human rights: vision, praxis, and courage. Oxford: Oxford University Press, 2012:1-49.
19. United Nations. Vienna Declaration and program of action. Vienna: United Nations, 1993.
20. Mann J, Gostin L, Gruskin S et al. Health and human rights. Health Hum Rights 1994;1:6-23.
21. Gostin LO, Gable L. The human rights of persons with mental disabilities: a global perspective on the application of human rights principles to mental health. Georgetown Law Faculty Publications and Other Works 2004;63:20-121.
22. United Nations. Principles for protection of persons with mental illness and for the improvement of mental health care. New York: United Nations, 1991.
23. Perlin ML, Szeli E. Mental health law and human rights – evolution and contemporary challenges. In: Dudley M, Silove D, Gale F (eds). Mental health and human rights: vision, praxis, and courage. Oxford: Oxford University Press, 2012:80-94.
24. Callard F, Sartorius N, Arboleda-Flórez J et al. Mental illness, discrimination and the law: fighting for social justice. Hoboken: Wiley, 2012.
25. Harding T. Human rights law in the field of mental health: a critical review. Acta Psychiatr Scand 2000;101:24-30.
26. Weller PJ. Lost in translation: human rights and mental health law. In: McSherry B, Weller P (eds). Rethinking rights-based mental health laws. Oxford: Hart Publishing, 2010:51-72.
27. Bartlett P. Implementing a paradigm shift: implementing the Convention on the Rights of Persons with Disabilities in the context of mental disability law. In: Centre for Human Rights and Humanitarian Law, American University Washington College of Law (ed). Torture in healthcare settings: reflections on the Special Rapporteur on Torture's 2013 Thematic Report. Washington: Centre for Human Rights and Humanitarian Law, American University Washington College of Law, 2014:169-80.
28. McSherry B. Mental health laws: where to from here. Monash University Law Review 2014;40:175-97.
29. United Nations Committee on the Rights of Persons with Disabilities. General Comment No. 1 - Article 12: Equal recognition before the law. https://www.ohchr.org.
30. Minkowitz T. Abolishing mental health laws to comply with the Convention on the Rights of Persons with Disabilities. In: McSherry B, Weller P (eds). Rethinking rights-based mental health laws. Oxford: Hart Publishing, 2010:151-77.
31. Callaghan SM, Ryan C. Is there a future for involuntary treatment in rights-based mental health law? Psychiatry Psychol Law 2014;21:747-66.
32. Dawson J. A realistic approach to assessing mental health laws' compliance

with the UNCRPD. Int J Law Psychiatry 2015;40:70-9.
33. Freeman MC, Kolappa K, de Almeida JMC et al. Reversing hard won victories in the name of human rights: a critique of the General Comment on Article 12 of the UN Convention on the Rights of Persons with Disabilities. Lancet Psychiatry 2015;2:844-50.
34. World Psychiatric Association. Implementing alternatives to coercion: a key component of improving mental health care. Position Statement. www.wpanet.org.
35. Herrman H, Allan J, Galderisi S et al. Alternatives to coercion in mental health care: WPA Position Statement and Call to Action. World Psychiatry 2022;21:159-60.
36. Mezzina R, Rosen A, Amering M et al. The practice of freedom: human rights and the global mental health agenda. In: Mezzina R, Rosen A, Amering M et al (eds). Advances in psychiatry. Cham: Springer, 2019:483-515.
37. Savage MK, Lepping P, Newton-Howes G et al. Comparison of coercive practices in worldwide mental healthcare: overcoming difficulties resulting from variations in monitoring strategies. BJPsych Open 2024;10:e26.
38. World Psychiatric Association. QualityRights Gujarat: a case study of alternatives to coercion in mental health care. Geneva: World Psychiatric Association, 2020.
39. Sartorius N, Gill N, Virani S. Fighting for human rights and social justice and the promotion of mental health: complementary efforts. World Soc Psychiatry 2023;5:97-100.
40. Maker Y, McSherry B. Human rights and the social determinants of mental health: fostering interdisciplinary research collaboration. Psychiatry Psychol Law 2023; doi: 10.1080/13218719.2023.2243297.
41. Sen A. Development as freedom. New York: Oxford University Press, 1999.
42. Nussbaum MC. Creating capabilities – The human development approach. Cambridge: Harvard University Press, 2011.
43. Marmot M. Social determinants of health inequalities. Lancet 2005;365:1099-104.
44. Marmot M. Boyer lectures – Fair Australia: social justice and the health gap. www.abc.net.au.
45. Gill NS. Human rights framework: an ethical imperative for psychiatry. Aust N Z J Psychiatry 2019;53:8-10.
46. Kestel D. Transforming mental health for all: a critical role for specialists. World Psychiatry 2022;21:333-4.
47. Moeti M, Gao GF, Herrman H. Global pandemic perspectives: public health, mental health, and lessons for the future. Lancet 2022;400:e3-7.
48. Rosen A, Gill NS, Salvador-Carulla L. The future of community psychiatry and community mental health services. Curr Opin Psychiatry 2020;33:375-90.
49. Campbell T, Heginbotham C. Mental illness: prejudice, discrimination and the law. London: Dartmouth, 1991.
50. Dawson J, Szmukler G. Fusion of mental health and incapacity legislation. Br J Psychiatry 2006;188:504-9.
51. Szmukler G. Men in white coats: treatment under coercion. Oxford: Oxford University Press, 2018.
52. Funk M, Bold ND. WHO's QualityRights initiative: transforming services and promoting rights in mental health. Health and Human Rights 2020;22:69-76.
53. Grisso T, Appelbaum PS. Assessing competence to consent to treatment: a guide for physicians and other health professionals. Oxford: Oxford University Press, 1998.
54. Flynn S, Rodway C, Appleby L et al. Serious violence by people with mental illness: national clinical survey. J Interpers Violence 2014;29:1438-58.
55. Fusar-Poli P, Sunkel C, Larrauri CA et al. Violence and schizophrenia: the role of social determinants of health and the need for early intervention. World Psychiatry 2023;22:230-1.
56. Szmukler G, Daw R, Dawson J. A model law fusing incapacity and mental health legislation. J Ment Health Law 2010;20:1-140.
57. Harper C, Davidson G, McClelland R. No longer 'anomalous, confusing and unjust': the Mental Capacity Act (Northern Ireland). Int J Ment Health Capacit Law 2016;22:57-70.
58. Northern Ireland Assembly. Mental Capacity Act (Northern Ireland) 2016. www.legislation.gov.uk.
59. Series L, Nilsson A. Article 12 CRPD: equal recognition before the law. In: Bantekas I, Stein MA, Anastasiou D (eds). The UN Convention on the Rights of Persons with Disabilities: a commentary. Oxford: Oxford University Press, 2018:339-82.
60. Szmukler G. "Capacity", "best interests", "will and preferences" and the UN Convention on the Rights of Persons with Disabilities. World Psychiatry 2019;18:34-41.
61. Scholten M, Gieselmann A, Gather J et al. Psychiatric advance directives under the Convention on the Rights of Persons with Disabilities: why advance instructions should be able to override current preferences. Front Psychiatry 2019;10:631.
62. Szmukler G. The UN Convention on the Rights of Persons with Disabilities: 'rights, will and preferences' in relation to mental health disabilities. Int J Law Psychiatry 2017;54:90-7.
63. Ward A. A major step forward in CRPD compliance by the German Federal Constitutional Court? www.lexology.com.
64. Australian Law Reform Commission. Equality, capacity and disability in Commonwealth laws. www.alrc.gov.au.
65. Duffy J. Mental capacity, dignity and the power of international human rights. Cambridge: Cambridge University Press, 2023.
66. Stein DJ, Shoptaw SJ, Vigo DV et al. Psychiatric diagnosis and treatment in the 21st century: paradigm shifts versus incremental integration. World Psychiatry 2022;21:393-414.
67. Zeavin H. The distance cure: a history of teletherapy. Cambridge: MIT Press, 2021.
68. Wilcock AD, Huskamp HA, Busch AB et al. Use of telemedicine and quality of care among Medicare enrollees with serious mental illness. JAMA Health Forum 2023;4:e233648.
69. Pendse SR, Nkemelu D, Bidwell NJ et al. From treatment to healing: envisioning a decolonial digital mental health. Presented at the CHI Conference on Human Factors in Computing Systems, New Orleans, April-May, 2022.
70. Caliskan A, Bryson JJ, Narayanan A. Semantics derived automatically from language corpora contain human-like biases. Science 2017;356:183-6.
71. Oswald FL, Mitchell G, Blanton H et al. Predicting ethnic and racial discrimination: a meta-analysis of IAT criterion studies. J Personal Soc Psychol 2013; 105:171-92.
72. Obermeyer Z, Powers B, Vogeli C et al. Dissecting racial bias in an algorithm used to manage the health of populations. Science 2019;366:447-53.
73. Kim J. Data brokers and the sale of Americans' mental health data. Durham: Duke Sanford School of Public Policy, 2023.
74. US Federal Trade Commission. FTC to ban BetterHelp from revealing consumers' data, including sensitive mental health information, to Facebook and others for targeted advertising. www.ftc.gov.
75. YLE News. Hacked therapy centre's ex-CEO gets 3-month suspended sentence. YLE News, April 18, 2023. https://yle.fi/a/74-20027665.
76. Ralston W. They told their therapists everything. Hackers leaked it all. Wired, May 4, 2021. www.wired.com.
77. Kirp D. The cyber attack that rocked the nation. Helsinki Times, December 22, 2020. www.helsinkitimes.fi.
78. Picchi A. Eating disorder helpline shuts down AI chatbot that gave bad advice. CBS News, June 1, 2023. www.cbsnews.com.
79. Jargon J. A chatbot was designed to help prevent eating disorders. Then it gave dieting tips. Wall Street Journal, June 1, 2023. www.wsj.com.
80. Xiang C. "Horribly unethical": startup experimented on suicidal teens on social media with chatbot. Vice, March 7, 2023. www.vice.com.
81. World Health Organization. The ongoing journey to commitment and transformation: digital health in the WHO European Region. Copenhagen: WHO Regional Office for Europe, 2023.
82. Oh KJ, Lee D, Ko B et al. A chatbot for psychiatric counseling in mental healthcare service based on emotional dialogue analysis and sentence generation. Presented at the 18th IEEE International Conference on Mobile Data Management, Daejeon, May-June, 2017.
83. Corsico P. The risks of risk. Regulating the use of machine learning for psychosis prediction. Int J Law Psychiatry 2019;66:101479.
84. Marks M. Artificial intelligence based suicide prediction. Yale Journal of Law and Technology 2019;21:98.
85. Flore J. Ingestible sensors, data, and pharmaceuticals: subjectivity in the era of digital mental health. New Media Soc 2020;23:2034-51.
86. Miller S. The use of monitoring conditions (GPS tracking devices)Re CMX [2014] QMHC 4. Psychiatry Psychol Law 2015;22:321-6.
87. Bossewitch J, Brown LXZ, Gooding P et al. Digital futures in mind: reflecting on technological experiments in mental health and crisis support. Melbourne: University of Melbourne, 2022.
88. Torous J, Roberts LW. Needed innovation in digital health and smartphone applications for mental health: transparency and trust. JAMA Psychiatry 2017;74:437-8.
89. Taylor NP. Digital health funding jumps to new high as investors bet big on mental health startups: report. MedTech Dive, January 21, 2022. www.medtechdive.com.
90. DeAngelis T. As funding cools, venture capitalists shift investments in mental health. American Psychological Association, January 1, 2023. www.apa.org.
91. Kumar A, Ross JS, Patel NA et al. Studies of prescription digital therapeutics of-

ten lack rigor and inclusivity: study examines prescription digital therapeutics standards. Health Aff 2023;42:1559-67.

92. Day S, Shah V, Kaganoff S et al. Assessing the clinical robustness of digital health startups: cross-sectional observational analysis. J Med Internet Res 2022;24:e37677.
93. Gooding P, Kariotis T. Ethics and law in research on algorithmic and data-driven technology in mental health care: scoping review. JMIR Ment Health 2021;8:e24668.
94. Steindl E. Safeguarding privacy and efficacy in e-mental health: policy options in the EU and Australia. Int Data Priv Law 2023;13:207-24.
95. Gooding P, Wee R. eMHIC position statement on the ethics and law of e-mental health (& call to action). https://emhicglobal.com.
96. Burr C, Morley J, Taddeo M et al. Digital psychiatry: risks and opportunities for public health and wellbeing. IEEE Trans Technol Soc 2020;1:21-33.
97. Burr C, Morley J. Empowerment or engagement? Digital health technologies for mental healthcare. In: Burr C, Milano S (eds). The 2019 yearbook of the digital ethics lab. Cham: Springer, 2020:67-88.
98. Fiske A, Henningsen P, Buyx A. Your robot therapist will see you now: ethical implications of embodied artificial intelligence in psychiatry, psychology, and psychotherapy. J Med Internet Res 2019;21:e13216.
99. Coghlan S, D'Alfonso S. Digital phenotyping: an epistemic and methodological analysis. Philos Technol 2021;34:1905-28.
100. Martinez-Martin N, Greely HT, Cho MK. Ethical development of digital phenotyping tools for mental health applications: Delphi study. JMIR Mhealth Uhealth 2021;9:e27343.
101. Martinez-Martin N, Insel TR, Dagum P et al. Data mining for health: staking out the ethical territory of digital phenotyping. NPJ Digit Med 2018;1:68.
102. Slack SK, Barclay L. First-person disavowals of digital phenotyping and epistemic injustice in psychiatry. Med Health Care Philos 2023;26:605-14.
103. Kariotis TC, Prictor M, Chang S et al. Impact of electronic health records on information practices in mental health contexts: scoping review. J Med Internet Res 2022;24:e30405.
104. Bondre A, Pathare S, Naslund JA. Protecting mental health data privacy in India: the case of data linkage with Aadhaar. Glob Health Sci Pract 2021;9:467-80.
105. Torous J, Andersson G, Bertagnoli A et al. Towards a consensus around standards for smartphone apps and digital mental health. World Psychiatry 2019; 18:97-8.
106. Goldberg SB, Sun S, Carlbring P et al. Selecting and describing control conditions in mobile health randomized controlled trials: a proposed typology. NPJ Digit Med 2023;6:181.
107. Torous J, Myrick K, Aguilera A. The need for a new generation of digital mental health tools to support more accessible, effective and equitable care. World Psychiatry 2023;22:1-2.
108. Robotham D, Satkunanathan S, Doughty L et al. Do we still have a digital divide in mental health? A five-year survey follow-up. J Med Internet Res 2016; 18:e309.
109. Ennis L, Rose D, Denis M et al. Can't surf, won't surf: the digital divide in mental health. J Ment Health 2012;21:395-403.
110. Spanakis P, Wadman R, Walker L et al. Measuring the digital divide among people with severe mental ill health using the essential digital skills framework. Perspect Public Health 2024;144:21-30.
111. Zhao X, Schueller SM, Kim J et al. Real-world adoption of mental health support among adolescents: cross-sectional analysis of the California Health Interview Survey. J Pediatr Psychol 2023; doi: 10.1093/jpepsy/jsad082.
112. Ghafur S, Van Dael J, Leis M et al. Public perceptions on data sharing: key insights from the UK and the USA. Lancet Digit Health 2020;2:e444-6.
113. Singh S, Sagar R. Time to have effective regulation of the mental health apps market: maximize gains and minimize harms. Indian J Psychol Med 2022;44: 399-404.
114. Cohen ZD, Schueller SM. Expanding, improving, and understanding behaviour research and therapy through digital mental health. Behav Res Ther 2023; 167:104358.
115. Perret S, Alon N, Carpenter-Song E et al. Standardising the role of a digital navigator in behavioural health: a systematic review. Lancet Digit Health 2023;5:e925-32.
116. Torous J. A path towards progress: lessons from the hard things about digital mental health. World Psychiatry 2022;21:419-20.
117. Australian Commission on Safety and Quality in Health Care. National safety and quality digital mental health standards – Guide for service providers. www.safetyandquality.gov.au.
118. European Commission. Regulatory framework proposal on artificial intelligence. https://digital-strategy.ec.europa.eu.
119. Kelly B. New technology, psychiatry, and the law: navigating panic, prudence, and possibility. Presented at the 1st International Conference on Decision Making in Medicine and Law: Opportunities and Pitfalls of Information Technologies, Rome, December 2023.
120. Campion J, Bhui K, Bhugra D. European Psychiatric Association (EPA) guidance on prevention of mental disorders. Eur Psychiatry 2012;27:68-80.
121. Howes OD, Whitehurst T, Shatalina E et al. The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. World Psychiatry 2021;20:75-95.
122. Menculini G, Verdolini N, Gobbicchi C et al. Clinical and psychopathological correlates of duration of untreated illness (DUI) in affective spectrum disorders. Eur Neuropsychopharmacol 2022;61:60-70.
123. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry 2022;9:137-50.
124. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. Lancet Psychiatry 2016;3:171-8.
125. Fusar-Poli P, Correll CU, Arango C et al. Preventive psychiatry: a blueprint for improving the mental health of young people. World Psychiatry 2021;20:200-21.
126. Fusar-Poli P, Salazar de Pablo G, Correll CU et al. Prevention of psychosis: advances in detection, prognosis, and intervention. JAMA Psychiatry 2020;77: 755-65.
127. Schmidt SJ, Schultze-Lutter F, Schimmelmann BG et al. EPA guidance on the early intervention in clinical high risk states of psychoses. Eur Psychiatry 2015;30:388-404.
128. Schultze-Lutter F, Michel C, Schmidt SJ et al. EPA guidance on the early detection of clinical high risk states of psychoses. Eur Psychiatry 2015;30:405-16.
129. Ratheesh A, Cotton SM, Davey CG et al. Ethical considerations in preventive interventions for bipolar disorder. Early Interv Psychiatry 2017;11:104-12.
130. Fusar-Poli P, Bonoldi I, Yung AR et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry 2012;69:220-9.
131. Oliver D, Arribas M, Radua J et al. Prognostic accuracy and clinical utility of psychometric instruments for individuals at clinical high-risk of psychosis: a systematic review and meta-analysis. Mol Psychiatry 2022;27:3670-8.
132. Fusar-Poli P, Radua J, Jauhar S. Lack of robust meta-analytic evidence to favour cognitive behavioural therapy for prevention of psychosis. World Psychiatry 2021;20:443-44.
133. Davies C, Cipriani A, Ioannidis JPA et al. Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. World Psychiatry 2018;17:196-209.
134. Fusar-Poli P, Schultze-Lutter F, Cappucciati M et al. The dark side of the moon: meta-analytical impact of recruitment strategies on risk enrichment in the clinical high risk state for psychosis. Schizophr Bull 2016;42:732-43.
135. Ajnakina O, David AS, Murray RM. 'At risk mental state' clinics for psychosis – an idea whose time has come – and gone! Psychol Med 2019;49:529-34.
136. McCrone P. Does early intervention for psychosis services make economic sense? Ment Health Today 2012;Jan-Feb:30-3.
137. Amos A. Unsystematic review shows neither that early intervention in psychosis is cost-effective nor cost-minimising. Br J Psychiatry 2019;215:744.
138. Rosenheck R. The challenge of cost-effectiveness research on first-episode psychosis. Br J Psychiatry 2019;215:386-7.
139. Cuijpers P, Smit F, Furukawa TA. Most at-risk individuals will not develop a mental disorder: the limited predictive strength of risk factors. World Psychiatry 2021;20:224-5.
140. van Os J, Guloksuz S. A critique of the "ultra-high risk" and "transition" paradigm. World Psychiatry 2017;16:200-6.
141. Carpenter WT, van Os J. Should attenuated psychosis syndrome be a DSM-5 diagnosis? Am J Psychiatry 2011;168:460-3.
142. Shrivastava A, McGorry PD, Tsuang M et al. "Attenuated psychotic symptoms syndrome" as a risk syndrome of psychosis, diagnosis in DSM-V: the debate. Indian J Psychiatry 2011;53:57-65.
143. Yang LH, Wonpat-Borja AJ, Opler MG et al. Potential stigma associated with inclusion of the psychosis risk syndrome in the DSM-V: an empirical question. Schizophr Res 2010;120:42-8.
144. Koren D. Early detection and intervention in psychiatry in the post-DSM-5 publication era: is it time to rethink the trees we bark up? Early Interv Psychiatry 2013;7:235-7.
145. Tsuang MT, van Os J, Tandon R et al. Attenuated psychosis syndrome in DSM-5. Schizophr Res 2013;150:31-5.
146. Corcoran C, Malaspina D, Hercher L. Prodromal interventions for schizo-

phrenia vulnerability: the risks of being "at risk". Schizophr Res 2005;73:173-84.
147. Colizzi M, Ruggeri M, Lasalvia A. Should we be concerned about stigma and discrimination in people at risk for psychosis? A systematic review. Psychol Med 2020;50:705-26.
148. DeLuca JS, Yang LH, Lucksted AA et al. Reducing stigma among youth at risk for psychosis: a call to action. Schizophr Bull 2021;47:1512-4.
149. Rüsch N, Heekeren K, Theodoridou A et al. Stigma as a stressor and transition to schizophrenia after one year among young people at risk of psychosis. Schizophr Res 2015;166:43-8.
150. Yang LH, Link BG, Ben-David S et al. Stigma related to labels and symptoms in individuals at clinical high-risk for psychosis. Schizophr Res 2015;168:9-15.
151. Anglin DM, Greenspoon MI, Lighty Q et al. Spontaneous labelling and stigma associated with clinical characteristics of peers 'at-risk' for psychosis. Early Interv Psychiatry 2014;8:247-52.
152. Corcoran CM. Ethical and epidemiological dimensions of labeling psychosis risk. AMA J Ethics 2016;18:633-42.
153. Yung AR, Wood SJ, Malla A et al. The reality of at risk mental state services: a response to recent criticisms. Psychol Med 2021;51:212-8.
154. Mittal VA, Dean DJ, Mittal J et al. Ethical, legal, and clinical considerations when disclosing a high-risk syndrome for psychosis. Bioethics 2015;29:543-56.
155. Firth J, Solmi M, Wootton RE et al. A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. World Psychiatry 2020;19:360-80.
156. Reeve S, Nickless A, Sheaves B et al. Sleep duration and psychotic experiences in patients at risk of psychosis: a secondary analysis of the EDIE-2 trial. Schizophr Res 2019;204:326-33.
157. Wang J, Eccles H, Nannarone M et al. Does providing personalized depression risk information lead to increased psychological distress and functional impairment? Results from a mixed-methods randomized controlled trial. Psychol Med 2020;52:2071-9.
158. Meiser B, Mitchell PB, McGirr H et al. Implications of genetic risk information in families with a high density of bipolar disorder: an exploratory study. Soc Sci Med 2005;60:109-18.
159. Alder RG, Young JL, Russell EI et al. The impact and desirability of news of risk for schizophrenia. PLoS One 2013;8:e62904.
160. Ruiz B, Ceccolini CJ, Shah BB et al. Stigma and coping experiences in Latinx individuals at clinical high-risk for psychosis. Early Interv Psychiatry 2022;16:34-41.
161. Bortolotti L, Widdows H. The right not to know: the case of psychiatric disorders. J Med Ethics 2011;37:673-6.
162. Duttge G. The right to know and not to know: predictive genetic diagnosis and non-diagnosis. Recent Results Cancer Res 2021;218:67-83.
163. Andorno R. The right not to know: an autonomy based approach. J Med Ethics 2004;30:435-40.
164. Carpiniello B, Wasserman D. European Psychiatric Association policy paper on ethical aspects in communication with patients and their families. Eur Psychiatry 2020;63:e36.
165. Woodberry KA, Powers KS, Bryant C et al. Emotional and stigma-related experiences relative to being told one is at risk for psychosis. Schizophr Res 2021; 238:44-51.
166. Schiffman J, Horton LE, Landa Y et al. Considerations for providing feedback to patients and families regarding clinical high-risk for psychosis status. Schizophr Res 2022;244:55-7.
167. Appelbaum PS. Ethical challenges in the primary prevention of schizophrenia. Schizophr Bull 2015;41:773-5.
168. Moritz S, Gawęda Ł, Heinz A et al. Four reasons why early detection centers for psychosis should be renamed and their treatment targets reconsidered: we should not catastrophize a future we can neither reliably predict nor change. Psychol Med 2019;49:2134-40.
169. Falkenberg I, Valmaggia L, Byrnes M et al. Why are help-seeking subjects at ultra-high risk for psychosis help-seeking? Psychiatry Res 2015;228:808-15.
170. Addington J, Cornblatt BA, Cadenhead KS et al. At clinical high risk for psychosis: outcome for nonconverters. Am J Psychiatry 2011;168:800-5.
171. Olvet DM, Carrión RE, Auther AM et al. Self-awareness of functional impairment in individuals at clinical high-risk for psychosis. Early Interv Psychiatry 2015;9:100-7.
172. Beck K, Andreou C, Studerus E et al. Clinical and functional long-term outcome of patients at clinical high risk (CHR) for psychosis without transition to psychosis: a systematic review. Schizophr Res 2019;210:39-47.
173. Salazar de Pablo G, Soardo L, Cabras A et al. Clinical outcomes in individuals at clinical high risk of psychosis who do not transition to psychosis: a meta-analysis. Epidemiol Psychiatr Sci 2022;31:e9.
174. Herrera SN, Sarac C, Phili A et al. Psychoeducation for individuals at clinical high risk for psychosis: a scoping review. Schizophr Res 2023;252:148-58.
175. World Psychiatric Association. Social justice for the mentally ill. Int J Soc Psychiatry 2015;61:213-4.
176. Fusar-Poli P. Why ultra high risk criteria for psychosis prediction do not work well outside clinical samples and what to do about it. World Psychiatry 2017;16:212-3.
177. Ajnakina O, Morgan C, Gayer-Anderson C et al. Only a small proportion of patients with first episode psychosis come via prodromal services: a retrospective survey of a large UK mental health programme. BMC Psychiatry 2017; 17:1-9.
178. Morgan C, Knowles G, Hutchinson G. Migration, ethnicity and psychoses: evidence, models and future directions. World Psychiatry 2019;18:247-58.
179. Hagler MA, Ferrara M, Yoviene Sykes LA et al. Sampling from different populations: sociodemographic, clinical, and functional differences between samples of first episode psychosis individuals and clinical high-risk individuals who progressed to psychosis. Schizophr Res 2023;255:239-45.
180. Fridgen GJ, Aston J, Gschwandtner U et al. Help-seeking and pathways to care in the early stages of psychosis. Soc Psychiatry Psychiatr Epidemiol 2013;48: 1033-43.
181. Allan SM, Hodgekins J, Beazley P et al. Pathways to care in at-risk mental states: a systematic review. 2021;15:1092-103.
182. Satinsky E, Fuhr DC, Woodward A et al. Mental health care utilisation and access among refugees and asylum seekers in Europe: a systematic review. Health Policy 2019;123:851-63.
183. Carson N, Lê Cook B, Alegria M. Social determinants of mental health treatment among Haitian, African American, and White youth in community health centers. J Health Care Poor Underserved 2010;21(Suppl. 2):32-48.
184. Burke T, Thompson A, Mifsud N et al. Proportion and characteristics of young people in a first-episode psychosis clinic who first attended an at-risk mental state service or other specialist youth mental health service. Schizophr Res 2022;241:94-101.
185. Geros H, Sizer H, Mifsud N et al. Migrant status and identification as ultra-high risk for psychosis and transitioning to a psychotic disorder. Acta Psychiatr Scand 2020;141:52-9.
186. Valmaggia LR, Byrne M, Day F et al. Duration of untreated psychosis and need for admission in patients who engage with mental health services in the prodromal phase. Br J Psychiatry 2015;207:130-4.
187. Lu W, Todhunter-Reid A, Mitsdarffer ML et al. Barriers and facilitators for mental health service use among racial/ethnic minority adolescents: a systematic review of literature. Front Public Health 2021;9:641605.
188. McGorry PD, Tanti C, Stokes R et al. headspace: Australia's national youth mental health foundation – where young minds come first. Med J Aust 2007; 187(Suppl. 7):S68-70.
189. McGorry P, Trethowan J, Rickwood D. Creating headspace for integrated youth mental health care. World Psychiatry 2019;18:140-1.
190. Rickwood D, Paraskakis M, Quin D et al. Australia's innovation in youth mental health care: the headspace centre model. Early Interv Psychiatry 2019;13: 159-66.
191. Buckley R, Illback R, O'Brien G et al. Description and outcome evaluation of Jigsaw: an emergent Irish mental health early intervention programme for young people. Ir J Psychol Med 2015;32:71-7.
192. O'Reilly A, O'Brien G, Moore J et al. Evolution of Jigsaw - a national youth mental health service. Early Interv Psychiatry 2022;16:561-7.
193. Iyer SN, Boksa P, Lal S et al. Transforming youth mental health: a Canadian perspective. Ir J Psychol Med 2015;32:51-60.
194. Malla A, Iyer S, Shah J et al. Canadian response to need for transformation of youth mental health services: ACCESS Open Minds (Esprits ouverts). Early Interv Psychiatry 2019;13:697-706.
195. Read H, Kohrt BA. The history of coordinated specialty care for early intervention in psychosis in the United States: a review of effectiveness, implementation, and fidelity. Community Ment Health J 2022;58:835-46.
196. Hughes F, Hebel L, Badcock P et al. Ten guiding principles for youth mental health services. Early Interv Psychiatry 2018;12:513-9.
197. van Amelsvoort T, Leijdesdorff S. Peer involvement and accessibility as key ingredients for 21st century youth mental health care services. World Psychiatry 2022;21:82-3.
198. McGorry PD, Goldstone SD, Parker AG et al. Cultures for mental health care of young people: an Australian blueprint for reform. Lancet Psychiatry 2014;1:559-68.
199. McGorry PD, Mei C, Chanen A et al. Designing and scaling up integrated youth mental health care. World Psychiatry 2022;21:61-76.
200. Rickwood D, McEachran J, Saw A et al. Sixteen years of innovation in youth

mental healthcare: outcomes for young people attending Australia's headspace centre services. PLoS One 2023;18:e0282040.

201. Kisely SR, Bastiampillai T, Allison S et al. More smoke and mirrors: fifteen further reasons to doubt the effectiveness of headspace. Australas Psychiatry 2023;31:282-91.
202. Kisely S, Looi JC. Latest evidence casts further doubt on the effectiveness of headspace. Med J Aust 2022;217:388-90.
203. Goldney RD. Early intervention services. Australas Psychiatry 2020;28:599.
204. Iorfino F, Carpenter JS, Cross SP et al. Social and occupational outcomes for young people who attend early intervention mental health services: a longitudinal study. Med J Aust 2022;216:87-93.
205. Iorfino F, McHugh C, Richards M et al. Patterns of emergency department presentations for a youth mental health cohort: data-linkage cohort study. BJPsych Open 2023;9:e170.
206. Looi JC, Allison S, Bastiampillai T. Leviathans: headspace-like behemoths swallow resources. Aust N Z J Psychiatry 2019;53:1050-1.
207. Looi JC, Kisely SR, Bastiampillai T et al. Commentary: Is Australian headspace socioculturally westernised, educated, industrialised, rich and democratic in conceptualisation and accessibility? Australas Psychiatry 2023;31:255-7.
208. Boonstra A, van Mastrigt G, Evers S et al. @ease peer-to-peer youth walk-in centres in The Netherlands: a protocol for evaluating longitudinal outcomes, follow-up results and cost-of-illness. Early Interv Psychiatry 2023;17:929-38.
209. Shah JL, Moinfar Z, Anderson KK et al. Return on investment from service transformation for young people experiencing mental health problems: approach to economic evaluations in ACCESS Open Minds (Esprits ouverts), a multi-site pan-Canadian youth mental health project. Front Psychiatry 2023;14:1030407.
210. Iyer SN, Shah J, Boksa P et al. A minimum evaluation protocol and stepped-wedge cluster randomized trial of ACCESS Open Minds, a large Canadian youth mental health services transformation project. BMC Psychiatry 2019;19:273.
211. Looi JCL, Allison S, Bastiampillai T et al. Headspace, an Australian youth mental health network: lessons for Canadian mental healthcare. J Can Acad Child Adolesc Psychiatry 2021;30:116-22.
212. McMahon J, Ryan F, Cannon M et al. Where next for youth mental health services in Ireland? Ir J Psychol Med 2019;36:163-7.
213. Brannan C, Foulkes AL, Lázaro-Muñoz G. Preventing discrimination based on psychiatric risk biomarkers. Am J Med Genet B Neuropsychiatr Genet 2019;180:159-71.
214. Smith WR, Appelbaum PS, Lebowitz MS et al. The ethics of risk prediction for psychosis and suicide attempt in youth mental health. J Pediatr 2023;263:113583.
215. Beauchamp TL. The right to die as the triumph of autonomy. J Med Philos 2006;31:643-54.
216. Meisel A. The legal consensus about foregoing life-sustaining treatment: its status and its prospects. Kennedy Inst Ethics J 1992;2:309-45.
217. Emanuel LL. Advance directives. Annu Rev Med 2008;59:187-98.
218. Calati R, Olié E, Dassa D et al. Euthanasia and assisted suicide in psychiatric patients: a systematic review of the literature. J Psychiatr Res 2021;135:153-73.
219. Emanuel EJ. Euthanasia. Historical, ethical, and empiric perspectives. Arch Intern Med 1994;154:1890-901.
220. Gunderson M, Mayo DJ. Altruism and physician assisted death. J Med Philos 1993;18:281-95.
221. Mroz S, Dierickx S, Deliens L et al. Assisted dying around the world: a status quaestionis. Ann Palliat Med 2021;10:3540-53.
222. Nicolini ME, Kim SYH, Churchill ME et al. Should euthanasia and assisted suicide for psychiatric disorders be permitted? A systematic review of reasons. Psychol Med 2020;50:1241-56.
223. Coelho R, Maher J, Gaind KS et al. The realities of medical assistance in dying in Canada. Palliat Support Care 2023;21:871-8.
224. Nicolini ME, Gastmans C, Kim SYH. Psychiatric euthanasia, suicide and the role of gender. Br J Psychiatry 2022;220:10-3.
225. Appelbaum PS. Physician-assisted death in psychiatry. World Psychiatry 2018;17:145-6.
226. Liu RT, Kleiman EM, Nestor BA et al. The hopelessness theory of depression: a quarter century in review. Clin Psychol 2015;22:345-65.
227. Lemmens T. When death becomes therapy: Canada's troubling normalization of health care provider ending of life. Am J Bioeth 2023;23:79-84.
228. Gamage M. She sought help in crisis and was suggested MAID instead. The Tyee, August 9, 2023. https://thetyee.ca.
229. Appelbaum PS. Assessment of patients' competence to consent to treatment. N Engl J Med 2007;357:1834-40.
230. Doernberg SN, Peteet JR, Kim SY. Capacity evaluations of psychiatric patients requesting assisted death in the Netherlands. Psychosomatics 2016;57:556-65.
231. American Medical Association. AMA Code of Medical Ethics. https://code-medical-ethics.ama-assn.org.
232. American Psychiatric Association. Position statement on medical euthanasia. Washington: American Psychiatric Association, 2016.
233. Carpenter T, Vivas L. Ethical arguments against coercing provider participation in MAiD (medical assistance in dying) in Ontario, Canada. BMC Med Ethics 2020;21:46.
234. Kim SYH. Canadian medical assistance in dying and the hegemony of privilege. Am J Bioeth 2023;23:1-6.
235. Appelbaum PS. Physician-assisted death for psychiatric disorders: ongoing reasons for concern. World Psychiatry 2024;23:56-7.
236. Lo B, Field MJ (eds). Conflict of interest in medical research, education, and practice. Washington: National Academies Press, 2009.
237. McCoy MS, Emanuel EJ. Why there are no "potential" conflicts of interest. JAMA 2017;317:1721-2.
238. Dana J, Loewenstein G. A social science perspective on gifts to physicians from industry. JAMA 2003;290:252-5.
239. Feldman AM, Mann DL. Restoring public trust in scientific research by reducing conflicts of interest. J Clin Invest 2019;129:3971-3.
240. United Nations. Report of the Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health. New York: United Nations, 2020.
241. Stuart H, Sartorius N, Liinamaa T. Images of psychiatry and psychiatrists. Acta Psychiatr Scand 2015;131:21-8.
242. Sartorius N. Guidance on how to combat stigmatization of psychiatry and psychiatrists. World Psychiatry 2012;11:61-2.
243. Bhugra D, Sartorius N, Fiorillo A et al. EPA guidance on how to improve the image of psychiatry and of the psychiatrist. Eur Psychiatry 2015;30:423-30.
244. Angermeyer MC, Van der Auwera S, Carta MG et al. Public attitudes towards psychiatry and psychiatric treatment at the beginning of the 21st century: a systematic review and meta-analysis of population surveys. World Psychiatry 2017;16:50-61.
245. Gaebel W, Zäske H, Zielasek J et al. Stigmatization of psychiatrists and general practitioners: results of an international survey. Eur Arch Psychiatry Clin Neurosci 2015;265:189-97.
246. Fadlallah R, Alkhaled L, Brax H et al. Extent of physician-pharmaceutical industry interactions in low- and middle-income countries: a systematic review. Eur J Public Health 2018;28:224-30.
247. Katz D, Caplan AL, Merz JF. All gifts large and small: toward an understanding of the ethics of pharmaceutical industry gift-giving. Am J Bioeth 2003;3:39-46.
248. King M, Bearman PS. Gifts and influence: conflict of interest policies and prescribing of psychotropic medications in the United States. Soc Sci Med 2017;172:153-62.
249. Mitchell AP, Trivedi NU, Gennarelli RL et al. Are financial payments from the pharmaceutical industry associated with physician prescribing? A systematic review. Ann Intern Med 2021;174:353-61.
250. Brax H, Fadlallah R, Al-Khaled L et al. Association between physicians' interaction with pharmaceutical companies and their clinical practices: a systematic review and meta-analysis. PLoS One 2017;12:e0175493.
251. Ansari B. Industry payments and physicians prescriptions: effect of a payment restriction policy. Soc Sci Med 2021;278:113942.
252. Mitchell A, Sarpatwari A, Bach PB. Industry payments to physicians are kickbacks. how should stakeholders respond? J Health Polit Policy Law 2022;47:815-33.
253. Alkhaled L, Kahale L, Nass H et al. Legislative, educational, policy and other interventions targeting physicians' interaction with pharmaceutical companies: a systematic review. BMJ Open 2014;4:e004880.
254. Grundy Q, Habibi R, Shnier A et al. Decoding disclosure: comparing conflict of interest policy among the United States, France, and Australia. Health Policy 2018;122:509-18.
255. Zarei E, Ghaffari A, Nikoobar A et al. Interaction between physicians and the pharmaceutical industry: a scoping review for developing a policy brief. Front Public Health 2022;10:1072708.
256. Appelbaum P, Arboleda-Florez J, Javed A et al. WPA recommendations for relationships of psychiatrists, health care organizations working in the psychiatric field and psychiatric associations with the pharmaceutical industry. World Psychiatry 2011;10:155-9.
257. Höschl C, Fialová L. European Psychiatric Association guidance on the conflicts of interest. Eur Psychiatry 2012;27:142-6.
258. Fadlallah R, Nas H, Naamani D et al. Knowledge, beliefs and attitudes of patients and the general public towards the interactions of physicians with the pharmaceutical and the device industry: a systematic review. PLoS One 2016;

11:e0160540.
259. American Medical Association. Physician financial transparency reports (Sunshine Act). ama-assn.org/go/sunshine.
260. European Federation of Pharmaceutical Industries and Associations (EFPIA). EFPIA code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organisations. www.efpia.eu.
261. Loewenstein G, Sunstein CR, Golman R. Disclosure: psychology changes everything. Annu Rev Econom 2014;6:391-419.
262. Stoll M, Hubenschmid L, Koch C et al. Physicians' attitudes towards disclosure of payments from pharmaceutical companies in a nationwide voluntary transparency database: a cross-sectional survey. BMJ Open 2022;12:e055963.
263. Tringale KR, Hattangadi-Gluth JA. Truth, trust, and transparency – the highly complex nature of patients' perceptions of conflicts of interest in medicine. JAMA Netw Open 2019;2:e191929.
264. Kanter GP, Carpenter D, Lehmann LS et al. US nationwide disclosure of industry payments and public trust in physicians. JAMA Netw Open 2019;2:e191947.
265. Taylor J, Denegri S. Industry links with patient organisations. BMJ 2017;356:j1251.
266. Rose SL. Patient advocacy organizations: institutional conflicts of interest, trust, and trustworthiness. J Law Med Ethics 2013;41:680-7.
267. Rose SL, Highland J, Karafa MT et al. Patient advocacy organizations, industry funding, and conflicts of interest. JAMA Intern Med 2017;177:344-50.
268. Khabsa J, Semaan A, El-Harakeh A et al. Financial relationships between patient and consumer representatives and the health industry: a systematic review. Health Expect 2020;23:483-95.
269. Chimonas S, Mamoor M, Zimbalist SA et al. Mapping conflict of interests: scoping review. BMJ 2021;375:e066576.
270. King M, Essick C, Bearman P et al. Medical school gift restriction policies and physician prescribing of newly marketed psychotropic medications: difference-in-differences analysis. BMJ 2013;346:f264.
271. Epstein AJ, Busch SH, Busch AB et al. Does exposure to conflict of interest policies in psychiatry residency affect antidepressant prescribing? Med Care 2013;51:199-203.
272. Fabbri A, Hone KR, Hrõbjartsson A et al. Conflict of interest policies at medical schools and teaching hospitals: a systematic review of cross-sectional studies. Int J Health Pol 2021;11:1274-85.
273. Guy-Coichard C, Perraud G, Chailleu A et al. Inadequate conflict of interest policies at most French teaching hospitals: a survey and website analysis. PLoS One 2019;14:e0224193.
274. Scognamiglio P, Morena D, Di Fazio N et al. Vox clamantis in deserto: a survey among Italian psychiatrists on defensive medicine and professional liability. Front Psychiatry 2023;14:1244101.
275. Jena AB, Seabury S, Lakdawalla D et al. Malpractice risk according to physician specialty. N Engl J Med 2011;365:629-36.
276. Passmore K, Leung WC. Defensive practice among psychiatrists: a questionnaire survey. Postgrad Med J 2002;78:671-3.
277. Reuveni I, Pelov I, Reuveni H et al. Cross-sectional survey on defensive practices and defensive behaviours among Israeli psychiatrists. BMJ Open 2017;7:e014153.
278. Lundh A, Lexchin J, Mintzes B et al. Industry sponsorship and research outcome. Cochrane Database Syst Rev 2017;2:MR000033.
279. Waqas A, Baig AA, Khalid MA et al. Conflicts of interest and outcomes of clinical trials of antidepressants: an 18-year retrospective study. J Psychiatr Res 2019;116:83-7.
280. Nejstgaard CH, Bero L, Hróbjartsson A et al. Association between conflicts of interest and favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: systematic review. BMJ 2020;371:m4234.
281. Tibau A, Bedard PL, Srikanthan A et al. Author financial conflicts of interest, industry funding, and clinical practice guidelines for anticancer drugs. J Clin Oncol 2015;33:100-6.
282. International Committee of Medical Journal Editors. Disclosure of financial and non-financial relationships and activities, and conflicts of interest. International Committee of Medical Journal Editors, 2022.
283. Schünemann HJ, Al-Ansary LA, Forland F et al. Guidelines International Network: principles for disclosure of interests and management of conflicts in guidelines. Ann Intern Med 2015;163:548-53.
284. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical practice guidelines we can trust. Washington: National Academies Press, 2011.
285. National Health Medical Research Council. NHMRC guidelines for guidelines: identifying and managing conflicts of interest. Canberra: National Health Medical Research Council, 2018.
286. Resnik DB, Ariansen JL, Jamal J et al. Institutional conflict of interest policies at U.S. academic research institutions. Acad Med 2016;91:242-6.
287. Resnik DB. Institutional conflicts of interest in academic research. Sci Eng Ethics 2019;25:1661-9.
288. Kahr B, Hollingsworth M. Massive faculty donations and institutional conflicts of interest. J Sci Pract Integr 2019;1:1-33.
289. Nichols-Casebolt A, Macrina FL. Current perspectives regarding institutional conflict of interest: commentary on "Institutional conflicts of interest in academic research". Sci Eng Ethics 2019;25:1671-7.
290. Graham SS, Karnes MS, Jensen JT et al. Evidence for stratified conflicts of interest policies in research contexts: a methodological review. BMJ Open 2022;12:e063501.
291. Cappola AR, FitzGerald GA. Confluence, not conflict of interest: name change necessary. JAMA 2015;314:1791-2.
292. Wiersma M, Kerridge I, Lipworth W et al. Should we try to manage non-financial interests? BMJ 2018;361:k1240.
293. Lieb K, von der Osten-Sacken J, Stoffers-Winterling J et al. Conflicts of interest and spin in reviews of psychological therapies: a systematic review. BMJ Open 2016;6:e010606.
294. Munder T, Brütsch O, Leonhart R et al. Researcher allegiance in psychotherapy outcome research: an overview of reviews. Clin Psychol Rev 2013;33:501-11.
295. Miller S, Wampold B, Varhely K. Direct comparisons of treatment modalities for youth disorders: a meta-analysis. Psychother Res 2008;18:5-14.
296. Cuijpers P, Driessen E, Hollon SD et al. The efficacy of non-directive supportive therapy for adult depression: a meta-analysis. Clin Psychol Rev 2012;32:280-91.
297. Dragioti E, Dimoliatis I, Fountoulakis KN et al. A systematic appraisal of allegiance effect in randomized controlled trials of psychotherapy. Ann Gen Psychiatry 2015;14:25.
298. Bero L. Addressing bias and conflict of interest among biomedical researchers. JAMA 2017;317:1723-4.
299. Sniderman AD, Furberg CD. Pluralism of viewpoints as the antidote to intellectual conflict of interest in guidelines. J Clin Epidemiol 2012;65:705-7.
300. Viswanathan M, Carey TS, Belinson SE et al. A proposed approach may help systematic reviews retain needed expertise while minimizing bias from nonfinancial conflicts of interest. J Clin Epidemiol 2014;67:1229-38.
301. Grundy Q. A politics of objectivity: biomedicine's attempts to grapple with "non-financial" conflicts of interest. Sci Eng Ethics 2021;27:37.
302. Scheffer PJ, Guy-Coichard C, Outh-Gauer D et al. Conflict of interest policies at French medical schools: starting from the bottom. PLoS One 2017;12:e0168258.
303. Varley CK, Jibson MD, McCarthy M et al. A survey of the interactions between psychiatry residency programs and the pharmaceutical industry. Acad Psychiatry 2005;29:40-6.
304. Accreditation Council for Continuing Medical Education. Standards for integrity and independence in accredited continuing education. Chicago: Accreditation Council for Continuing Medical Education, 2020.
305. Varetto T, Costa DC. Continuing Medical Education Committee and UEMS-EACCME. Eur J Nucl Med Mol Imaging 2013;40:470-4.
306. Union Européenne des Médecins Spécialiste/European Union of Medical Specialists. The Charter on CME of Medical Specialists in the European Union. www.uems.eu.
307. European Federation of Pharmaceutical Industries and Associations. The EFPIA Code of Practice. www.efpia.eu.
308. Union Européenne des Médecins Spécialiste/European Union of Medical Specialists. Criteria for international accreditation of CME. www.uems.eu.
309. Golestaneh L, Cowan E. Hidden conflicts of interest in continuing medical education. Lancet 2017; 390:2128-30.
310. Barnes BE. Financial conflicts of interest in continuing medical education: implications and accountability. JAMA 2017;317:1741-2.
311. Wallcraft J, Amering M, Freidin J et al. Partnerships for better mental health worldwide: WPA recommendations on best practices in working with service users and family carers. World Psychiatry 2011;10:229-36.
312. WPA Working Group on Developing Partnerships with Service Users and Family Carers. WPA position paper on developing partnerships with persons with lived experience of mental health conditions and family and informal carers. www.wpanet.org.
313. World Health Organization. WHO framework for meaningful engagement of people living with noncommunicable diseases, and mental health and neurological conditions. Geneva: World Health Organization, 2023.
314. Laitila M, Nummelin J, Kortteisto T et al. Service users' views regarding user

involvement in mental health services: a qualitative study. Arch Psychiatr Nurs 2018;32:695-701.
315. Newman D, O'Reilly P, Lee SH et al. Mental health service users' experiences of mental health care: an integrative literature review. J Psychiatr Ment Health Nurs 2015;22:171-82.
316. Stacey D, Légaré F, Lewis K et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2017;4:CD001431.
317. Davidson L, Guy K. Peer support among persons with severe mental illnesses: a review of evidence and experience. World Psychiatry 2012;11:123-8.
318. Solomon P. Peer support/peer provided services underlying processes, benefits, and critical ingredients. Psychiatr Rehabil J 2004;27:392.
319. Reif S, Braude L, Lyman DR et al. Peer recovery support for individuals with substance use disorders: assessing the evidence. Psychiatr Serv 2014;65:853-61.
320. Charbonneau DH, Akers KG. Information needs and sources for family members of individuals living with mental disorders. In: Dalmer NK, Barringe S (eds). Family matters: mapping information phenomena within the context of the family. Chicago: University of Illinois, 2022:133-48.
321. Reinhard SC. Living with mental illness: effects of professional support and personal control on caregiver burden. Res Nurs Health 1994;17:79-88.
322. Sin J, Gillard S, Spain D et al. Effectiveness of psychoeducational interventions for family carers of people with psychosis: a systematic review and meta-analysis. Clin Psychol Rev 2017;56:13-24.
323. Leff J, Kuipers L, Berkowitz R et al. A controlled trial of social intervention in the families of schizophrenic patients. Br J Psychiatry 1982;141:121-34.
324. Grant C, Ballard ED, Olson-Madden JH. An empowerment approach to family caregiver involvement in suicide prevention: implications for practice. Fam J 2015;23:295-304.
325. Bradley E. Carers and co-production: enabling expertise through experience? Ment Health Rev J 2015;20:232-41.
326. Szmukler G. Ethics in community psychiatry. Aust N Z J Psychiatry 1999;33:328-38.
327. Livingston G, Cooper C. User and carer involvement in mental health training. Adv Psychiatr Treat 2004;10:85-92.
328. Kaiser BN, Varma S, Carpenter-Song E et al. Eliciting recovery narratives in global mental health: benefits and potential harms in service user participation. Psychiatr Rehabil J 2020;43:111-20.
329. Trivedi P. 'Nothing about us, without us' – A user/survivor perspective of global mental health. Int Rev Psychiatry 2014;26:544-50.
330. Sunkel C. A lived experience perspective on the new World Mental Health Report. World Psychiatry 2022;21:390-1.
331. Bell J, Lim A, Williams R et al. 'Nothing about us without us': co-production ingredients for working alongside stakeholders to develop mental health interventions. Adv Ment Health 2023;21:4-16.
332. Isom J, Balasuriya L. Nothing about us without us in policy creation and implementation. Psychiatr Serv 2021;72:121.
333. Beames JR, Kikas K, O'Gradey-Lee M et al. A new normal: integrating lived experience into scientific data syntheses. Front Psychiatry 2021;12:763005.
334. Fusar-Poli P, Estradé A, Stanghellini G et al. The lived experience of psychosis: a bottom-up review co-written by experts by experience and academics. World Psychiatry 2022;21:168-88.
335. Fusar-Poli P, Estradé A, Stanghellini G et al. The lived experience of depression: a bottom-up review co-written by experts by experience and academics. World Psychiatry 2023;22:352-65.
336. Happell B, Roper C. Consumer participation in mental health research: articulating a model to guide practice. Australas Psychiatry 2007;15:237-41.
337. Van de Bovenkamp HM, Trappenburg MJ, Grit KJ. Patient participation in collective healthcare decision making: the Dutch model. Health Expect 2010;13:73-85.
338. Ennis L, Wykes T. Impact of patient involvement in mental health research: longitudinal study. Br J Psychiatry 2013;203:381-6.
339. Fortuna KL, Myers A, Brooks J et al. Co-production of the quality of patient-centered outcomes research partnerships instrument for people with mental health conditions. Patient Exp J 2021;8:148.
340. Bloch S, Kenn F, Lim I. Codes of ethics for psychiatrists: past, present and prospect. Psychol Med 2022;52:1201-7.
341. Elwyn G, Frosch DL, Kobrin S. Implementing shared decision-making: consider all the consequences. Implement Sci 2016;11:114.
342. Slade M. Implementing shared decision making in routine mental health care. World Psychiatry 2017;16:146-53.
343. Davidson L, Tondora J. Person-centred care planning as foundational to clinical practice. World Psychiatry 2022;21:1-2.
344. World Health Organization. Peer support mental health services: promoting person-centred and rights-based approaches. www.who.int.

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Ethical challenges in mental health care: moving beyond aspirations

The paper by Galderisi et al[1] raises an array of ethical challenges, each of which would warrant an extended response. Here I will focus on a few overarching issues.

First, it is extremely heartening to see the paper's engagement with the Convention on the Rights of Persons with Disabilities (CRPD). This has not always been the case: engagement from psychiatrists has in the past been frosty at best. The emphasis on autonomy, dignity and involvement of people with lived experience (PWLE) of psychiatric systems in care, treatment and decision-making about them is of a type that would have been uncommon twenty years ago in this sort of paper. The acknowledgement that compulsion has been and continues to be significantly over-used in psychiatry internationally, buttressed by the establishment of a working group at the WPA on developing alternatives to compulsion, suggests a significant shift in attitudes. As the paper notes, the 2020 revisions to the WPA Code of Ethics continue the movement of previous Codes towards a world where PWLE are not psychiatric objects but citizens warranting respect and dignity – a core value of the CRPD. The discussion in the paper puts some flesh on those bones from a psychiatric perspective.

As the authors acknowledge, this engagement will not satisfy those adopting a strong view of the CRPD. However, the paper does provide the hope for a productive dialogue among the diverse array of CRPD commentators about how services and support should be provided. If this takes place with a view to the values that the parties share, there is real potential for change in peoples' lives. That would be potentially significant.

The challenge is how to get these newer attitudes into effect on the ground. History is not promising in this regard. Much of the encouraging language of the 2020 WPA Code of Ethics had its roots in the earlier Declaration of Madrid, originally passed by the WPA in 1996, and even the Declaration of Hawaii passed in 1983. Those documents also spoke of therapeutic relationships founded on "mutual agreement" and trust. The Declaration of Madrid expressly enjoined psychiatrists to "devise therapeutic interventions that are least restrictive to the freedom of the patient". The patient was to be "accepted as a partner by right in the therapeutic process", and the psychiatrist was to "empower the patient to come to a rational decision according to his or her personal values and preferences". Even when the patient lacked capacity, the document enjoined that "no treatment should be provided against the patient's will, unless withholding treatment would endanger the life of the patient and/or those who surround him or her".

All too frequently, twenty-eight years after the Declaration was adopted, this continues not to be the experience of PWLE. That is reflected in their writings. Numerous reports of international inspectorates – the Council of Europe Committee for the Prevention of Torture[2] and the United Nations Subcommittee on Prevention of Torture[3] being the most obvious examples – and national non-governmental organizations make this clear. Too frequently, the principles of ethical documents have little impact on the lives of those affected. Galderisi et al acknowledge this when they say that "many mental health professionals are unaware of [the WPA Code's] principles". It is fair to ask how far changing the language of a Code which has no or little traction will actually change things.

Galderisi et al go on to state that "everyone in theory agrees" with a transition away from paternalist care and towards the new vision of patient involvement and autonomous decision-making, but "in practice there is resistance". Given the persistence of the old approaches, it is fair to ask whether in fact "everyone in theory agrees" with the new ones. Some of the inspectorate reports and the experience of law and policy reformers would suggest that sometimes the resistance comes from the majority of professionals in some countries. How do we engage professionals who really do not want to get with the programme?

Certainly, nudging towards good practice is an appropriate strategy, but a certain scepticism is appropriate. Good practice statements, manuals and guidance have been around for decades. As noted, it is not obvious that they have had an adequate impact. Certainly, the WPA initiative with the World Health Organization on implementing alternatives to coercion[4] is a positive step; but will it really be taken up by the practitioners who have thus far seemed resistant to change? It is at best doubtful.

As Galderisi's paper notes, legal reforms may help. We have seen that in the provision of research ethics committees in the countries that have introduced them (by no means all, internationally). While one can certainly debate the appropriateness of the processes that these bodies use, and the merits of individual decisions, they do have their effects. In some circumstances, law can work.

I am a lawyer, so I am obviously not going to argue against the provision of good laws governing mental health provision; and yes, new laws can provide a marker of change that gives good practice more space to flourish. Equally, though, as someone who has done a good deal of international work and read a lot of mental health law, I think I have never seen a statute so rigidly drafted that it can preclude bad practice if practitioners want to exercise undue control.

This suggests that individual accountability is the key issue. How is that to be enforced? Law may be of little help here. Often, domestic courts look at overall standards within a country and, if a doctor's practice is broadly consistent with a significant minority of his/her colleagues, the court will decline to be involved.

Medicine is generally a self-governing profession. Will national professional bodies provide sticks with the carrots, both leading from the top in terms of the promotion of ethics, and also censuring practitioners who do not meet the international standards? This seems doubtful. Even in countries with quite developed complaints systems, it is hard to imagine a governing body censuring a practitioner for lacking respect for the views and preferences of a PWLE, or being too quick to exercise compulsion. Galderisi's paper notes that only 15 out of the 143 Member Societies of the WPA have formal ethical documents. This does not inspire confidence that the standards envisaged in the 2020 WPA Code will be given priority in most of the world.

How should we deal with failure to engage at the level of national organizations? In principle, human rights bodies such as the European Court of Human Rights could insist on standards of medical ethics that are consistent with the developments in the field of human rights, but thus far they have been remarkably reluctant to do so. Would the WPA or similar international organizations be prepared to exert political pressures, such as naming and shaming? This seems also doubtful, and is a high-risk strategy since it destroys goodwill between the organization and the national body.

That said, failure to intervene means that nothing will actually change on the ground. And it is on the ground that the changes need to happen.

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1. Galderisi S, Appelbaum PS, Gill N et al. World Psychiatry 2024;23:364-86.
2. European Committee for the Prevention of Torture and Inhuman or Degrading Treatment or Punishment. https://www.coe.int/en/web/cpt/states.
3. United Nations Subcommittee on Prevention of Torture. https://www.ohchr.org/en/treaty-bodies/spt.
4. Herrman H, Allan J, Galderisi S et al. World Psychiatry 2022;21:159-60.

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Shifting the pendulum – but with checks and balances

The most important advances in mental health care in this millennium have not come, as many had expected, from neurobiological research, funded with billions of dollars worldwide. Nor has digitalization been as powerful and scalable a tool as initially thought, due to a number of technical and ethical issues, as outlined by Galderisi et al[1]. The most important, and hopefully sustainable, progress worldwide has not come from techniques, but from an idea – the idea of universal and inalienable human rights.

These fundamental rights are outlined by the United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD), but they are the same rights that apply to everyone. The recognition of what in many ways seems self-evident today has taken a shamefully long time. The use of coercion in the treatment of mentally ill people, the need for shared decision-making, the importance of informed consent in research and treatment; the rights to informed self-determination, to see one's own clinical records and, last but not least, to decide about one's own life and its end – these are all issues that were hardly discussed at psychiatric meetings and in psychiatric journals thirty years ago.

This was not a problem specific to psychiatry. In medicine as a whole, it was only a few decades ago that patients began to be seen not just as objects of treatment and research, but also as subjects whose experiences needed to be studied. Even issues such as patient satisfaction and quality of life were considered to be of little professional or scientific interest until then in the paternalistic structures of health care and research. It was only in 2018 that the World Medical Association added the phrase "I will respect the autonomy and dignity of my patient" to the Declaration of Geneva, the modern Hippocratic Oath[2]. But now this phrase appears as the third of the thirteen statements in the Declaration, which shows that the pendulum has swung – "towards respecting the autonomy and dignity of people with lived experience of mental health conditions"[1].

However, there is not only reason for relief. Psychiatry is only one of a number of stakeholders in the field, and psychiatrists as a profession have been blamed using harsh words, including torture[3]. There is a deep divide between those who claim human rights as a unique selling point and propose a simple solution to a complex problem – the complete abolition of coercion in psychiatry, along with the relevant laws – and the other side, represented by psychiatrists, medical ethics, legislations in almost all countries, and courts such as the German Constitutional Court. As with many other issues in our societies, shaming and blaming have become more prevalent than open discussion and the exchange of arguments between positions.

In this regard, human rights would be a perfect starting point for the debate. There are a number of clearly defined human rights to be respected, listed in the CRPD, including the right to life (Article 10), equal recognition before the law (Article 12), freedom from torture or cruel, inhuman or degrading treatment or punishment (Article 15), freedom from exploitation, violence and abuse (Article 16), independent living and inclusion/participation in the community (Article 19), respect for home and family (Article 23), health (Article 25), habilitation and rehabilitation (Article 26), and adequate standard of living and social protection (Article 28). Among these fundamental rights, there is no hierarchy. No single right is superior to another. Around the world, we have learned many lessons in this regard during the COVID-19 pandemic.

A characteristic of these rights is that they are not absolute but mutually limiting. This even applies to the right to life. The right that one's will and preferences are taken into account – the famous Article 12 of the CRPD – can be limited by the same rights of other people, and must be balanced against other rights such as the right to health and the right to be included in a community. Similarly, in principle-based medical ethics, patient's autonomy can be limited by the principles of beneficence and nonmaleficence, and vice versa. However, this only applies when severe mental conditions hamper the patient's capacity to build an autonomous and free will. Consequently, decisions on the use of coercion must be based not only on existing law but also on a comprehensive individual consideration, taking into account not only the medical conditions but also all aspects of the patient's individual personality and history and his/her family and social environment.

Coercion is itself an aspect of maleficence and violates several human rights. Nevertheless, weighing it against other rights may in some cases lead to the conclusion that refraining from coercion would have even more harmful consequences[4]. Therefore, the shifting of the pendulum towards greater patient autonomy needs to be accompanied by a close look at where the pendulum is fixed and whether this is in line with a comprehensive view of human rights for all parties involved.

In this respect, a matter of concern is that, in several countries, the provision of mental health services is characterized by a steady decline in the number of beds in general psychiatric facilities and a substantial and continuing increase in the number of beds in forensic psychiatric and prison facilities. This applies to Europe[5], but also to Latin American countries[6]. It means that an increasing proportion of people with severe mental illness have lost their freedom and their right to inclusion in the community for a long time, are subjected to a considerable amount of coercion, and have significantly violated the rights of others. This negative outcome at the societal level must be part of the discussion.

Similarly, we have come a long way from the medieval religious belief that suicide was a sin and that sinners were denied the right to be buried in cemeteries. The Enlightenment has finally achieved its goal. People have the right to decide on themselves. However, again some checks and balances are needed. Some countries – such as Belgium, the Netherlands and Colombia – have introduced fairly liberal legislations on assisted suicide and euthanasia. On the other hand, considerable thresholds have been established there, including the requirement for expert opinions and specialized centres. Nevertheless, the number of cases is increasing, both in general and as regards those involving mental disorders[7,8].

One threshold for admissibility in those countries is “intolerable suffering”, which means that other people (physicians) have to judge what level of suffering is tolerable for an individual. This is contrary to the idea of autonomy. In 2020, the German Constitutional Court opened up a different pathway. It ruled that everyone has the right to receive assistance in dying, regardless of his/her individual motives. However, the person should be acting in “free responsibility”, explicitly free from acute mental disorder and from social or psychological pressure. In 2023, two draft legislations for further regulations did not pass the parliament.

The German Association for Psychiatry, Psychotherapy and Psychosomatics has expressed concern that a “grey”, unregulated practice will spread, with a lack of protection for people with mental illness and little transparency. A suicide prevention law is deemed urgently necessary as a counterbalance. Furthermore, as with the use of coercion, we need transparent data on health outcomes and practices. On the basis of such data, we need to have an unbiased discussion on how best to adjust the pendulum swinging between autonomy and care.

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1. Galderisi S, Appelbaum PS, Gill N et al. World Psychiatry 2024;23:364-86.
2. World Medical Association. Declaration of Geneva. www.wma.net.
3. Méndez JE, UN Human Rights Council. Report of the Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment. www.ohchr.org.
4. Steinert T. J Med Ethics 2023; doi: 10.1136/jme-2023-109578.
5. Mundt AP, Delhey S, Martínez P et al. Psychiatr Serv 2024;75:48-54.
6. Mundt AP, Rozas Serri E, Siebenförcher M et al. Lancet Reg Health Eur 2021;7:100137.
7. van Eenennaam RM, Kruithof W, Beelen A et al. Lancet Neurol 2023;22:591-601.
8. Dierickx S, Deliens L, Cohen J et al. BMC Psychiatry 2017;17:203.

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Aligning the “single law” proposal to the CRPD standard of “will and preferences”

Galderisi et al[1] provide an excellent overview of the complex ethical challenges in psychiatry. We subscribe to the authors’ criticism of mental health laws employing a “disorder + risk” schema for involuntary intervention, and their conclusion that these laws discriminate against people with a mental health condition. The authors put forward instead a “single law” proposal in which “involuntary treatment would only be permitted when the objecting person has an impairment of decision-making ability – from any cause – and if treatment is in the person’s best interests”[1]. We strongly endorse the core of this proposal, but would like to suggest three refinements to it.

First, we propose combining capacity assessment with supported decision-making, to ensure that no one is found to lack decision-making capacity before all reasonably available resources of supported decision-making have been exhausted. Second, we propose replacing the best interests standard by the substituted judgment standard, to achieve a closer alignment of substitute decisions with the will and preferences of the person concerned. Third, we suggest to explicitly define additional criteria for involuntary intervention, to avoid what we will call “the fallacious inference from substitute decision-making to coercion”. The proposed refinements are based on what we call the “combined supported decision-making model”, a model for the informed consent process that provides a non-discriminatory basis for decision-making about involuntary intervention[2-5]. In this commentary, we focus on the last two refinements.

Galderisi et al refer to a terminological distinction used in a judgment of the German Federal Constitutional Court to show that the “single law” proposal is consistent with the general principles of the United Nations (UN) Convention on the Rights of People with Disabilities (CRPD) and the wording of Article 12, particularly its insistence that “measures relating to the exercise of legal capacity respect the rights, will and preferences of the person”. The terminological distinction is between “free will” (*freier Wille*) and “natural will" (*natürlicher Wille*), which, according to the authors, maps on to the CRPD's distinction between "will" and "preferences".

This terminological distinction plays an important role in the legal discourse around the German guardianship law (*Betreuungsrecht*), which is part of the German Civil Code and applies to all people who need support in managing their own affairs, regardless of whether they have a mental health condition[6]. The term "free will" (*freier Wille*) refers to the contemporaneous preferences of a person who possesses decision-making capacity regarding the decision at hand. Expressions of a person's free will must be respected by clinicians and have the status of consent or withdrawal of consent; that is, they can make interventions permissible which would otherwise be not permissible and vice versa. The term "natural will" (*natürlicher Wille*), on the other hand, refers to the contemporaneous preferences of a person who lacks decision-making capacity regarding the decision at hand. Expressions of a person's natural will must be carefully considered in medical decision-making but can, in some instances, be overridden based on other considerations, to be specified below. They amount to what is commonly described as "assent" and "dissent" in the research ethics literature. Any medical intervention against a person's natural will (i.e., any medical intervention to which the person dissents) counts as "coercive medical treatment" (*ärztliche Zwangsmaßnahme*) under German guardianship law and is hence subject to strict conditions.

Galderisi et al propose that expressions of a person's natural will can only be overridden if doing so is in the person's best interests. Although the authors make clear that the standard of best interests should be interpreted subjectively in terms of the person's beliefs and values, we are concerned that it will nonetheless be understood objectively in clinical practice. The best interests standard originally derives from a paternalistic "doctor knows best" approach and – despite the authors' careful qualifications – may be understood by clinicians in the light of what Hawkins[7] calls "welfare medicalism", the persistent idea among clinicians that what is in a person's best interests is what is medically indicated in the person's situation. To avoid this potential misunderstanding, we propose replacing the best interests standard by the substituted judgment standard. This latter standard gives center stage to the person's will and preferences: it assigns to the substitute decision-maker the task of making the treatment decision that the person would have made if he/she had had decision-making capacity[8].

German guardianship law employs a substituted judgment standard and requires that substitute decisions be justified by reference to concrete evidence about the person's will and preferences[6]. The law introduces two additional concepts in this context. The first is that of the person's "previously declared will" (*vorausverfügter Wille*), denoting the preferences that a person has documented in an advance directive at a time at which he/she had decision-making capacity. Advance directives are legally binding under the German Civil Code and apply to both physical and mental health conditions. The second concept is that of the person's "presumed will" (*mutmaßlicher Wille*), denoting the preferences of a person which can be reconstructed based on the preferences and personal values and convictions that he/she expressed when he/she had decision-making capacity. In accord with the substituted judgment approach, the person's previously declared or presumed will serves as a proxy for the person's free will.

Consistency with the person's previously declared or presumed will is a necessary condition for the permissibility of involuntary treatment under German guardianship law. This means that, if this consistency is not ascertained, involuntary treatment may not be carried out – even if withholding treatment is not in the objective best interests of the person. All references to the term "well-being" (*Wohl*) were omitted from the guardianship law during the latest reform to underline this, even though the term was understood subjectively before the reform[6].

We now turn to the fallacious inference from substituted decision-making to coercion. It is often assumed that, if a medical intervention is consistent with the person's previously declared or presumed will, that intervention may be carried out involuntarily against the person's natural will. This inference is invalid. The reason is that consistency with the person's previously declared or presumed will is a necessary but not sufficient condition for the permissibility of involuntary intervention.

While Galderisi et al in no way make the fallacious inference from substituted decision-making to coercion, we believe that it is important to make explicit and emphasize that additional criteria must be fulfilled for an involuntary intervention to be justified. Besides being consistent with the person's previously declared or presumed will, an involuntary intervention must also be suitable, necessary and proportionate in order to be permissible[9]. An involuntary intervention is *suitable* if it is effective in preventing the person from behaving in ways that are inconsistent with his/her previously declared or presumed will. It is *necessary* if there are no less restrictive alternatives to prevent the person from behaving in these ways. It is *proportionate* if its risk-benefit profile is more favorable than that of the option of not carrying out the intervention. Only if these three criteria are met may the person's previously declared or presumed will be prioritized over his/her natural will, and the involuntary intervention be carried out. If any of these three conditions is not met, involuntary intervention is not permissible and the person's natural will or contemporaneous preferences must be followed.

Implementation of the "single law" proposal would be a major step forward for psychiatry. We believe that the proposal can be brought into closer alignment with the CRPD's standard of "will and preferences" if capacity assessment is combined with supported decision-making; the best interests standard is replaced by the substituted judgment standard; and the proposed additional criteria for involuntary intervention are explicitly added.

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1. Galderisi S, Appelbaum PS, Gill N et al. World Psychiatry 2024;23:364-86.
2. Scholten M, Braun E, Gather J et al. Am J Bioethics 2021;21:45-7.

3. Scholten M, Gather J. J Med Ethics 2018;44:226-33.
4. Scholten M, Gather J, Vollmann J. J Med Philos 2021;46:108-36.
5. Scholten M, Gieselmann A, Gather J et al. Front Psychiatry 2019;10:631.
6. Henking T, Scholten M. In: Kong C, Coggon J, Cooper P et al (eds). Capacity, participation, and values in comparative legal perspective. Bristol: Bristol University Press, 2023:203-25.
7. Hawkins J. J Med Philos 2021;46:656-83.
8. Buchanan AE, Brock DW. Deciding for others: the ethics of surrogate decision making. Cambridge: Cambridge University Press, 1990.
9. Gather J, Juckel G, Henking T et al. Int J Law Psychiatry 2020;73:101615.

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Advance care planning: a multifaceted contributor to human rights-based care

Galderisi et al[1] address advance directives in the section on non-discriminatory mental health law, illustrating the need for better operationalization of concepts such as “will and preferences”, if we are to honor persons’ autonomy consistently and meaningfully. Advance directives provide useful fodder for debating autonomy and decision-making capacity in the midst of health crises. However, I would like to expand here upon their broader relevance to a human rights framework of mental health care.

Advance directives – and the overarching practice of advance care planning – instantiate several of the core principles and concerns of the human rights framework, and do so well before they may be relied upon during a period of decision-making incapacity. Advance care planning is an essential component of person-centered care. It empowers individuals to consider and express their health care values. Its process and products (e.g., an advance directive) are literal exercises in self-determination, autonomy, empowerment and responsibility. Indeed, individuals with mental illnesses who have completed advance directives report increased feelings of self-determination, autonomy and empowerment[2].

A corollary of the emphasis on self-direction in recovery is recognition that all individuals have personal responsibility for their own self-care and actively take part in their recovery journey. This focus on responsibility coincides with an understanding of mental illness as a chronic health condition, one that requires ongoing efforts by people to not only attain but maintain their wellness.

Although there is no universal definition of recovery, common elements in addition to autonomy and self-determination include relationships and respect[3]. Recovery may emphasize and center people in their own care and well-being, but it also recognizes the importance of relationships with loved ones and communities. Among the responsibilities of communities is providing resources and opportunities to address discrimination and to promote inclusion. Respect is included because acceptance of and appreciation for people with mental illnesses by communities and systems, including health care systems and actors, are requisite for achieving recovery. Relatedly, individuals with mental illnesses who have completed advance directives report increased feelings of working alliance with providers[2].

Thus, in these ways and others[4], the process of advance care planning and the resultant advance directive serve a range of important goals in recovery-oriented, human rights-based care, and do so before acute circumstances raise difficult questions about decision-making capacity, will and preferences, and whether coercive interventions are justifiable. Speaking for a moment to acute circumstances, however, research does suggest that advance directives with instructions for mental health care may contribute to reduced likelihood of experiencing coercive interventions[5].

Advance directives, despite their intuitive appeal and relevance to recovery-oriented, person-centered care, continue to be underutilized. Several factors likely contribute, including misunderstandings about administrative requirements, difficulty in sharing copies across providers, provider misapprehensions about restrictive instructions and refusals, and others[6,7].

The idea has endured, however, and improvements in how advance planning is conceptualized (e.g., as more than a form to fill out, but rather a process of exploring and documenting values and preferences) and supported (e.g., facilitators to assist individuals) are helping to realize how this planning, if normative, could enhance public mental health. Rather than circumscribing consideration to only instances in which a decision must be made and an indication of the person’s will or preference is sought, the larger process of advance care planning as a regular part of health care serves the prevention and promotion aims of public mental health. A meaningful integration of advance care planning into standard practice, so that it becomes a common point of discussion, and robust resources are available and accessible, would significantly contribute to the culture shift called for by Galderisi et al.

Psychiatrists may rarely be the professionals able to set aside sufficient time to be primary facilitators of advance care planning. Nonetheless, they can and should find ways to support the expansion of this planning. Informing the people they serve about advance care planning opportunities and tools, and encouraging clients’ interest in such topics, will be impactful.

One factor contributing to the slow uptake of advance directives is that some individuals doubt that providers will honor, or even seek out, their advance care planning documents. Psychiatrists can build and maintain trust (incidentally, a public health moral consideration) by validating the worth of undertaking advance care planning to the persons they serve, thus communicating a commitment to recovery-oriented care and respect for persons’ autonomy. In addition to supporting persons they serve, psychiatrists can also further advance care planning in everyday practice by supporting efforts by colleagues in their institutions who are championing the integration of this planning.

In sum, advance care planning and advance directives are practices that enshrine positive rights and the exercise of persons' autonomy, rather than just "protecting" negative rights of individuals by restricting a State's detention power. That being said, policy establishing and supporting advance care planning has the potential to reify stereotypes about legal capacity and discriminatory practices. The potential of advance directives in the mental health field has long been recognized[8], but, for the last several decades, discussion and legislation have tended to segregate planning for mental health care.

While terms such as "psychiatric advance directives" were understandably in line with the generally segregated approach to mental health care, and may have been helpful for making their applicability to mental illnesses explicit, the time has come to de-emphasize the distinction. Enabling legislation that presents advance directives for mental health as separate from existing law about advance care planning reifies a distinction that contemporary conceptualizations of "whole health" have moved past.

Policies that require more steps – such as evaluation by a physician to document capacity – for mental health advance care documents are instances of discriminatory mental health law. Concerns are similarly raised by differential policies and criteria for overriding advance directives that are predicated upon a presumed categorical difference between "medical" and "psychiatric" advance directives.

Less obvious ways by which discriminatory use of advance directives for mental health may arise include a paucity of training and understanding about what decision-making capacity entails and how to assess it[7]. Relatedly, defensive practices may lead providers to inadvertently and even purposely delay or avoid obtaining and reviewing an advance directive for a person with mental illness out of concern that it will contain impractical and restrictive instructions (a scenario that research suggests is in fact quite rare[9]).

Advance care planning could be transformational *if* the process as well as the products and their application receive equal emphasis, *if* they are widely and consistently integrated into health care systems without discrimination, and *if* providers "embrace the human rights framework and champion the promotion of mental health and prevention of mental disorders"[1]. Advance care planning and advance directives are archetypal of a recovery-oriented, human rights-based approach to mental health care, and we should capitalize on all they have to offer.

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1. Galderisi S, Appelbaum PS, Gill N et al. World Psychiatry 2024;23:364-86.
2. Nicaise P, Lorant V, Dubois V. Health Soc Care Community 2013;21:1-14.
3. US Substance Abuse and Mental Health Services Administration. SAMHSA's working definition of recovery. Rockville: Substance Abuse and Mental Health Services Administration, 2012.
4. Morrissey F. Medico-Legal J Ireland 2010;16:21-33.
5. Swanson JW, Swartz M, Elbogen EB et al. J Mental Health 2008;17:255-67.
6. Zelle H, Kemp K, Bonnie RJ. World Psychiatry 2015;14:278-80.
7. Swartz MS, Swanson JW, Easter MM et al. Psychiatr Serv 2021;72:219-21.
8. Appelbaum PS. N Engl J Med 1979;301:788.
9. Elbogen EB, Van Dorn R, Swanson JW et al. Psychol Public Policy Law 2007;13:273-88.

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Human rights and early intervention: ethics as a positive force

As a medical student in the 1970s, my deep concern about the civil rights of the mentally ill was one of the main reasons for my interest in psychiatry and which ultimately inspired me to enter the field. These were "negative rights" which needed to be addressed and still do.

Galderisi et al[1] devote most of their paper to the protection of these civil rights. Less extensively addressed are the "positive rights", that is the economic, social and cultural rights of the mentally ill. This includes the structural neglect of the mentally ill within the health care and medical research systems across all societies, including high-income countries[2].

A global average of just around 2% of the health care budget is spent on the care of the mentally ill. Even in WEIRD (Western, Educated, Industrialized, Rich and Democratic) countries of the Global North, access to and quality of care are dramatically lower than for physical illness, such as cancer and cardiovascular diseases.

This gross global neglect is a major driver of coercive cultures of care, which in turn are an inevitable result of late intervention, with treatment only being offered as a last resort. Neglect also contributes to high rates of premature death from suicide and preventable and treatable medical causes, marginalization and immiseration.

In 2023, the World Mental Health Day celebrated mental health as a universal human right. However, the meaning of this – as eloquently argued by Patel[3] – is ideologically loaded. He points out that the population has the right to be protected from "known harms to mental health". Such harms result from government policies and new megatrends that have created powerful structural forces which undermine mental health and produce higher levels of mental ill-health. They do so through creating increased poverty and marginalization, disproportionate exposure to violence and displacement, and surging wealth inequality.

The paradigm shift that began in the early 1990s to make early intervention a belated addition to the spectrum of treatment and care in psychiatry should be seen as part of the response to the above gross global neglect. Early intervention began within the field of schizophrenia and psychotic disorders and profoundly challenged and ultimately transformed this field. Subsequently it spread as a principle and goal across the full spectrum of mental disorders.

With K. Schaffner, I co-edited a special issue of *Schizophrenia*

Research in 2001 on the ethics of early detection and intervention in schizophrenia. The main topic clearly is the balance between non-maleficence and beneficence, or risks versus benefits. Galderisi et al focus on the clinical high risk (CHR) for psychosis field in discussing the relevant issues. Ultra high risk (UHR) – or, in the US, CHR – is a concept that my colleagues and I introduced and operationally defined in the early 1990s. Proof of concept then led to our formulation of a wider transdiagnostic clinical and research framework, the clinical staging model, which allows ethical issues to be considered while enhancing the clinical utility of diagnosis[4].

The ethical issues in psychiatry are very similar to those which apply in medicine generally, with the added complexity of enhanced stigma and challenges in establishing competency to give informed consent in certain obvious circumstances. The goal of early intervention is to reduce the impact of a potentially serious and persistent illness, via either cure or disease modification and amelioration. This means a proactive approach to treatment rather than a reactive and delayed one, which is in itself manifestly harmful, while guarding against over-treatment of patients, which may unnecessarily expose them to harmful effects. Clinical research has helped to define this “sweet spot”.

While Galderisi et al ultimately come to a largely valid set of conclusions, their account of the CHR literature and field is somewhat US- and UK/Euro-centric, with a tendency to rely on meta-analyses rather than work of those who conducted and interpreted the landmark studies in the field. Furthermore, the critiques of the CHR concept and its value are fully cited, while the rebuttals are mostly not, particularly those demonstrating the value of offering interventions at this stage in terms of ameliorating and perhaps even delaying transition[5]. The studies supporting the cost-effectiveness of intervening in the CHR stage, and those showing that positive predictive values can be enhanced through such strategies as risk calculators or joint modelling[6], are neglected.

Finally, the research on stigma is more mixed than the authors suggest. Crucially, this is a risk that can be minimized through communicating in an accurate but broadly optimistic manner about care for current needs and future potential risk, not merely of psychosis, but of ongoing symptoms and disability. Stigma can also be greatly reduced by offering the care in youth-friendly, co-designed settings, and not in clinics which also provide care to older patients with longer-standing and established psychotic illness.

Nevertheless, consistent with my own experience over 30 years of treating such patients, the authors do ultimately conclude that offering care to help-seeking young people with genuine warning signs of psychosis, along with other comorbid symptoms and functional impairment, which may turn out to be the first stage of a sustained psychotic disorder, is of definite value under the right conditions.

One of the valid points raised by critics of the CHR concept is that the standalone, “pure” or narrow-cast CHR clinic model, relying on passive help-seeking alone, implies that only a small percentage of those who manifest the CHR phenotype and who progress to a fully-fledged stage of sustained or “first episode” psychosis are able to be engaged, with the remainder entering care via emergency departments and other pathways when they have already crossed the boundary to psychosis.

Galderisi et al are correct to state that universal, one-step screening strategies are not the appropriate solution to this problem. Instead, the enhanced primary care or integrated youth services model of care, as developed in Australia and subsequently in many other countries[7], is a potential solution. For example, we were able to recruit 310 CHR patients from a local headspace system for a clinical trial in just over 2 years[8], and we estimated that at least 20-30% of all patients who access headspace services experience attenuated psychotic symptoms.

However, the advantages of such a “soft entry”, co-designed, and therefore low-stigma and youth-friendly portal and care environment are much broader. They allow early intervention across the full spectrum of emerging mental ill-health in young people, and dilute the need to focus on specific trajectories of illness. Young people can be helped with their presenting clinical issues and their broader needs, including vocational support and other personal and social needs.

More general statements can be made about the need to act now, aiming to prevent the symptoms and syndromes getting worse or developing into other or additional problems. This approach is well accepted, and even the introduction of such terms as bipolar or psychosis can be held without the deterministic and pessimistic shadows that traditional psychiatry tends to cast.

Headspace has operated in Australia for 18 years and is now in over 160 communities. It has had its opponents, as do all genuine reforms. However, the rebuttals that dealt with these critiques are sometimes overlooked. Ultimately, this is a model of care with strong consumer and community support, and a recent independent evaluation has confirmed that it is effective and cost-effective, particularly for early stage and mild-to-moderate levels of disorder[9]. Similar studies have been conducted in a range of service settings in Europe and Canada.

Future progress will depend on strengthening the clinical capacity of these frontline primary care platforms, and backing them up with options for more specialized multidisciplinary care for later stages of illness.

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1. Galderisi S, Appelbaum PS, Gill N et al. World Psychiatry 2024;23:364-86.
2. Patel V, Saxena S, Lund C et al. Lancet 2018;392:1553-98.
3. Patel V. Lancet 2023;402:1412-3.
4. McGorry PD, Hickie IB (eds). Clinical staging in psychiatry: making diagnosis work for research and treatment. Cambridge: Cambridge University Press, 2019.
5. McGorry PD, Nelson B. JAMA Psychiatry 2020;77:559-60.
6. Yuen HP, Mackinnon A, Hartmann J et al. Schizophr Res 2018;202:333-40.
7. McGorry PD, Mei C, Chanen A et al. World Psychiatry 2022;21:61-76.
8. McGorry PD, Mei C, Amminger GP et al. JAMA Psychiatry 2023;80:875-85.
9. KPMG. Evaluation of the national headspace program. Sydney: KPMG, 2022.

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A broader approach to ethical challenges in digital mental health

Galderisi et al[1] provide an insightful overview of current ethical challenges in psychiatry, including those presented by digital psychiatry, as well as recommendations for addressing these challenges. As they discuss, "digital psychiatry" encompasses an array of different digital tools, including mental health apps, chatbots, telehealth platforms, and artificial intelligence (AI). These tools hold promise for improving diagnosis and care, and could facilitate access to mental health services by marginalized populations. In particular, digital mental health tools can assist in expanding mental health support in lower-to-middle income countries.

Many of the ethical challenges identified by the authors in the use of digital tools reflect inequities and challenges within broader society. For example, in the US, lack of mental health insurance and insufficient representation of racialized minorities in medical research contribute to the difficulties with access and fairness in digital psychiatry. In many ways, the ethical challenges presented by digital psychiatry reflect long-standing concerns about who benefits, and who does not, from psychiatry. The array of forward-looking recommendations advanced by Galderisi et al show that these ethical challenges can also be seen as opportunities for moving towards greater equity and inclusion in psychiatry.

Discussions of the ethics of digital health benefit from broadening the scope of issues to include social context. Galderisi et al refer to inequities in how mental health care is researched, developed and accessed, and to historical power imbalances in psychiatry due to which patient voices are undervalued and overlooked. A broader approach to ethical challenges related to digital health technologies recognizes that issues affecting these technologies often emerge due to their interactions with the social institutions in which they are developed and applied[2]. For example, privacy and safety of digital psychiatry tools must be understood within the context of the specific regulatory environment and infrastructure (e.g., broadband, hardware) in which they are being used.

Digital health tools and medical AI are often promoted for improving cost-effectiveness, but this business-oriented emphasis can obscure discussion of what trade-offs in costs are considered acceptable, such as whether lesser-quality services are deemed acceptable for low-income groups. Institutions that regulate medical devices often struggle when they have to deal with softwares or AI. Consumers and patients too often find it difficult to obtain information that can help them decide which digital psychiatry tools are appropriate and effective for their needs.

There have been pioneering efforts to assist with evaluating effective digital mental health tools, such as American Psychiatric Association's mental health app evaluator[3]. However, new models for evaluation which are responsive to the ways in which clinicians and patients realistically engage with mental health care tools are still needed. For example, some of the measures that regulators or insurance companies use to evaluate and approve digital mental health tools may not capture the aspects of a tool that, from a consumer or patient perspective, offer meaningful improvements to their lives. There has also been growing recognition that meaningful evaluation of the effectiveness of digital health tools needs to look beyond the tool itself in order to evaluate the tool's effectiveness as it is used within a particular system[4]. More engagement of diverse communities and those with lived experience during the development of digital psychiatry tools is imperative for improving these tools.

Unfortunately, the hype around digital mental health often goes hand-in-hand with rapid adoption of unproven technologies. For example, large language models (LLMs) and generative AI are being quickly taken up within health care, including psychiatry[5]. These digital tools are embraced as cost-effective time-savers before there is sufficient opportunity to determine the extent to which they are in fact ready for the purposes for which they are being used[6]. Potential problems with generative AI in health care continue to emerge, from the potential discriminatory biases in information, to the potential collection and disclosure of personal data[7]. There is a need to exercise more caution in the adoption of new digital tools in psychiatry, in order to give time for evaluation and guidance for specific purposes.

Privacy continues to pose significant concerns for digital psychiatry. Digital mental health tools often gather information that psychiatrists and patients are not aware of, such as location data, which may seem insignificant, but can allow for behavioral analyses that infer sensitive or predictive information regarding users[8]. In today's data landscape, brokerage of personal data can generate billions of dollars. These data practices have repercussions on patients that they may not be able to anticipate. Even de-identified data can increasingly be re-identified, and user profiles that are compiled from such data can be utilized to target people for fraudulent marketing schemes, or lead to downstream implications for employment or educational opportunities. Furthermore, in countries such as the US, where mental health care may be unaffordable for many individuals, people may effectively be put in the position of trading data for health care.

Because of fairness and bias issues, there are also real questions on how much digital and AI tools actually work for different populations. One common source of bias is that the data that are used to train and develop digital tools may be insufficiently representative of the target population, such as participants of diverse race and gender or with disability[9]. The potential for bias goes beyond the question of algorithmic bias, as tools may be simply designed in ways that do not work effectively for different populations, or the use of those tools in specific contexts may lead to unfair outcomes. Addressing fairness will require ensuring that researchers and clinicians from diverse backgrounds are included in the development and design of digital psychiatry tools.

As Galderisi et al note, the discipline and tools of psychiatry have a long history of being used for social control, such as in the criminal justice and educational systems. The tools of digital psychiatry may be applied to put vulnerable and minoritized groups at particular risk of punitive interventions from government institutions. It is, therefore, important that members of the psychiatric profession put considered effort into anticipating and addressing the social and legal implications of the use of digital psychiatry tools in other domains of society.

Development of digital psychiatry tools requires identifying specific ethical challenges, but also taking the time to reflect and envision the system and world that these tools will help create. Galderisi et al set out a number of action items that, taken together, envision a more equitable and inclusive future for psychiatry. This is an important moment to take these opportunities for building new frameworks and systems for psychiatry, in which digital tools can be used to support human empathy and creativity, allowing mental well-being to flourish.

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1. Galderisi S, Appelbaum PS, Gill N et al. World Psychiatry 2024;23:364-86.
2. Shaw JA, Donia J. Front Digit Health 2021;3:725088.
3. Lagan S, Emerson MR, King D et al. Psychiatr Serv 2021;72:1095-8.
4. Gerke S, Babic B, Evgeniou T et al. NPJ Digit Med 2020;3:53.
5. Andreou A. Generative AI could help solve the U.S. mental health crisis. Psychology Today, March 9, 2023.
6. Torous J, Blease C. World Psychiatry 2024;23:1-2.
7. Fui-Hoon Nah F, Zheng R, Cai J et al. J Inf Technol Case Appl Res 2023;25:277-304.
8. Martinez-Martin N, Greely HT, Cho MK. JMIR mHealth uHealth 2021;9:e27343.
9. Gianfrancesco MA, Tamang S, Yazdany J et al. JAMA Intern Med 2018;178:1544-7.

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Physician-assisted dying in people with mental health conditions – whose choice?

Galderisi et al[1] quite rightly draw our attention to the ethical dilemmas that emerge when one considers ending life. An area fraught with complexity takes a quantum leap when mental ill-health is added.

The need to rethink a position is nothing new. Whilst we may perceive change as gradual, over a decade it may become seismic, and constant re-evaluation of values may be necessary. The ground-shaking judgment in Roe v. Wade case in the US, and its recent reversal, is one example of how what seems right and proper can change overnight.

Even the most ardent supporters of choice would not support physician-assisted dying (PAD) in populations who lack decision-making capability, although some take the view that the Convention on the Rights of People with Disabilities (CRPD)[2] would dispute that those with mental illness cannot make their own choices.

Where is the boundary? Compromised is not impaired, let alone without value or meaning. In Japan, the Restaurant of Mistaken Orders employs staff with dementia, resulting in 37% of orders being mistaken, but 99% of customers report that they are happy[3].

The CRPD emphasizes multiple rights: the right to life (Article 10); to adequate standards of living and social protection (Article 28); to "legal capacity" – that is to legal standing as well as legal agency – on an equal basis with others" (Article 12); "…the existence of a disability shall in no case justify a deprivation of liberty" (Article 14); "…every person with disability has a right to respect for his or her physical and mental integrity on an equal basis with others" (Article 17).

How do we reconcile these rights with the existence of PAD? Not a Pandora's box but a stack. One group states that those with mental illness must be allowed to participate equally. Yet, few psychiatrists would support that those with psychotic beliefs or severe depression should have access to PAD. How are these contrasting views, on conditions which may distort the ability to weigh up and evaluate choices, to be balanced?

The WPA Code of Ethics calls for the autonomy of persons with mental ill-health, but recognizes that involuntary interventions may be required, as a last resort, when less restrictive interventions have failed, to protect safety and to restore the person's autonomy. PAD will never "restore" autonomy; it implements it for a last time! The line of reasoning that permits coercion is in the context of interventions that improve quality of life and return autonomy. There is no reasonable world in which PAD promotes these.

For individuals who lack a formal mental disorder, but are facing the existential angst and distress of a terminal condition, or of unbearable suffering, the guiding principle shifts. The relief of suffering becomes more important. Autonomy takes priority when beneficence is unrealistic, and non-maleficence manifests as not making people suffer more than they choose to.

Many clinicians will be familiar with the lack of parity between physical and mental health care, that the resource allocation is uneven and unequal, particularly galling when the World Health Organization identifies mental ill-health as one of the leading causes of disability-adjusted life years. Is it perverse that a call for parity means access to PAD on an equal basis?

Another thread to concerns about PAD is: "How free is such a decision?". There are concerns about societal pressures, not only involving human interactions. What is the influence of social media, and is that influence even human? Automated algorithms make a comprehensive and competent assessment of requests for PAD crucial.

Given the finality of PAD, a cautious approach to criteria for consent is appropriate. Apart from the Netherlands and Belgium, countries which have an enshrined right to PAD do not extend that right to minors. One might consider that sensible for those with impaired capacity, whether developmental or pathological.

That frameworks exist for the assessment of capacity does not take away from the need for staff to be properly trained. Despite teaching from national organizations, there is still widespread disparity in the quality of assessments, in this author's experience, even when workshops are delivered at meetings of the European Psychiatric Association or the American Psychiatric Association. Where death is the outcome, this is truly disturbing.

I note that Galderisi et al allege that medical associations have moved to neutrality over time, "perhaps to spare members who participate in these now-legal interventions from being labelled as unethical". In the UK, the movement of professional associations towards neutrality or being in favour of legalization, whilst lagging behind public opinion, precedes legislative change, suggesting that it is the reverse. Changing attitudes rather than avoiding regulatory proceedings seem to be the cause of the shift[4].

Another fear, that legalization and normalization of PAD will lead to a decline in palliative care for life-limiting conditions, is not borne out by an international evidence base[5]. Nor is it evident that PAD for psychological causes will open the floodgates, with only 5% of requests on this basis being approved[6].

As suffering is purely subjective, whether psychic or physical, disputes about its definition seem ironic. On the contrary, discussions about treatability are not subjective and can be evidence based. That only treatments which patients are willing to accept would be used in determining treatability is a challenge to autonomy, when set against societal values that life should be preserved. What is "untreatable" has been well analyzed before in this journal[7], and the same arguments are as valid here.

At the end of the day, disagreements about definitions do not invalidate the principle. It is the pragmatic that is questioned. Whilst the devil is in detail, it does not mean that the relief of irremediable unbearable suffering does not justify the legalization of PAD. It is a truly terrible decision, one that deserves compassion and empathy. When a process to leave this world is clearly articulated and lawful, evidence from EXIT (Switzerland) shows that, of those enquiring for PAD, 68% make a choice to live[8].

Societies have to make several hard decisions. When is capacity to exercise a choice for PAD present? What is "untreatable"? At what point is the burden of treatment such that more can be refused whilst retaining access to PAD? What would a compassionate caring process look like? In any case, vigilance to ensure that the principles are maintained, without deviation, will be required. In such a scenario, PAD has a place in civil society. A choice I hope you never need.

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1. Galderisi S, Appelbaum PS, Gill N et al. World Psychiatry 2024;23:364-86.
2. UN Department of Economic and Social Affairs. Convention on the Rights of Persons with Disabilities (CRPD). https://social.desa.un.org.
3. Salmon M. Dining with empathy: the unique concept of the Restaurant of Mistaken Orders. https://thedigitalage.co.uk.
4. British Medical Association. Physician-assisted dying. www.bma.org.uk.
5. UK Parliament. Assisted dying/assisted suicide. https://publications.parliament.uk.
6. Snijdewind M, Willems D, Deliens L et al. JAMA Intern Med 2015;175:1633-40.
7. McIntyre RS, Alsuwaidan M, Baune BT et al. World Psychiatry 2023;22:394-412.
8. EXIT. EXIT at a glance. www.exit.ch.

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Ethics from the lens of the social dimension of psychiatry

From a historical perspective, Engel[1] conceptualized psychopathology as resulting from an interaction of three orders of factors: biological, psychological and social. The first half of the 20th century has been mostly devoted to conceptualizing the psychological component of mental disorders, the second half to the understanding of the biological component. We are now, in the 21st century, busy at better understanding the role of social processes that impact treatment approaches to psychopathology as well as the psychiatrist-patient relationship.

Even more than other medical disciplines, psychiatry is influenced by external events that plague society, such as epidemics, natural disasters and wars. These events often require the involvement of ethics committees that will determine the duties and rights of the physician in potentially conflictual ethical contexts, such as triage situations (i.e., choosing whom to treat first). The COVID-19 pandemic has shown how deeply interwoven the epidemiology of mental disorders and the access to mental health services are with both social factors and somatic health. Grief, isolation, loss of income and fear exacerbate existing mental health problems or create new ones. The pandemic has demonstrated that the biological and social dimensions of medicine and public health are inextricably linked[2].

Profound changes in social values and norms, such as the legitimization of medical procedures for transgender individuals, or the availability of euthanasia in some countries, require a redefinition of the psychiatrist's role within the medical staff, and the development of ethical guidelines that take into account a variety of emotional, religious and ideological aspects pertaining to both the patient and the physician.

This changing scenario is extensively reflected in Galderisi et al's paper[3]. I will focus here on three of the issues discussed by the authors. The first is stigma related to mental disorders in society in general, and particularly in the medical world. Studies documenting the importance of social/environmental components in the development of psychopathology[4], as well as those showing the close relationship between physical illness and emotional states, have contributed to reduce that stigma. The inclusion of psychiatric wards within general hospitals has been both a consequence and a further determinant of this evolution. Likewise, the importance of the psychiatrist's presence in transdisciplinary medical teams, as well as in hospital ethics committees, has become more obvious than in the past. It is also increasingly clear that codes of ethics of physical medicine and psychiatry overlap to a large extent, especially with regard to the therapist-patient relationship.

The second topic I wish to emphasize is the changing relationship between psychiatrists and representatives of patients and families. In the recent past, we witnessed against-psychiatry demonstrations by former hospitalized patients, their families and human rights organizations. Our involvement at the societal level has led to a move from a paternalistic stance to a more listening, egalitarian position. We have started to invite those demonstrators to "cross the street", to come and participate in our meetings to share with us their point of view and to discuss with us the dilemmas regarding issues of quality of life, patients' rights, effectiveness of our treatments versus side effects, and coercive situations, in a context marked by mutual respect. Today, in many countries, representatives of psychiatric patients are invited to participate in committees that discuss these issues and allocate resources for research. In some countries, former patients and/or their relatives also participate in teaching medical students and residents. This collaboration has increased the transparency of our ways of thinking and working, and is contributing to reduce the stigma attached to psychiatry. This change of attitude is clearly reflected in the WPA Code of Ethics[2].

One of the issues that remain conflictual, and feed the stigma towards the psychiatric profession, is the use of coercive measures, that seems to deny the patient's right to autonomy, one of the four basic principles of any medical code of ethics, along with beneficence, non-maleficence and justice[4]. The term autonomy reflects the patient's right to refuse medical treatment. In the case of a psychotic patient, the definition of "autonomy" is very complex, as the patient's "free" will is colored by his/her psychotic symptoms and lack of insight. The goal of treatment, including coercion, is to restore the patient's judgment capacity necessary for independent functioning. The growing attention to this issue has already led in many countries to a decrease in the number of involuntary hospitalizations and physical coercive measures, and the increasing use of alternative treatment solutions, such as the development of crisis units and "balancing houses" in the community, as an alternative to hospitalization[5,6].

Another issue related to the patient's right to autonomy is that of euthanasia. What is the psychiatrist's role, if any, in the process of fulfilling a patient's desire to end his/her life while freely choosing to prioritize quality of life over longevity? The renowned surgeon C. Bernard stated: "I have learned in my many years that death is not always the enemy. Sometimes it is the right medical treatment. It often achieves what medicine could no longer offer – an end to suffering"[7]. In my opinion, the psychiatrist has two roles in this respect: the first is to make sure that the patient's request is given out of "clarity of mind", the second is to ascertain that the patient's wish to die is not a masked suicidal intent secondary to the psychopathology from which he/she suffers. Unfortunately, tools for a truly reliable assessment of these issues are not available.

A recent development regarding euthanasia is the ethical legitimation for the psychiatrist to act in accordance with his/her moral and/or religious views, possibly (but not necessarily) deferring the question to a colleague who agrees to be part of the medical team that is supposed to examine the request. It is important to discuss this issue with medical students and residents during their professional training.

Unfortunately, teaching of ethics does not occupy an adequate place in professional curricula, in psychiatry as in other medical disciplines. Also, the number of national psychiatric associations that have produced their own code of ethics is minimal, probably also due to the feeling that the existence of a code of ethics is a coercive factor that limits the clinician's freedom of action. We need to emphasize the advantages of having a code of ethics, such as the personal moral and legal protection that a set of guidelines provides to the psychiatrist in the implementation of his/her values and expertise. This protection is very important, especially in situations where the patient's best interest is not clear or is in conflict with the professional best practice.

Particularly neglected in psychiatry and other medical professions is the ethics of clinical management in children and adolescents. For example, to whom should the psychiatrist extend fidelity: to the child, to the guardian, to the family as a whole, to the referring agency, to the institution that pays him/her? Even though the child's consent is clinically essential, it is not required by law. Nevertheless, the psychiatrist should aspire for the child to have a good understanding of the therapeutic process, according to his/her age and cognitive and emotional development.

In conclusion, we better appreciate nowadays the interplay between society and psychiatry. National and international ethics committees must be involved in this "dialogue" between the patient's rights and the psychiatrist's duties and rights. Increasing transparency of the diagnostic and treatment processes can lead to a partial, but very significant, reduction of the stigma attached to mental disorders and our profession.

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1. Engel G. Science 1977;196:129-36.
2. Kvim A, Greene J. Cult Med Psychiatry 2021;45:333-42.
3. Galderisi S, Appelbaum PS, Gill N et al. World Psychiatry 2024;23:364-86.
4. Beauchamp TL, Childress JF. Principles of biomedical ethics, 5th ed. Oxford: Oxford University Press, 2001.
5. Herrman H, Allan J, Galderisi S et al. World Psychiatry 2022;21:159-60.
6. Johnson S, Dalton-Locke C, Baker J et al. World Psychiatry 2022;21:220-36.
7. Barnard C. Good life good death: a doctor's case for euthanasia and suicide. Hoboken: Prentice Hall Direct, 1980.

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Improving mechanisms of involvement of people with lived experience in decision-making processes

The involvement of people with lived experience (PWLE) in the mental health field has been and still is very debated from several points of view[1]. One of the most discussed areas refers to their involvement in decision-making processes[2]. These processes occur at the individual level, where PWLE need to be involved in decisions concerning treatment and care; at the social level, where PWLE have to be integrated as full contributors to the society enjoying all the relevant rights[3]; and at the policy level, where PWLE need to be involved in the development and adoption of policies and regulations that have an impact on their life.

At the individual level, several national legislations and ethical codes describe the situations and the procedures that need to be followed when the decision to proceed with compulsory treatment is taken by a professional, by an expert commission, or by a court of law[4]. These situations and procedures should be and often are very clearly settled.

However, in order to give his/her consent to psychiatric treatment, a PWLE first of all needs to understand his/her diagnosis and how the treatment will help decrease his/her symptoms and increase functionality. Moreover, a PWLE needs to know what are the potential side effects of the proposed medication(s), what are the alternative and/or complementary available treatments, such as psychotherapy, and what is the expected length of the treatment.

This is essential information whose provision requires time and availability from the relevant professional. While the time that a professional allocates to an individual patient largely depends upon organization of care, the availability mainly reflects the professional's personal skills, among which empathy is the crucial one. Empathy is a learnable skill, which one may develop by practicing repeatedly. It helps professionals become better doctors and better persons[5]. When empathy is present, there is a good chance that a therapeutic relationship will be established[6] and the patient will adhere to treatment.

What happens if things are not going this way and a PWLE feels that the doctor is not there with and for him/her? The answer is quite simple: the PWLE will, most likely, not consent to treatment. In this situation everybody loses: the PWLE does not get the opportunity to improve his/her medical situation and increase his/her quality of life, and the doctor loses the opportunity to exercise his/her professional role, both situations leading to frustration.

Universities need to devote more attention and allocate more time to developing empathy and communication skills within doctors' training curricula. The use of patient decision aids may be useful, but human interaction based on empathy appears to be preferable and more efficient. Artificial intelligence is a great discovery and may be of help, but has limitations regarding empathy. Human interaction should be valued and remains an essential asset of the mankind.

At the social level, PWLE should be encouraged to exercise their rights in order to get education, job and participation in the society according to their desires and capabilities. Important steps have been made in the last fifty years, especially in the Western part of Europe, with regards to inclusive education, job integration and social representation. On the contrary, in the Eastern part of Europe, there is a low number of PWLE who come out and speak about their experiences and the need for enjoying all their rights. Stigmatization is still present and powerful[7].

Attitudes of people have started to change, but the reliance on a system mostly based on institutions and lacking community facilities does not offer people the possibility to understand that PWLE can manage their illness within their own environment. The COVID-19 pandemic favored the change of attitudes, due to a reduction in hospital admissions. Many PWLE have had the opportunity to realize that they are able to recover in their environment, and many service providers have seen that most PWLE can be treated in the community, provided that some support from mental health services and the social network is available.

The user organizations aiming to protect the rights and interests of the PWLE have started to be more active in the last two decades. They are enabling PWLE, rather than feeling helpless and powerless in the face of the care system and of policy and decision-making processes, to feel that they are part of them and have the power to change them. There is a need for getting stronger support for such organizations, as they have an essential role in ensuring that the human rights of PWLE are respected, and their voice is heard in situations requiring attention. They can and should be the gatekeepers against initiatives that do not take into account the PWLE rights and opinions.

At the policy level, there are still many aspects that could be improved in order to overcome the tokenistic involvement of PWLE[8]. For example, PWLE are often not really involved in the elaboration of legislation or policy documents, but rather just asked to endorse or approve proposals that have been already elaborated. Of course, participation in the elaboration process requires knowledge and training. Efforts in this respect should be made on both sides: on the one hand, training should be provided by governments and professionals; on the other, PWLE who want to be involved should request training and take advantage of it. Regular feedback and consultation with PWLE should be part of policy development, to ensure that the proposed solutions are practical and relevant, so that the "co-creation" concept becomes indeed a reality.

The same mechanism applies to the research area, even if this requires a wealth of knowledge that not many PWLE have[9]. Researchers should get more in contact with PWLE and listen what their needs are, so that the outcome of their research work is more likely to decrease the treatment gap by improving current interventions, reducing their adverse effects, and developing new treatments which support a better quality of life. It is still very rare that experts who do research aimed to develop new interventions meet with people who could have a benefit out of their work. Only by direct experience will experts realize how beneficial PWLE's input may be.

In conclusion, implementing the PWLE motto "Nothing about us without us" requires a significant effort that needs to be done by all those involved in providing care and elaborating policies: professionals working in psychiatric care, medical professionals generally, policy and decision makers, communities, non-governmental organizations, and people with lived experience of a mental health problem.

Raluca Nica
Global Alliance of Mental Illness Advocacy Networks (GAMIAN) - Europe; Romanian League for Mental Health

1. Sunkel C, Sartor C. BJPsych Bull 2022;46:160-4.
2. World Health Organization. Meaningful engagement of people with lived experience of noncommunicable diseases and mental health and neurological conditions. www.who.int.
3. Veldmeijer L, Terlouw G, van Os J et al. JMIR Ment Health 2023;10:e46590.
4. Veldmeijer L, Terlouw G, van 't Veer J et al. Design Health 2023;7:5-23.
5. Masuood S. Why empathy is more helpful than sympathy for my patients. Medscape, June 29, 2022.
6. Stubbe DE. Focus 2018;16:402-3.
7. Corrigan PW. World Psychiatry 2022;21:388-9.
8. Sartor C. Glob Ment Health 2023;10:e38.
9. Krysinska K, Ozols I, Ross A et al. BMC Psychiatry 2023;23:496.

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Development and temporal validation of a clinical prediction model of transition to psychosis in individuals at ultra-high risk in the UHR 1000+ cohort

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The concept of ultra-high risk for psychosis (UHR) has been at the forefront of psychiatric research for several decades, with the ultimate goal of preventing the onset of psychotic disorder in high-risk individuals. Orygen (Melbourne, Australia) has led a range of observational and intervention studies in this clinical population. These datasets have now been integrated into the UHR 1000+ cohort, consisting of a sample of 1,245 UHR individuals with a follow-up period ranging from 1 to 16.7 years. This paper describes the cohort, presents a clinical prediction model of transition to psychosis in this cohort, and examines how predictive performance is affected by changes in UHR samples over time. We analyzed transition to psychosis using a Cox proportional hazards model. Clinical predictors for transition to psychosis were investigated in the entire cohort using multiple imputation and Rubin's rule. To assess performance drift over time, data from 1995-2016 were used for initial model fitting, and models were subsequently validated on data from 2017-2020. Over the follow-up period, 220 cases (17.7%) developed a psychotic disorder. Pooled hazard ratio (HR) estimates showed that the Comprehensive Assessment of At-Risk Mental States (CAARMS) Disorganized Speech subscale severity score (HR=1.12, 95% CI: 1.02-1.24, p=0.024), the CAARMS Unusual Thought Content subscale severity score (HR=1.13, 95% CI: 1.03-1.24, p=0.009), the Scale for the Assessment of Negative Symptoms (SANS) total score (HR=1.02, 95% CI: 1.00-1.03, p=0.022), the Social and Occupational Functioning Assessment Scale (SOFAS) score (HR=0.98, 95% CI: 0.97-1.00, p=0.036), and time between onset of symptoms and entry to UHR service (log transformed) (HR=1.10, 95% CI: 1.02-1.19, p=0.013) were predictive of transition to psychosis. UHR individuals who met the brief limited intermittent psychotic symptoms (BLIPS) criteria had a higher probability of transitioning to psychosis than those who met the attenuated psychotic symptoms (APS) criteria (HR=0.48, 95% CI: 0.32-0.73, p=0.001) and those who met the Trait risk criteria (a first-degree relative with a psychotic disorder or a schizotypal personality disorder plus a significant decrease in functioning during the previous year) (HR=0.43, 95% CI: 0.22-0.83, p=0.013). Models based on data from 1995-2016 displayed good calibration at initial model fitting, but showed a drift of 20.2-35.4% in calibration when validated on data from 2017-2020. Large-scale longitudinal data such as those from the UHR 1000+ cohort are required to develop accurate psychosis prediction models. It is critical to assess existing and future risk calculators for temporal drift, that may reduce their utility in clinical practice over time.

Key words: Ultra-high risk for psychosis, prediction of transition to psychosis, UHR 1000+ cohort, disorganized speech, unusual thought content, negative symptoms, psychosocial functioning, brief limited intermittent psychotic symptoms, prediction model calibration, temporal validation

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The ultra high-risk (UHR) for psychosis criteria were devised in Australia in the mid-1990s in order to identify individuals at high risk of developing a psychotic disorder and to draw up preventive treatment strategies for this group[1-7]. Since then, the UHR criteria – otherwise known as the "clinical high risk" (CHR) criteria – have gained attention globally and currently represent the most widely used method for identifying individuals at high risk of developing a psychotic disorder[8].

UHR individuals are defined by one or more of the following characteristics: a) attenuated psychotic symptoms (APS) – i.e., having experienced subthreshold, attenuated forms of positive psychotic symptoms during the past year; b) brief limited intermittent psychotic symptoms (BLIPS) – i.e., having experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated; and c) trait and state risk factor (Trait) – i.e., having a first-degree relative with a psychotic disorder or having a schizotypal personality disorder, plus having shown a significant decrease in functioning during the previous year.

A recent meta-analysis estimated that 25% of people who meet UHR criteria transition to first-episode psychosis over a 3-year period[9], demonstrating a considerably higher risk compared to the general population and other clinical populations (0.05% and 3.9%, respectively[10]). Outcomes for UHR patients remain heterogenous, highlighting the need for a more accurate calculation of risk at the individual level, for which multimodal data may be required[11].

There has been a wide range of studies to advance detection and prognosis for UHR individuals and to explore individualized intervention strategies[12]. In a meta-analysis, these prognostic models of transition to psychotic disorder in UHR individuals reached a sensitivity of 67% and a specificity of 78%[13]. In recent years, collaborative efforts between national and international multisite projects – such as PRONIA (www.pronia.eu), PSYSCAN (www.psyscan.eu) and NAPLS-3 (http://campuspress.yale.edu/napls) – have delivered large scale databases in order to further develop accurate prognostic models. However, most of these cohorts have a short follow-up period of 1-2 years, precluding the ability to establish longer-term clinical outcomes and to investigate temporal changes in UHR samples. Hence, there is a need for UHR databases that are large in scale, include multimodal data, and have long follow-up periods.

In order to generate stronger evidence for implementation, focus has shifted towards assessing the transportability or generalizability of prediction models[14-16], using external validation of predictive accuracy in samples from different geographical locations and patient populations, or using different predictor measurements[17]. However, predictive performance of a transition to psychosis model is not only affected by differences between geographical locations, but also by drift in UHR samples over time, with evolving models of assessment or clinical care and referral pathways, and shifting patient populations, that may manifest as a decline in rates of transition to psychosis[18-21]. Such drift means that previously validated prediction models could be temporally biased as they were derived from "snapshots" of data that are unsuitable for the evolving nature of populations, clinical settings, and current care[22].

For example, temporal validation of a clinical prediction model examining mortality after cardiothoracic surgery ("EuroSCORE") revealed a loss in calibration over time, as shown by a divergence between observed and predicted mortality[23]. At the individual level, mortality risk was inflated using the model derived from older data, potentially leading to an overly conservative approach to surgical decision-making. Thus, temporal validation is required to assess whether models are stable over different timepoints in the same clinical setting across months, years, and ultimately decades.

Little is known about how changes in UHR populations and treatment over time affect the performance of predictive models. One previous study[24] reported a multimodal machine learning-based psychosis prediction model with the sample split based on the mid-point of data collection, resembling a temporal validation, but the aim was not to specifically examine temporal drift.

Another limitation of many previous models is that they have focused on predictive accuracy without assessing the precision of individualized estimates of risk. Models may assign a specific risk to a patient, but the predicted risk value can deviate from the observed risk – i.e., the model is not well calibrated. A limited number of studies have analyzed calibration in psychosis prediction models[25-29]. Poor calibration can have an impact on the utility of decisions made using a model, where the choice to intervene is made based on a threshold probability (i.e., stratifying individuals into groups of predicted risks). While such decision-making processes tend to include patient preference and clinician attitude towards risk[30], they can be represented more simplistically by net benefit curves (i.e., the balance between intervention risk and benefit for a given threshold probability)[26,29,31]. Defining the potential for drift of accuracy and calibration over time is critical to build the case for formal implementation of psychosis prediction models in clinical care.

The present study aimed to investigate the predictive accuracy of transition to psychosis using a large dataset, and to determine if individualized prediction of psychosis risk is stable over time. We aggregated data of >1,000 UHR individuals from previous studies conducted at Orygen, Melbourne between 1995 and 2020, making it the largest UHR cohort to date with the most extensive longitudinal follow-up.

METHODS

Sample

The sample consisted of UHR individuals who participated in studies conducted at Orygen, Melbourne, between 1995 and 2020. The studies were primarily carried out in Metropolitan Melbourne, at the Personal Assessment and Crisis Evaluation (PACE) clinic [32], the Early Psychosis Prevention and Intervention Centre (EPPIC), and four headspace centres (Sunshine, Craigieburn, Werribee and Glenroy). One study collected additional data (198 individuals) at sites in Amsterdam, Basel, Copenhagen, Jena, Hong Kong, Melbourne, Singapore, Sydney, Vienna, and Zurich[33]. Table 1 lists the 14 studies within which the individuals included in the cohort were recruited (five clinical trials[33-38] and nine longitudinal observational studies[3,39-46]) (see also supplementary information).

Inclusion and exclusion criteria

Inclusion criteria for the cohort were: a) ability to provide informed consent, and b) meeting criteria for at least one of the three UHR groups (see also supplementary information). Exclusion criteria for all studies were: a) current or past psychotic disorder or manic episode; b) past exposure to antipsychotic medication equivalent to a total continuous haloperidol dose of more than 15-50 mg, depending on the original study; c) substance-induced psychotic disorder; d) known history of a medical condition that may account for symptoms leading to initial referral (e.g., epilepsy); e) diagnosis of a serious developmental disorder; f) documented history of developmental delay or intellectual disability (IQ<70); and g) insufficient English language skills to participate in study assessments.

Table 1 Studies within which the individuals included in the UHR 1000+ cohort were recruited

Study	Recruitment years	Age at baseline	UHR (N)	Timepoints
Yung et al[3]	1995-1996	14-30 years	48	BL, months 1-11
McGorry et al[34]	1996-1999	14-30 years	92	BL, months 6-12
Thompson et al[39]	2000	14-30 years	39	BL, months 1-11
Berger et al[36]	2000-2005	14-30 years	30	BL, months 1-23
Yung et al[35]	2000-2007	14-30 years	111	BL, months 1-23
Phillips et al[40]	2000-2005	14-30 years	78	BL, months 1-23
Nelson et al[46]	2008-2010	15-25 years	49	BL
Amminger et al[33] McGorry et al[38]	2010-2014	13-40 years	304	BL, months 1-12-24
EU-GEI[43]	2012-2015	15-35 years	35	BL, months 12-24
Nelson et al[45]	2014-2018	15-25 years	48	BL, month 12
Hartmann et al[42]	2016-2018	12-25 years	31	BL, month 12
Nelson et al[37]	2016-2019	12-25 years	342	BL, months 1-3-6-9-12-18-24
Tognin et al[44]	2017-2019	15-25 years	26	BL, months 3-6-9-12-18
Bayer et al[41]	2018-2021	12-25 years	12	BL, month 12

UHR – ultra-high risk state, BL – baseline

UHR status

Between 1995 and 1996, UHR status at baseline was assessed using the Brief Psychiatric Rating Scale (BPRS)[47], the Comprehensive Assessment of Symptoms and History (CASH)[48], and the Global Assessment of Functioning (GAF)[49]. Between 1996 and 1999, the Comprehensive Assessment of At-Risk Mental States (CAARMS)[50] and the GAF were used. Since 1999, the UHR status was established using the CAARMS and the Social and Occupational Functioning Assessment Scale (SOFAS)[51].

Outcome measures

The main outcome of interest was transition to psychotic disorder, defined using the respective criteria at the time of the study. Before 1999, psychosis threshold was determined using both the BPRS/CASH and the CAARMS, while the concurrent validity of the CAARMS was being established. Since 1999, the CAARMS replaced the BPRS/CASH for the determination of psychosis status. State public mental health records were accessed in cases for whom CAARMS data were not available in order to establish psychosis transition outcome status[52].

Candidate predictors of transition to psychosis

Transition to psychotic disorder was analysed using a Cox proportional hazards model. We selected variables based on prior research, including CAARMS positive symptom subscale (Disorganized Speech, Perceptual Abnormalities, and Unusual Thought Content) severity scores; positive symptoms quantified by the BPRS total score; negative symptoms quantified by the Scale for the Assessment of Negative Symptoms (SANS)[53] total score; level of functioning assessed with the GAF or SOFAS score; duration of symptoms prior to referral to UHR service; gender; age at baseline; and UHR subgroup (BLIPS, APS or Trait) (see also supplementary information).

We also included a variable indicating whether the participant received standard care or a non-standard intervention as part of a clinical trial, to test for any differences based on treatment exposure. Standard treatment included case management and treatment of symptoms and distress. Examples of non-standard intervention included treatment with ω-3 polyunsaturated fatty acids, or cognitive behavior therapy (CBT) and risperidone.

UHR individuals were stratified for symptom severity using CAARMS inclusion groups: BLIPS, APS and Trait. Individuals who met more than one category were classified by their highest severity: any BLIPS; APS or APS+Trait; only Trait. GAF scores were transformed into SOFAS scores using equipercentile linking[54]. Duration of symptoms prior to referral to UHR service was log-transformed prior to analysis.

Statistical analysis

We handled missing data using multiple imputation with chained equations (MICE) under the missing at random assumption[55] (see also supplementary information). A Cox model was fitted in each imputed dataset, and the pooled estimates for each candidate predictor were calculated using Rubin's rules[56,57]. Follow-up time was calculated from the baseline assessment date to transition to psychosis or censoring (lost to follow-up, or reached end of study period), whatever came first. We then developed a full Cox proportional hazards model predicting transition to psychosis within 2 and 10 years, respectively, using the clinical variables that were identified as being predictive of transition to psychosis in the previous step, and internally validated the models using bootstrapping (N=1,000). Bootstrapping involves the building of multiple models (1,000 in this case) using random samples with replacement of the study data, to determine the performance of the model on the same patient population[58]. Both the 2 and 10 year outcome points were used in order to determine model performance over both the near and longer term.

We split the cohort based on baseline years into a development set (1995-2016) and a validation set (2017-2020). Further, we investigated a reduced development set that contained all studies from the PACE 400 dataset (1995-2007)[52], to simulate an even older development set. Models were initially fitted in each imputed dataset using data from 1995-2016 and 1995-2007, respectively; internally validated using bootstrapping (N=1,000) to estimate their performance; and then temporally validated using data from 2017-2020. Temporal validation was performed by predicting the two-year transition probability only in individuals who presented at a UHR service in Melbourne, to remove any potential geographical differences in the dataset.

For each model, performance drift was assessed by comparing discrimination scores, calibration values, and decision curve analysis derived from internal validation and temporal validation.

Discrimination is the ability of a model to assign higher risk predictions to individuals who transitioned to psychosis than to individuals who did not[59]. Although discrimination is critical to know if a model can differentiate between those with higher risk and those with lower risk, it is equally important to assess the calibration of a prognostic model (i.e., the closeness of the observed and predicted probability). For example, a model that correctly differentiates between two patients by assigning double the risk to patient 2 as compared to patient 1 may not be well calibrated if the predicted probabilities are 40% and 20% but the actual observed probabilities are 10% and 5%[60].

Decision curve analysis is a method for evaluating predictive models[31], where the benefit/harm ratio of a clinical decision is considered in the context of the true positive rate for a given predicted probability threshold for a model, is described as "net benefit", and is compared between scenarios where everyone or no one is treated[61]. These curves are based on the actual probability of events, and are superior to the positive predictive value (PPV) and negative predictive value (NPV), which are sensitive to error if the underlying base rate of illness changes over time[30]. A higher net benefit means that more true positive cases are identified by the model, who can then be appropriately treated. For psychosis prediction, benefits may refer to preventing the transition to full episode psychosis from UHR state, and harms may include unnecessary treatment and stigma[26].

Analysis was performed in R 4.1.173 using the mice[62], survival[63,64], and rms[65] packages.

RESULTS

Sample characteristics

Table 2 summarizes the baseline characteristics of the transitioned and non-transitioned groups in the UHR 1000+ cohort. In total, 1,245 UHR individuals were included. Participants' mean age was 18.5±3.6 years; 55% of them were female. The average time between first symptoms and presentation at UHR service was 646.6±1021.7 days. Non-standard intervention as part of a clinical trial was received by 667 individuals (54%). The largest group of individuals met criteria for APS (85.2%), either alone or in combination with Trait criteria, followed by individuals meeting the Trait criteria alone (7.8%). Only 86 individuals were classified as having BLIPS (6.9%).

Rate of onset of psychotic disorder

In total, 220 of the 1,245 UHR individuals transitioned to psychosis (17.7%). The transition rates for the individuals of each clinical study included in this cohort are reported in Table 3. The median number of days until transition was 210.0 (interquartile range, IQR = 500.5 days). Two individuals were excluded from analysis because their date of transition was not known.

Candidate predictors of transition to psychosis

As reported in Figure 1, CAARMS Disorganized Speech severity score (hazard ratio, HR=1.12, 95% CI: 1.02-1.24, p=0.024); CAARMS Unusual Thought Content severity score (HR=1.13, 95% CI: 1.03-1.24, p=0.009); SANS total score (HR=1.02, 95% CI: 1.00-1.03, p=0.022); SOFAS score (HR=0.98, 95% CI: 0.97-1.00, p=0.036); and time between onset of symptoms and entry to UHR service (log transformed) (HR=1.10, 95% CI: 1.02-1.19, p=0.013) were predictive of transition to psychosis in the whole UHR 1000+ cohort. Results for the time between onset of symptoms and entry to the UHR service need to be interpreted cautiously, due to a large amount of imputed data (~20%).

UHR individuals who met the BLIPS criteria had a higher probability of transitioning to psychosis than those who met the APS or APS+Trait criteria (HR=0.48, 95% CI: 0.32-0.73, p=0.001), and those who met the Trait criteria only (HR=0.43, 95% CI: 0.22-0.83, p=0.013).

Non-standard intervention as part of a clinical trial was associated with a reduced risk of transitioning to psychosis compared to standard treatment (HR=0.74, 95% CI: 0.56-0.98, p=0.038). However, when combined with the study identifier, the predictive value of the treatment variable became non-significant (HR=1.18, 95% CI: 0.80-1.72, p=0.40). This was most likely due to the fact that data from observational studies were merged with those of clinical trials, while the former were conducted earlier and had higher transition rates. Hence, we excluded the treatment variable from further analysis.

Table 2 Socio-demographic and clinical characteristics at baseline of individuals who transitioned or did not transition to psychosis

	Non-transition (N=1,025)	Transition to psychosis (N=220)
Age, years (mean±SD)	18.4±3.6	18.9±3.7
Female (%)	55.7	52.7
With spouse or civil partner (%)	4.2	7.4
With children (%)	3.8	5.4
Educational level (%)		
Secondary education ongoing	44.0	45.1
Secondary education completed	31.1	28.8
Technical and further education	11.0	16.3
Undergraduate education unfinished	10.5	7.1
Undergraduate education finished	2.5	1.1
Post-graduate education unfinished	0.6	1.1
Post-graduate education finished	0.2	0.5
Immigrated from another country (%)	14.0	8.3
One or both parents immigrated from another country (%)	39.8	40.6
Time between first symptoms and entry to UHR service, days (mean±SD)	621.5±983.4	754.5±1168.8
UHR subgroup (%)		
BLIPS	5.5	13.7
APS or APS + Trait	86.5	79.5
Only Trait	8.0	6.8
Received non-standard intervention treatment as part of a trial (%)	55	45
CAARMS Disorganized Speech, severity score (mean±SD)	1.6±1.4	2.2±1.4
CAARMS Perceptual Abnormalities, severity score (mean±SD)	3.3±1.5	3.3±1.7
CAARMS Unusual Thought Content, severity score (mean±SD)	2.8±1.8	3.5±1.6
BPRS total score (mean±SD)	43.9±9.2	48.2±10.7
SANS total score (mean±SD)	17.6±11.8	22.9±13.3
SOFAS score (mean±SD)	56.7±11.7	53.3±10.9

UHR – ultra-high risk state, BLIPS – brief limited intermittent psychotic symptoms, APS – attenuated psychotic symptoms, CAARMS – Comprehensive Assessment of At-Risk Mental States, BPRS – Brief Psychiatric Rating Scale, SANS – Scale for the Assessment of Negative Symptoms, SOFAS – Social and Occupational Functioning Assessment Scale

Internal validation of a psychosis prediction model

We built a multivariate Cox regression model with CAARMS Disorganized Speech severity score on a scale from 0 to 6; CAARMS Unusual Thought Content severity score on a scale from 0 to 6; time between onset of symptoms and entry to UHR service (log transformed); SANS total score with a range of 0 to 100; SOFAS score with a range of 0 to 100; and UHR intake group as predictors. Based on a given set of predictor values, the model derives a continuous risk of transition to psychosis between 0 and 1 for an individual (see supplementary information).

Based on internal validation using bootstrapping, the model achieved a moderate discrimination (accuracy, C-index) of 0.65, meaning that it successfully assigned higher risk to the correct individual in approximately two thirds of cases. Internal validation estimated a low degree of overfitting (6-7%), suggesting that the model maintains accuracy across the range of clinical presentations in the sample (see supplementary information for calibration curves and decision curve analysis).

A "threshold probability" can be used to set a threshold for predicting psychosis onset within a certain time frame, i.e. those above the threshold are predicted to transition to psychosis within the time frame, while those below the threshold are not, effectively splitting the sample into two risk groups. In order to find the optimal threshold, prediction performance was tested on a range of thresholds and evaluated at 2 and 10 years follow-up. Table 4 lists prediction statistics across various risk thresholds.

At a threshold of 0.20 (i.e., the individual has 20% probability of transitioning to psychosis), the PPV of the model, representing the ratio of individuals accurately identified as transitioning to psychosis, was 29.72%, with a NPV of 87.91%, when predicting a 2-year onset of psychosis, while the PPV was 22.26% and the NPV was 91.56% when predicting a 10-year onset of psychosis. For a risk threshold of 0.50, the PPV increased to 49.69% with a NPV of 82.67% when predicting a 2-year onset of psychosis, and it was 39.35% with a NPV of 84.52% when predicting a 10-year onset of psychosis.

These metrics suggest that the model is more useful for ruling out individual psychosis risk (high NPV) than for identifying high risk cases (PPV). A higher threshold increased PPV but decreased NPV. Longer prediction interval (10 years compared to 2 years) improved NPV but decreased PPV.

Temporal validation of the psychosis prediction model

Table 5 summarizes calibration and discrimination values for internal and temporal validation of models – using the same predictors as in the previous step – developed in samples from 1995 to 2016, and from 1995 to 2007 (PACE 400[52]). Calibration curves and decision curve analysis for both models are shown in Figure 2.

Both models showed good calibration after internal validation within the time range of their development data, with an amount of overfitting of approximately 9% (9.4% for the PACE 400 model and 8.3% for the 1995-2016 model). Further, both models achieved a moderate discrimination score of 0.672-0.684.

When validated on later data from 2017-2020 from the same clinical services, both models showed a drift in calibration, as shown in Figure 2. In both cases, calibration curves in the validation set "drifted away" from the ideal calibration curve where the predicted probability matches the observed probability. For both models, the drop in calibration was 20.2-35.4%, resulting in an

Table 3 Transition rate and time from baseline assessment to transition

Study	Recruitment years	Length of follow-up (years)	Transition to FEP	Days from baseline assessment to transition, median (IQR)
Yung et al[3]	1995-1996	6-15	26/48 (54.2%)	120.0 (295.5)
McGorry et al[34]	1996-1999	6-15	36/92 (39.1%)	234.0 (672.75)
Thompson et al[39]	2000	6-15	12/39 (30.8%)	313.5 (1,280.5)
Berger et al[36] Yung et al[35] Phillips et al[40]	2000-2007	6-15	38/219 (17.3%)	363.5 (789.0)
Nelson et al[46]	2008-2010	1.5	13/49 (26.5%)	46.0 (65.0)
McGorry et al[38]	2010-2014	3.4	40/304 (13.1%)	229.0 (288.75)
EU-GEI[43]	2012-2015	2	6/35 (17.1%)	131.0 (87.75)
Nelson et al[45]	2014-2018	1	3/48 (6.2%)	77.0 (11.0)
Hartmann et al[42]	2016-2018	1	2/31 (6.4%)	31.0 (9.0)
Nelson et al[37]	2016-2019	2	37/342 (10.8%)	220.0 (409.5)
Tognin et al[44]	2017-2019	2	4/26 (15.4%)	257.5 (55.5)
Bayer et al[41]	2018-2021	1	3/12 (25.0%)	173.0 (111.5)
Total			**220/1,245 (17.7%)**	**210.0 (500.5)**

FEP – first-episode psychosis, IQR – interquartile range

overestimation of an individual's probability of transition to psychosis in the more recent sample.

For example, in the 1995-2016 sample, 30 of 100 individuals who had a predicted transition probability of 0.30 did indeed transition to psychosis, yielding a match between the predicted and observed risk. In the 2017-2020 sample, calibration curves show that only 25 of 100 individuals with similar symptoms and predicted transition risk (0.30) transitioned to psychosis, indicating a divergence between predicted and observed transition risk.

The potential impact of drift on decision-making is summarized in the net benefit decision curve, which shows a reduced true positive rate (net benefit) for a given probability threshold across the model (see Figure 2). This means that the model provides an overestimation of psychosis risk (e.g., a true probability of 0.25 versus the predicted probability of 0.30) in the more recent sample (2017-2020).

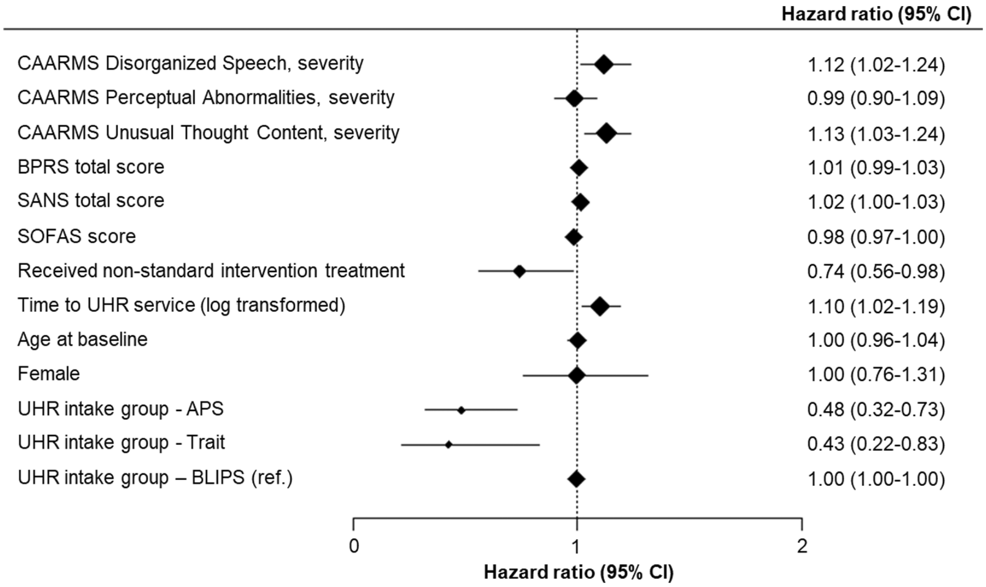

Figure 1 Candidate predictors of transition to psychosis (hazard ratios with 95% CIs). CAARMS – Comprehensive Assessment of At-Risk Mental States, BPRS – Brief Psychiatric Rating Scale, SANS – Scale for the Assessment of Negative Symptoms, SOFAS – Social and Occupational Functioning Assessment Scale, UHR – ultra-high risk state, BLIPS – brief limited intermittent psychotic symptoms, APS – attenuated psychotic symptoms.

Table 4 Prediction statistics for transition to psychosis across various risk thresholds using bootstrapping (N=1,000)

	Predicting 2-year onset of psychosis				Predicting 10-year onset of psychosis			
Risk threshold	**Specificity (%)**	**Sensitivity (%)**	**NPV (%)**	**PPV (%)**	**Specificity (%)**	**Sensitivity (%)**	**NPV (%)**	**PPV (%)**
0.05	3.10	99.54	96.98	17.93	0	100	0	17.54
0.10	28.64	88.00	91.82	20.78	4.86	98.18	92.65	18.00
0.15	53.44	66.89	88.36	23.41	19.01	91.77	91.58	19.42
0.20	73.68	52.32	87.91	29.72	37.92	83.55	91.56	22.26
0.25	86.38	37.63	86.69	37.04	51.60	67.96	88.33	23.00
0.30	91.65	24.34	85.07	38.31	64.81	60.11	88.43	26.66
0.35	95.88	11.93	83.66	38.12	77.97	48.68	87.72	31.98
0.40	97.86	7.30	83.23	42.02	85.49	38.06	86.65	35.83
0.45	99.42	4.97	83.11	64.37	90.56	29.30	85.76	39.80
0.50	99.61	1.82	82.67	49.69	93.65	19.34	84.52	39.35
0.55	99.61	1.36	82.60	42.47	96.08	11.59	83.63	38.67
0.60	99.90	0.90	82.58	65.28	97.87	7.87	83.32	44.02

Individuals above the risk threshold are predicted to transition to psychosis within the time frame, while those below the threshold are not. NPV – negative predictive value, PPV – positive predictive value.

DISCUSSION

The relatively low group-level transition rate in individuals who are at high risk for psychosis has sparked increased interest to develop and validate clinical prediction models to more precisely estimate an individual's risk of transition. While there are a number of large-scale cohorts now implemented, including PRONIA and NAPLS-3, similar studies with larger samples and longer follow-up are required to enable the investigation of temporal changes in UHR populations, and the monitoring of long-term outcomes.

We linked and harmonized data concerning UHR individuals recruited within 14 clinical studies, building up the UHR 1000+ cohort presented in this study, which is the largest collection of clinical data from individuals at high risk of transitioning to psychosis to date. Data were mostly collected (84%) in one geographical area (Melbourne, Australia), substantially reducing site effects. Additionally, >50% of the individuals in this cohort were followed up >2 years after presentation, making it the largest dataset of UHR individuals with long-term follow-up to date.

In the whole cohort, the pooled estimates for CAARMS Disorganized Speech and Unusual Thought Content, negative symptoms (SANS total score), social functioning measured by the SOFAS score, and duration of symptoms prior to UHR service entry were predictive of transition to psychosis. We also found a lower risk for UHR individuals meeting APS or Trait criteria at baseline as compared to UHR individuals meeting any BLIPS criteria, corroborating findings in a previous meta-analysis[66].

Receiving non-standard intervention as part of a clinical trial was negatively associated with transition to psychosis within the whole cohort, consistent with meta-analytic evidence of a positive effect of preventive interventions on psychosis transition in clinical trials[67]. Further analysis, however, showed that this association was apparently influenced by merging data from observational studies and clinical trials with varying transition rates over the years. Thus, analyses combining these different types of samples appear unreliable, and further detailed analysis of prediction models in a large longitudinal follow-up of clinical trials is warranted.

Clinical decision-making for UHR patients is complex, given the heterogeneity in presentation and the relatively low transition rates to psychosis. In clinical practice, complex risk models can be implemented as simplified risk calculators, allowing busy cli-

Table 5 Summary of internal and temporal validation performance metrics for both models, estimated across all imputed datasets (all values are means with 95% CI)

	Harrell's C index		Calibration-in-the-large		Slope	
Model	**Internal**	**2017-2020**	**Internal**	**2017-2020**	**Internal**	**2017-2020**
1995-2007	0.684 (0.683 - 0.686)	0.615 (0.611 - 0.618)	0.010 (0.010 - 0.010)	–0.075 (–0.079 to –0.071)	0.906 (0.904 - 0.908)	0.585 (0.565 - 0.604)
1995-2016	0.672 (0.671 - 0.674)	0.636 (0.633 - 0.638)	0.009 (0.008 - 0.009)	–0.023 (–0.023 to –0.022)	0.917 (0.916 - 0.919)	0.732 (0.717 - 0.747)

Harrell's C index quantifies the discrimination of a model. Calibration-in-the-large is the difference between average predicted risk and overall event rate. Calibration slope measures the divergence between predicted and observed risk. Internal validation was performed using bootstrapping (N=1,000) in the 1995-2007 and 1995-2016 samples. Temporal validation was performed by predicting the 2-year transition probability for individuals who presented at a UHR service between 2017 and 2020 using models developed in samples from 1995-2007 and 1995-2016.

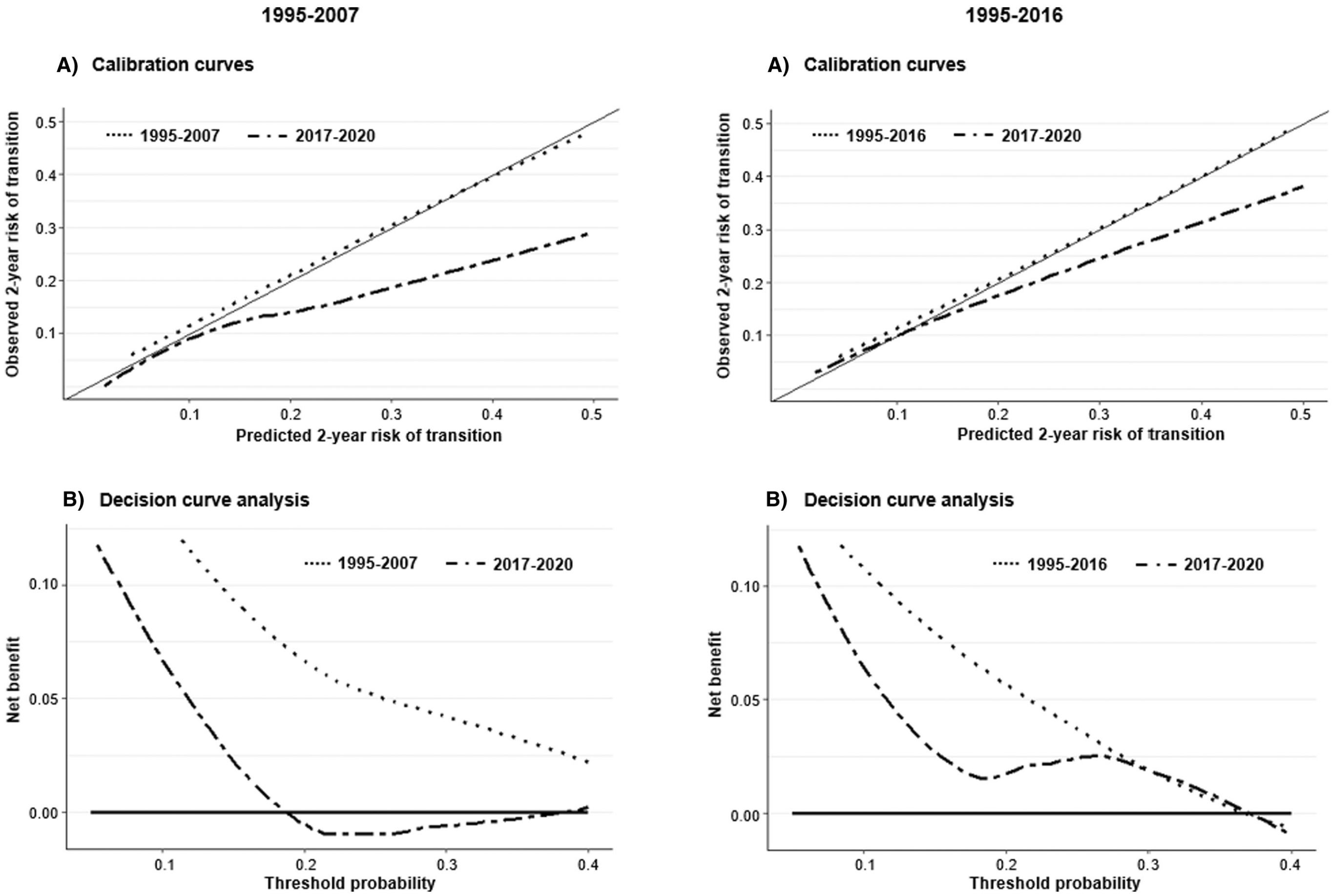

Figure 2 Change in performance over time for transition to psychosis prediction models developed in samples from 1995 to 2007 and from 1995 to 2016. A) Each plot displays the internal calibration curve using bootstrapping (N=1,000) and the temporal validation curve using individuals who presented at an UHR service between 2017 and 2020. The black diagonal line indicates an ideal calibration where the predicted probabilities match the observed probabilities. B) Each plot displays the decision curve analysis for the internal and temporal sample. Net benefit in the decision curve analysis is equivalent to true positive cases (i.e., a net benefit of 0.10 would be equivalent of identifying 10 individuals per 100, all of whom will transition to psychosis). A net benefit of zero (black horizontal line) is achieved when no individuals are treated.

nicians to enter a limited set of risk features to support decision-making for individual patients. Some such calculators have been proposed for psychosis risk[25-29]. Generally, when using risk calculators, a numerical threshold is determined as a cue for action – once the probability of an event is reached based on combined underlying factors, there is an indication to intervene. These thresholds can be determined by performance metrics such as accuracy, sensitivity and specificity, or PPV and NPV, which help clinicians to understand how well the calculator classifies those at high and low risk.

Our model, developed on the whole UHR 1000+ cohort, showed a moderate accuracy, with a discrimination of 0.65. The model also displayed high internal validity and was well calibrated in the derivation sample, suggesting robust and accurate performance in this specific context. The generalizability of this model remains to be tested outside of the UHR 1000+ sample. Combining clinical data with biomarkers for psychosis risk from neuroimaging, cognitive science, genomics and digital assessments may improve model accuracy[24,68-70], and large scale studies assessing this are currently underway[71]. Moreover, decision-making is complex in clinical practice, involving consideration of patient preference and varying with clinician attitude to the risks of intervention[30].

In the temporal validation of our models in the later data set (2017-2020), we saw a loss by 20.2-35.4% in calibration slope, suggesting an overprediction of transition risk, although the models showed good calibration and high within-sample reproducibility in the development sample. This finding highlights that, in addition to the evaluation of discrimination performance for calculators across cohorts and clinical services[72], clinicians need to consider the age of a psychosis prediction model when interpreting its output. The results in this study match those in other fields of medicine, where risk calculators have required periodic updating to maintain calibration accuracy[73-76].

The divergence between predicted and observed transition risk in the UHR 1000+ cohort may be explained by the variation in transition rate across studies over the years (22% in the 1995-2016 sample vs. 11% in the 2017-2020 sample). This may be partly attributable to sampling issues. Over time, in this cohort, increased numbers were recruited from headspace, a primary care-based youth mental health service, and proportionally less from Orygen's specialist PACE clinic. The more generalist nature of the headspace clinics is less enriched with psychosis risk compared to the PACE service, hence overall transition rates may have declined[77].

However, temporal changes may not only be attributed to the base risk of UHR individuals, but also to predictor-outcome relationships. For example, if there are changes in the clinical presentation of patients referred to a service or in the standard treatment they receive[18,78], these changes may alter the relationship between certain risk factors and transition to psychosis. This would result in the underlying prediction model needing updating or refitting. Examples would include the cohort shifting to largely patients with only trait risk and very limited positive psychotic symptoms, or a new treatment becoming standard for all presentations and mitigating the relationship between positive symptoms and transition to psychosis. The independent contributions of changes in baseline risk and potential changes in population characteristics or care processes in the UHR 1000+ sample remain to be defined.

A limitation of the dataset used in this study is the amount of missing data. Assessment batteries varied across included studies, with evolution of knowledge over time and the focus on specific research questions. Several assessments were replaced or updated between the first and last study. Harmonization of samples presented a unique challenge spanning over two decades. Moreover, survival analysis in this cohort is limited by the variation in follow-up period between studies, which may introduce uncertainty and a bias in analyses using time-to-event information. Finally, splitting the dataset by time reduced the sample size for development and validation, potentially leading to a higher risk of overfitting and less reliable evaluation results[79].

Overall, the UHR 1000+ dataset represents the largest sample of youth at risk of psychosis to date, with a follow-up of up to 16.7 years, and provides a unique resource for further investigation of prediction modelling across UHR outcomes. The value of this resource will be further expanded by integrating multimodal data such as those from neuroimaging, cognitive science, genomics and digital assessments.

Our results show that higher disorganized speech and unusual thought content as measured by CAARMS, higher negative symptom severity, lower social functioning, and a longer duration of symptoms prior to UHR service entry are predictive of transition to psychosis. The model, developed on the whole UHR 1000+ cohort, achieved a moderate accuracy of 0.65. However, our findings demonstrate that it is critical to assess existing and future risk calculators for temporal drift, that may reduce their utility in clinical practice over time.

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REFERENCES

1. Yung AR, Phillips LJ, McGorry PD et al. Prediction of psychosis: a step towards indicated prevention of schizophrenia. Br J Psychiatry 1998;172(Suppl. 33):14-20.
2. Yung AR, Phillips LJ, Yuen HP et al. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr Res 2004;67:131-42.
3. Yung AR, Phillips LJ, Yuen HP et al. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr Res 2003;60:21-32.
4. Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull 1996;22:353-70.
5. McGorry PD, Yung AR, Phillips LJ. The "close-in" or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. Schizophr Bull 2003;29:771-90.
6. Yung AR, McGorry PD. The initial prodrome in psychosis: descriptive and qualitative aspects. Aust N Z J Psychiatry 1996;30:587-99.
7. McGorry PD, Singh BS. Schizophrenia: risk and possibility of prevention. In: Raphael B, Burrows GD (eds). Handbook of preventive psychiatry. Amsterdam: Elsevier, 1995:492-514.
8. Fusar-Poli P, Borgwardt S, Bechdolf A et al. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 2013;70:107-20.
9. Salazar de Pablo G, Radua J, Pereira J et al. Probability of transition to psychosis in individuals at clinical high risk: an updated meta-analysis. JAMA Psychiatry 2021;78:970-8.
10. Lee TY, Lee J, Kim M et al. Can we predict psychosis outside the clinical high-risk state? A systematic review of non-psychotic risk syndromes for mental disorders. Schizophr Bull 2018;44:276-85.
11. Coutts F, Koutsouleris N, McGuire P. Psychotic disorders as a framework for precision psychiatry. Nat Rev Neurol 2023;19:221-34.
12. Fusar-Poli P, Salazar de Pablo G, Correll CU et al. Prevention of psychosis: advances in detection, prognosis, and intervention. JAMA Psychiatry 2020;77:755-65.
13. Sanfelici R, Dwyer DB, Antonucci LA et al. Individualized diagnostic and prognostic models for patients with psychosis risk syndromes: a meta-analytic view on the state of the art. Biol Psychiatry 2020;88:349-60.
14. Dwyer DB, Falkai P, Koutsouleris N. Machine learning approaches for clinical psychology and psychiatry. Annu Rev Clin Psychol 2018;14:91-118.
15. Worthington MA, Cao H, Cannon TD. Discovery and validation of prediction algorithms for psychosis in youths at clinical high risk. Biol Psychiatry Cogn Neurosci Neuroimaging 2020;5:738-47.
16. Studerus E, Ramyead A, Riecher-Rössler A. Prediction of transition to psychosis in patients with a clinical high risk for psychosis: a systematic review of methodology and reporting. Psychol Med 2017;47:1163-78.
17. Moons KGM, Kengne AP, Grobbee DE et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart 2012;98:691-8.
18. Hartmann JA, Yuen HP, McGorry PD et al. Declining transition rates to psychotic disorder in "ultra-high risk" clients: investigation of a dilution effect. Schizophr Res 2016;170:130-6.
19. Nelson B, Yuen HP, Lin A et al. Further examination of the reducing transition rate in ultra high risk for psychosis samples: the possible role of earlier intervention. Schizophr Res 2016;174:43-9.
20. Yung AR, Yuen HP, Berger G et al. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? Schizophr Bull 2007;33:673-81.
21. Spiteri-Staines AE, Yung AR, Lin A et al. Non-psychotic outcomes in young people at ultra-high risk of developing a psychotic disorder: a long-term follow-up study. Schizophr Bull 2024; doi:10.1093/schbul/sbae005.
22. Reynard C, Jenkins D, Martin GP et al. Is your clinical prediction model past its sell by date? Emerg Med J 2022;39:956-8.
23. Hickey GL, Grant SW, Murphy GJ et al. Dynamic trends in cardiac surgery: why the logistic EuroSCORE is no longer suitable for contemporary cardiac surgery and implications for future risk models. Eur J Cardio-Thoracic Surg 2013;43:1146-52.
24. Koutsouleris N, Dwyer DB, Degenhardt F et al. Multimodal machine learning workflows for prediction of psychosis in patients with clinical high-risk syndromes and recent-onset depression. JAMA Psychiatry 2021;78:195-209.

25. Cannon TD, Yu C, Addington J et al. An individualized risk calculator for research in prodromal psychosis. Am J Psychiatry 2016;173:980-8.
26. Rosen M, Betz LT, Schultze-Lutter F et al. Towards clinical application of prediction models for transition to psychosis: a systematic review and external validation study in the PRONIA sample. Neurosci Biobehav Rev 2021;125:478-92.
27. Studerus E, Beck K, Fusar-Poli P et al. Development and validation of a dynamic risk prediction model to forecast psychosis onset in patients at clinical high risk. Schizophr Bull 2020;46:252-60.
28. Malda A, Boonstra N, Barf H et al. Individualized prediction of transition to psychosis in 1,676 individuals at clinical high risk: development and validation of a multivariable prediction model based on individual patient data meta-analysis. Front Psychiatry 2019;10:345.
29. Fusar-Poli P, Rutigliano G, Stahl D et al. Development and validation of a clinically based risk calculator for the transdiagnostic prediction of psychosis. JAMA Psychiatry 2017;74:493-500.
30. Sox HC, Higgins MC, Owens DK. Measuring the outcome of care – expected utility analysis. In: Sox HC, Higgins MC, Owens DK (eds). Medical decision making, 2nd ed. Chichester: Wiley, 2013:204-42.
31. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Mak 2006;26:565-74.
32. Yung AR, McGorry PD, McFarlane CA et al. The Pace Clinic: development of a clinical service for young people at high risk of psychosis. Australas Psychiatry 1995;3:345-9.
33. Amminger GP, Nelson B, Markulev C et al. The NEURAPRO biomarker analysis: long-chain omega-3 fatty acids improve 6-month and 12-month outcomes in youths at ultra-high risk for psychosis. Biol Psychiatry 2020;87:243-52.
34. McGorry PD, Yung AR, Phillips LJ et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch Gen Psychiatry 2002;59:921-8.
35. Yung AR, Phillips LJ, Nelson B et al. Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis. J Clin Psychiatry 2011;72:430-40.
36. Berger GE, Wood SJ, Ross M et al. Neuroprotective effects of low-dose lithium in individuals at ultra-high risk for psychosis. A longitudinal MRI/MRS study. Curr Pharm Des 2012;18:570-5.
37. Nelson B, Amminger GP, Yuen HP et al. Staged treatment in early psychosis: a sequential multiple assignment randomised trial of interventions for ultra high risk of psychosis patients. Early Interv Psychiatry 2018;12:292-306.
38. McGorry PD, Nelson B, Markulev C et al. Effect of ω-3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders: the NEURAPRO randomized clinical trial. JAMA Psychiatry 2017;74:19-27.
39. Thompson KN, Phillips LJ, Komesaroff P et al. Stress and HPA-axis functioning in young people at ultra high risk for psychosis. J Psychiatr Res 2007;41:561-9.
40. Phillips LJ, Nelson B, Yuen HP et al. Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: study design and baseline characteristics. Aust N Z J Psychiatry 2009;43:818-29.
41. Bayer JMM, Spark J, Krcmar M et al. The SPEAK study rationale and design: a linguistic corpus-based approach to understanding thought disorder. Schizophr Res 2023;259:80-7.
42. Hartmann JA, Nelson B, Spooner R et al. Broad clinical high-risk mental state (CHARMS): methodology of a cohort study validating criteria for pluripotent risk. Early Interv Psychiatry 2019;13:379-86.
43. European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI). Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. Schizophr Bull 2014;40:729-36.
44. Tognin S, van Hell HH, Merritt K et al. Towards precision medicine in psychosis: benefits and challenges of multimodal multicenter studies – PSYSCAN: translating neuroimaging findings from research into clinical practice. Schizophr Bull 2020;46:432-41.
45. Nelson B, Lavoie S, Gawęda Ł et al. The neurophenomenology of early psychosis: an integrative empirical study. Conscious Cogn 2020;77:102845.
46. Nelson B, Thompson A, Yung AR. Basic self-disturbance predicts psychosis onset in the ultra high risk for psychosis "prodromal" population. Schizophr Bull 2012;38:1277-87.
47. Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep 1962;10:799-812.
48. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH): an instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 1992;49:615-23.
49. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington: American Psychiatric Publishing, 1994.
50. Yung AR, Yung AR, Pan Yuen H et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust N Z J Psychiatry 2005;39:964-71.
51. Goldman H, Skodol A, Lave T. Revising axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1992;149:1148-56.
52. Nelson B, Yuen HP, Wood SJ et al. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. JAMA Psychiatry 2013;70:793-802.
53. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). Iowa City: University of Iowa, 1983.
54. Samara MT, Engel RR, Millier A et al. Equipercentile linking of scales measuring functioning and symptoms: examining the GAF, SOFAS, CGI-S, and PANSS. Eur Neuropsychopharmacol 2014;24:1767-72.
55. Sterne JAC, White IR, Carlin JB et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393.
56. Marshall A, Altman DG, Holder RL et al. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol 2009;9:57.
57. Rubin DB. Multiple imputation. In: van Buuren S (ed). Flexible imputation of missing data, 2nd ed. Boca Raton: Chapman and Hall/CRC, 2018:29-62.
58. Steyerberg EW, Harrell FE, Borsboom GJJM et al. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001;54:774-81.
59. Steyerberg EW, Vickers AJ, Cook NR et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21:128-38.
60. Alba AC, Agoritsas T, Walsh M et al. Discrimination and calibration of clinical prediction models: users' guides to the medical literature. JAMA 2017;318:1377-84.
61. Vickers AJ, van Calster B, Steyerberg EW. A simple, step-by-step guide to interpreting decision curve analysis. Diagn Progn Res 2019;3:18.
62. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw 2011;45:1-67.
63. Therneau TM, Grambsch PM. The Cox model. In: Therneau TM, Grambsch PM (eds). Modeling survival data: extending the Cox model. New York: Springer, 2000:39-77.
64. Therneau TM. A Package for survival analysis in R. https://cran.r-project.org/package=survival.
65. Harrell FE Jr. rms: regression modeling strategies. https://cran.r-project.org/package=rms.
66. Fusar-Poli P, Cappucciati M, Borgwardt S et al. Heterogeneity of psychosis risk within individuals at clinical high risk: a meta-analytical stratification. JAMA Psychiatry 2016;73:113-20.
67. Mei C, van der Gaag M, Nelson B et al. Preventive interventions for individuals at ultra high risk for psychosis: an updated and extended meta-analysis. Clin Psychol Rev 2021;86:102005.
68. Hartmann S, Cearns M, Pantelis C et al. Combining clinical with cognitive or magnetic resonance imaging data for predicting transition to psychosis in ultra high-risk patients: data from the PACE 400 cohort. Biol Psychiatry Cogn Neurosci Neuroimaging 2024;9:417-28.
69. Dwyer D, Clark S, Amminger GP et al. Towards precision psychiatry for youth: the PRE-EMPT Centre of Research Excellence roadmap. https://www.authorea.com.
70. Abi-Dargham A, Moeller SJ, Ali F et al. Candidate biomarkers in psychiatric disorders: state of the field. World Psychiatry 2023;22:236-62.
71. Brady LS, Larrauri CA, AMP SCZ Steering Committee. Accelerating Medicines Partnership® Schizophrenia (AMP® SCZ): developing tools to enable early intervention in the psychosis high risk state. World Psychiatry 2023;22:42-3.
72. Chekroud AM, Hawrilenko M, Loho H et al. Illusory generalizability of clinical prediction models. Science 2024;383:164-7.
73. Tanner KT, Keogh RH, Coupland CAC et al. Dynamic updating of clinical survival prediction models in a changing environment. Diagn Progn Res 2023;7:24.
74. Davis SE, Lasko TA, Chen G et al. Calibration drift in regression and machine learning models for acute kidney injury. J Am Med Informatics Assoc 2017;24:1052-61.
75. Jenkins DA, Martin GP, Sperrin M et al. Comparing predictive performance of time invariant and time variant clinical prediction models in cardiac surgery. Stud Health Technol Inform 2024;310:1026-30.
76. Toll DB, Janssen KJM, Vergouwe Y et al. Validation, updating and impact of clinical prediction rules: a review. J Clin Epidemiol 2008;61:1085-94.
77. McGorry PD, Mei C, Chanen A et al. Designing and scaling up integrated

youth mental health care. World Psychiatry 2022;21:61-76.
78. Formica MJC, Phillips LJ, Hartmann JA et al. Has improved treatment contributed to the declining rate of transition to psychosis in ultra-high-risk cohorts? Schizophr Res 2022;243:276-84.
79. Collins GS, Dhiman P, Ma J et al. Evaluation of clinical prediction models (part 1): from development to external validation. BMJ 2024;384:e074819.

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Predicting the outcome of psychotherapy for chronic depression by person-specific symptom networks

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Psychotherapies are efficacious in the treatment of depression, albeit only with a moderate effect size. It is hoped that personalization of treatment can lead to better outcomes. The network theory of psychopathology offers a novel approach suggesting that symptom interactions as displayed in person-specific symptom networks could guide treatment planning for an individual patient. In a sample of 254 patients with chronic depression treated with either disorder-specific or non-specific psychotherapy for 48 weeks, we investigated if person-specific symptom networks predicted observer-rated depression severity at the end of treatment and one and two years after treatment termination. Person-specific symptom networks were constructed based on a time-varying multilevel vector autoregressive model of patient-rated symptom data. We used statistical parameters that describe the structure of these person-specific networks to predict therapy outcome. First, we used symptom centrality measures as predictors. Second, we used a machine learning approach to select parameters that describe the strength of pairwise symptom associations. We found that information on person-specific symptom networks strongly improved the accuracy of the prediction of observer-rated depression severity at treatment termination compared to common covariates recorded at baseline. This was also shown for predicting observer-rated depression severity at one- and two-year follow-up. Pairwise symptom associations were better predictors than symptom centrality parameters for depression severity at the end of therapy and one year later. Replication and external validation of our findings, methodological developments, and work on possible ways of implementation are needed before person-specific networks can be reliably used in clinical practice. Nevertheless, our results indicate that the structure of person-specific symptom networks can provide valuable information for the personalization of treatment for chronic depression.

Key words: Network theory, personalization of treatment, psychotherapy, depression, outcome prediction, machine learning, person-specific symptom networks, pairwise symptom associations, symptom centrality measures

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Several treatment options are available for depression, including a variety of pharmacotherapies and psychotherapies. These treatments are usually evaluated with respect to their overall efficacy in patient samples, and their average effect size has been reported to be moderate[1-3]. Still, a considerable number of people do not respond to current therapies[4-8].

While the available evidence suggests that treatment for depression reduces the average symptom severity of a whole group, such group-level effects cannot be directly applied to the individual patient[8]. Individual differences in treatment efficacy and their sources are commonly disregarded in group comparison designs such as those of randomized controlled trials[6]. This limits the information base for clinicians aiming to make evidence-based treatment choices for their individual patients[1,6,9,10]. Therefore, research on personalized mental health treatment, also called "precision mental health care", has gained considerable popularity[10-12].

A novel approach to the personalization of treatments is offered by the network theory of psychopathology. This theory assumes that mental disorders arise and are sustained because symptoms causally interact with each other[13]. The occurrence of one symptom is thought to cause the occurrence of further symptoms, and mutual interactions among symptoms cause the persistence of mental health problems. From this perspective, treatment should target factors causing specific symptoms, or specific symptoms, or associations among symptoms[14].

Person-specific symptom networks which show associations among symptoms for an individual have been proposed for individualized treatment planning[13,15,16]. More precisely, based on the network theory, it has been suggested that a person-specific symptom network could indicate which specific symptoms or symptom associations should be primarily targeted by treatment for a given individual[13,14,17]. The centrality hypothesis suggests that symptoms which are most central in the network, i.e. which have the most or strongest associations with other symptoms, should be targeted, because an improvement of these symptoms would lead to the improvement of many other symptoms[14,18,19]. Additionally, the theory suggests that treatment should reduce (strong) associations among symptoms, so that the occurrence of one symptom ceases to induce other symptoms[14].

So far, there is little empirical evidence to support the centrality hypothesis and the prioritization of strong symptom associations. Previous research showed that centrality indices based on cross-sectional between-person networks could not predict symptom change accurately, especially when compared to traditionally used non-network parameters, such as baseline symptom severity[18,19]. Similarly, the connectedness of baseline cross-sectional networks did not predict treatment response when accounting for baseline symptom severity variance[20].

However, studies of cross-sectional symptom networks are based on variation between individuals, i.e., on how different persons of a certain population differ in their symptom occurrence at a specific time point. They inform on whether individuals in a population showing a symptom at a specific time point are also more likely to show other symptoms at the same time point[21]. Thus, cross-sectional networks show symptom associations in a specific group. This contrasts to longitudinal symptom networks which can be constructed with repeated observations of each individual[22]. These networks are based on variation within each individual person over time, i.e. on how symptom occurrence differs over time for a given individual[21]. Consequently, longitudinal networks can show for a given person whether the occurrence of a symptom is related to the occurrence of another symptom at a neighbouring time point and, therefore, allow the investigation of person-specific symptom associations[15,21,23].

In sum, longitudinal networks indicate symptom associations specific to an individual, while cross-sectional networks show symptom associations for a certain group. It has been argued that findings obtained in cross-sectional analyses of group effects cannot be directly applied to an individual person without strong and frequently unrealistic assumptions[5,9]. Further, treatment is thought to introduce changes in symptom dynamics within each individual person[12]. Therefore, longitudinal person-specific networks seem more likely to entail relevant information for treatment response than cross-sectional networks[24,25].

Initial research on longitudinal symptom networks showed that treatment-related hypotheses of the network theory could be partially confirmed with empirical data[26]. Further, person-specific network parameters together with some covariates – i.e., initial functional impairment, sex, education level, personality style, and difficulty to attend treatment – predicted dropout during treatment for mood and anxiety disorders with notable accuracy[27].

Still, longitudinal person-specific symptom networks derived from repeated measurements diverged from the patients' own perception of their symptom networks[28], and methodological challenges for estimating longitudinal person-specific networks remain[15,25,29]. Furthermore, there is no consensus yet on how to select treatment targets based on person-specific symptom networks[29]. A major obstacle is that there is uncertainty about which of the various parameters describing the structure of the person-specific network should be selected for treatment planning. Two of the most frequently considered options are information on the centrality of symptoms and information on the pairwise associations among symptoms.

If parameters that describe the structure of person-specific symptom networks before treatment or their change during treatment are predictive of treatment outcome, this could provide further support to the value of symptom networks for planning and monitoring treatment. In this study, we aimed to assess how the structure of longitudinal person-specific symptom networks before treatment, and their change during psychotherapy (either disorder-specific or non-specific), relate to treatment outcome in patients with chronic depression.

METHODS

Procedure

This study used data from a large multisite randomized controlled trial of psychotherapy for chronic depression[30-32]. Patients from eight clinical sites in Germany were randomized to receive either disorder-specific (cognitive behavioral analysis system of psychotherapy, CBASP) or non-specific (supportive) psychotherapy over 48 weeks. Depression severity was measured at baseline, at treatment termination, and one and two years after treatment ended, using the 24-item version of the Hamilton Rating Scale for Depression (HRSD-24)[33]. The assessment was done by blinded, experienced and trained raters[31]. Additionally, patients rated their depression severity at each session using the 28-item Inventory of Depressive Symptomatology (IDS)[34]. We included only IDS items that align with the nine depression symptoms of the DSM-5, and dichotomized them before analysis.

The ethics committees of the University of Freiburg and of all participating centres approved the study, and all participants provided written consent. The original study was preregistered at clinicaltrials.gov (NCT00970437). All analyses performed in this study were preregistered on the Open Science Framework (see supplementary information).

Statistical analysis

Person-specific symptom networks

An overview of data analysis is provided in Figure 1. All person-specific symptom networks are based on the estimation of a univariate multilevel model for each symptom. This model estimates whether the presence of a symptom at each treatment session is associated with the presence of this symptom and all other symptoms at the previous session. In this model, temporal symptom associations can change linearly throughout treatment, i.e. get weaker or stronger, and these changes across time can differ between treatment groups.

The multilevel model includes random effects for each individual for the temporal symptom associations and their change. This means that, in addition to modelling the temporal symptom associations and their change during treatment at the group level, i.e. for the "average person", the model also provides so-called random effect estimates. These estimates indicate how strongly each individual person differs from the average, and show for each individual how strongly the symptoms are associated with each other at baseline and how these associations change during treatment.

We used the random effect estimates for each individual to construct person-specific symptom networks. We calculated for each individual how strongly all symptoms were associated with each other at each session and combined this information in person-specific symptom networks for that session. These networks show how each symptom at a given time point is related to itself and to all other symptoms at the next time point.

Panel B in Figure 1 shows an exemplary symptom network of an individual patient. In this example, at treatment start, the presence of sleep problems predicted the presence of this symptom at the next session, as indicated by the arrow pointing from this symptom to itself. Sleep problems also predicted loss of pleasure/interest, change in appetite/weight, depressed mood, reduced self-worth, and tiredness, as indicated by the respective arrows. The session-

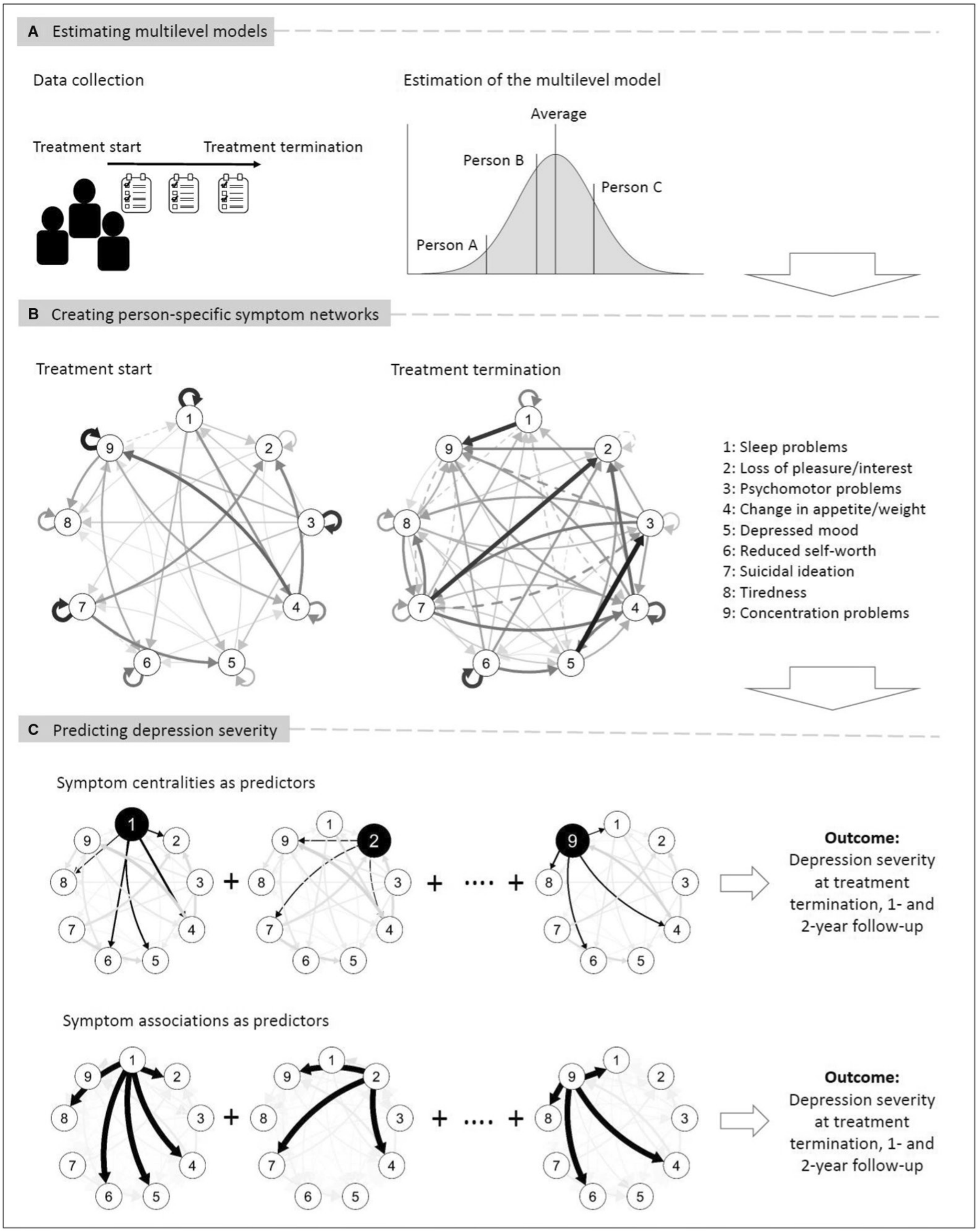

Figure 1 Overview of data analysis. As shown in Panel A, a multilevel model was first estimated for each symptom. As shown in Panel B, person-specific networks were constructed (in the network diagrams, each circle represents a symptom; the arrow pointing from one symptom to itself depicts the influence of this variable on itself over time; the arrow pointing from one symptom to another symptom refers to the influence of this variable on another variable over time). As shown in Panel C, the structure of the person-specific networks can be described with symptom-centrality and pairwise symptom-association information. Both network description measures were used to predict the severity of depression at treatment termination, one-year and two-year follow-up.

to-session associations of this symptom changed throughout treatment, which can be seen in the network at treatment termination.

To describe the person-specific symptom networks, we used symptom centrality and pairwise symptom association measures.

As symptom centrality measure, we used outstrength centrality, which shows how connected a symptom is in a given network. We calculated the outstrength of each symptom by summing the absolute strength of all "outgoing" associations of that symptom with all other symptoms in the respective person-specific network. In the example from an individual patient in Figure 1, the centrality of sleep problems at treatment start is calculated by summing up the strength of its outgoing associations with itself, loss of pleasure/interest, change in appetite/weight, depressed mood, reduced self-worth, and tiredness (see Figure 1, Panel C). We then computed the change in outstrength of each symptom during treatment.

As pairwise symptom association measure, we used the magnitude of each symptom association present in the network (i.e., the strength of each arrow in the network). The pairwise symptom associations were calculated for each possible pair of symptoms, ranging from the sleep problems → loss of pleasure/interest to the concentration problems → tiredness association in the exemplary patient depicted in Figure 1, Panel C. To evaluate the change of the pairwise symptom associations, we used the corresponding change estimates from the previously described multilevel model.

Prediction of observer-rated depression severity

The network symptom centralities and pairwise symptom associations were used to predict treatment outcomes (Figure 1, Panel C). Five different models with different predictors and different statistical approaches were evaluated. Table 1 provides an overview (see supplementary information for a more detailed description).

All predictive models were evaluated with respect to the outcome variables represented by observer-rated depression severity measured with the HRSD-24 at the end of treatment, and one year and two years after treatment termination. Missing data for observer-rated depression severity were imputed using the data augmentation algorithm[35].

The covariate model only included variables commonly used as predictors in randomized controlled trials, i.e. observer-rated baseline depression severity measured by the HRSD-24, treatment group, and trial site. The baseline symptom-centrality model and the change symptom-centrality model added symptom-wise parameters as predictor variables. The former included the centrality measure outstrength of all symptoms at baseline in addition to the common covariates as predictors. The latter also included the change of the outstrength of each symptom during treatment. These three models were evaluated using Bayesian hierarchical linear regression. We used Markov Chain Monte Carlo sampling methods with weakly informative priors to estimate the models.

Additionally, we used machine learning to investigate two models that incorporated also information on pairwise symptom associations. The baseline symptom-association model included observer-rated depression severity at baseline, treatment group, trial site, outstrength of all symptoms at baseline, and the strength of all symptom associations at baseline as potential predictors. The change symptom-association model also added, to the pool of potential predictors, the change of the outstrength of all symptoms during treatment, and the rate of change of all symptom associations during treatment. We used an Empirical Bayes Elastic Net (EBEN) algorithm[36] to select the most important from the large number of potential predictors for each model. The penalization parameters for the EBEN were determined using leave-one-out cross-validation. Based on the selection of non-zero predictors by the EBEN algorithm, we ran linear regression analyses using Markov Chain Monte Carlo sampling methods with weakly informative priors for the selected predictors and all outcomes (see also supplementary information).

Table 1 Overview of the evaluated models

Potential predictors	Covariate model	Baseline symptom-centrality model	Change symptom-centrality model	Baseline symptom-association model	Change symptom-association model
Common covariates	x	x	x	x	x
Symptom centrality of all symptoms before treatment		x	x	x	x
Change of the symptom centrality of all symptoms during treatment			x		x
All pairwise symptom associations before treatment				x	x
Change in all pairwise symptom associations during treatment					x
Number of (selected) predictors	10	19	28	24 (TT) 30 (FU1) 16 (FU2)	37 (TT) 27 (FU1) 14 (FU2)

Common covariates included observer-rated depression severity at baseline, treatment group, and trial site. TT – treatment termination, FU1 – one year after treatment termination, FU2 – two years after treatment termination.

As a measure of predictive accuracy, we calculated Bayesian R^2 and adjusted it by accounting for the number of predictors and sample size[37]. Further, for each model and each outcome, we investigated calibration plots contrasting observed and predicted values. To formally compare all models, we used the posterior distributions of the adjusted R^2 to calculate the probability that one model was superior to the other.

Several sensitivity analyses were conducted to evaluate the robustness of the results. First, we investigated if including the baseline severity of each specific symptom rather than the sum-score of all symptoms in the covariate model improved its predictive accuracy. Second, we assessed the effect of adding a two-way interaction term between the (change in) symptom centralities and the treatment group to the symptom-centrality models. Third, we calculated the symptom-association models including only symptom associations without symptom centralities in the pool of potential predictors. Fourth, we explored if using expected influence instead of outstrength as measure of symptom centrality influenced the predictive performance of the models. Expected influence is the sum of the raw strengths of each symptom's associations with other symptoms. Finally, we repeated all main analyses with complete cases only, to assess the impact of data imputation.

All analyses were done in R version 4.2.0 using the packages brms[38] and EBglmnet[36].

RESULTS

The current study included 254 patients (65.4% women, mean age: 44.9 years), who, on average, rated their depressive symptoms 23 times during treatment (5,842 data points). Data on the outcome measure (observer-rated depression severity measured by the HRSD-24[33]) were available for 254 persons at baseline, for 228 persons at the end of treatment, for 193 persons one year after treatment termination, and for 184 persons two years after treatment termination.

The explained variance for each model, as indicated by Bayesian R^2 adjusted for the number of predictors, is displayed for all models in Table 2 and Figure 2. This measure shows how much interindividual difference in depression severity after treatment can be explained by the predictor variables of each model. We also calculated the probability that a given model explains more variance than another model.

While common covariates (i.e., baseline depression severity, treatment group, and trial site) explained only 11% of the variance in post-treatment depression severity, the model also including the centrality of all symptoms at baseline accounted for 25% of the variance (see Table 2 and Figure 2). This baseline symptom-centrality model explained more variance than the covariate model with a probability of 0.99.

Adding the change of each symptom's centrality as predictor to the model increased the explained variance in depression severity at the end of treatment to 36% (see Table 2 and Figure 2). This change symptom-centrality model had a higher explained variance than the covariate and the baseline symptom-centrality model with a probability of 1 and 0.98, respectively.

Both models that used symptom associations as input had a higher predictive accuracy. Symptom associations and common covariates at baseline explained 42% of depression severity at treatment termination (see Table 2 and Figure 2). This symptom-association model outperformed the baseline symptom-centrality model with a probability of 1. Including the change in pairwise symptom associations during treatment increased the explained variance to 56% (see Table 2 and Figure 2). This change symptom-association model had a very high probability of outperforming any of the other models in predicting depression severity at treatment end (from 0.999 to 1).

The superiority of the prediction with symptom associations in contrast to common covariates was also visible for depression severity measured one and two years after treatment termination, while the superiority of the prediction with symptom associations compared to symptom centralities was evident one year but not two years after treatment ended (see Table 2 and Figure 2). The superiority of models that also included change in symptom centralities and symptom associations with respect to those that only included symptom centralities and symptom associations at baseline largely disappeared for depression severity one and two years after treatment termination (see Table 2 and Figure 2). For explaining the variance of depression severity two years after treatment, all models outperformed the common covariate model, without highly probable differences between them (see supplementary information). Analyses with non-adjusted R^2 instead of adjusted R^2 showed a similar pattern of findings, with slightly larger R^2 for all models (see supplementary information).

The predictive accuracy and the superiority of the symptom-association models are also reflected in the calibration plots contrasting observed and predicted values for depression severity at each time point and for each model (see Figure 3). The calibration plots show the weakest correspondence between predicted and observed values of depression severity at the end of treatment for the

Table 2 Adjusted R^2 of the evaluated models with 95% credible intervals

	Covariate model	Baseline symptom-centrality model	Change symptom-centrality model	Baseline symptom-association model	Change symptom-association model
Treatment termination	0.11 (0.05, 0.19)	0.25 (0.17, 0.33)	0.36 (0.29, 0.43)	0.42 (0.34, 0.48)	0.56 (0.50, 0.61)
1-year follow-up	0.12 (0.06, 0.20)	0.24 (0.16, 0.32)	0.29 (0.21, 0.37)	0.45 (0.38, 0.51)	0.45 (0.38, 0.51)
2-year follow-up	0.10 (0.03, 0.17)	0.18 (0.09, 0.25)	0.20 (0.12, 0.28)	0.24 (0.16, 0.32)	0.22 (0.14, 0.29)

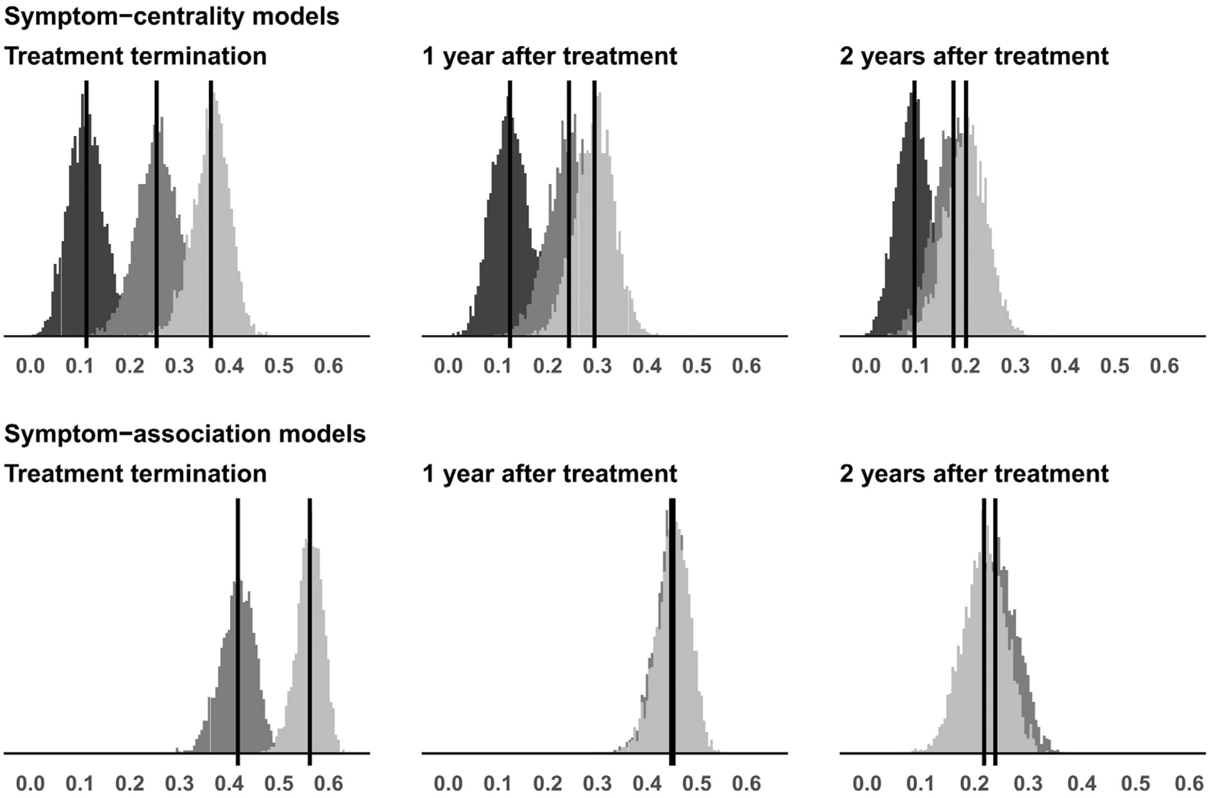

Figure 2 Posterior distribution of the adjusted R^2 for each model and each outcome. The dark grey color indicates the adjusted R^2 of the common covariate model; the medium grey color the adjusted R^2 of the models including baseline parameters; and the light grey color the adjusted R^2 for the models also including the change parameters. Vertical black lines indicate the mean of the respective posterior distribution.

common covariates model, and the strongest match between predicted and observed values for the symptom-association models. This pattern is replicated for depression severity one year after the end of treatment, whereas the models show roughly equal performance for predicting depression severity two years after the end of treatment (see Figure 3).

All sensitivity analyses suggested robustness of our results (see Table 3). First, including the severity of each individual symptom at the beginning of treatment instead of the summed baseline symptom severity improved the performance of the common covariate model only marginally. Second, adding an interaction term between treatment group and the network parameters to the symptom-centrality models did not markedly improve their predictive performance. Third, the symptom-association models that included only symptom associations as potential predictors showed comparable performance to the symptom-association models that also included the symptoms' outstrength. Fourth, the findings did not change substantially when we used the expected influence (i.e., the sum of the raw strengths of each symptom's associations with other symptoms) instead of outstrength for each symptom for measuring centrality. Finally, the sensitivity analyses with complete cases showed very similar findings (see Table 3 and supplementary information).

DISCUSSION

In this study, we assessed if and how the structure of person-specific symptom networks based on self-rated depression symptoms relates to treatment outcome, operationalized as observer-rated depression severity at three time points after treatment. We investigated models including symptom centrality information, i.e. the outstrength of each symptom, and models based on symptom association information, i.e., the magnitude of each pairwise symptom association.

We found that information on the person-specific symptom network structure strongly improved the accuracy of the prediction of depression severity after treatment compared to common covariates recorded at baseline. This improvement was also notable for predicting depression severity one and two years after treatment termination. Models including changes in symptom centralities or associations outperformed models including only baseline symptom centralities and/or associations for prediction of depression severity at treatment termination.

Furthermore, we found that models including pairwise symptom associations predicted depression severity at the end of treatment and one year after treatment termination substantially better than models including each symptom's centrality. However, this

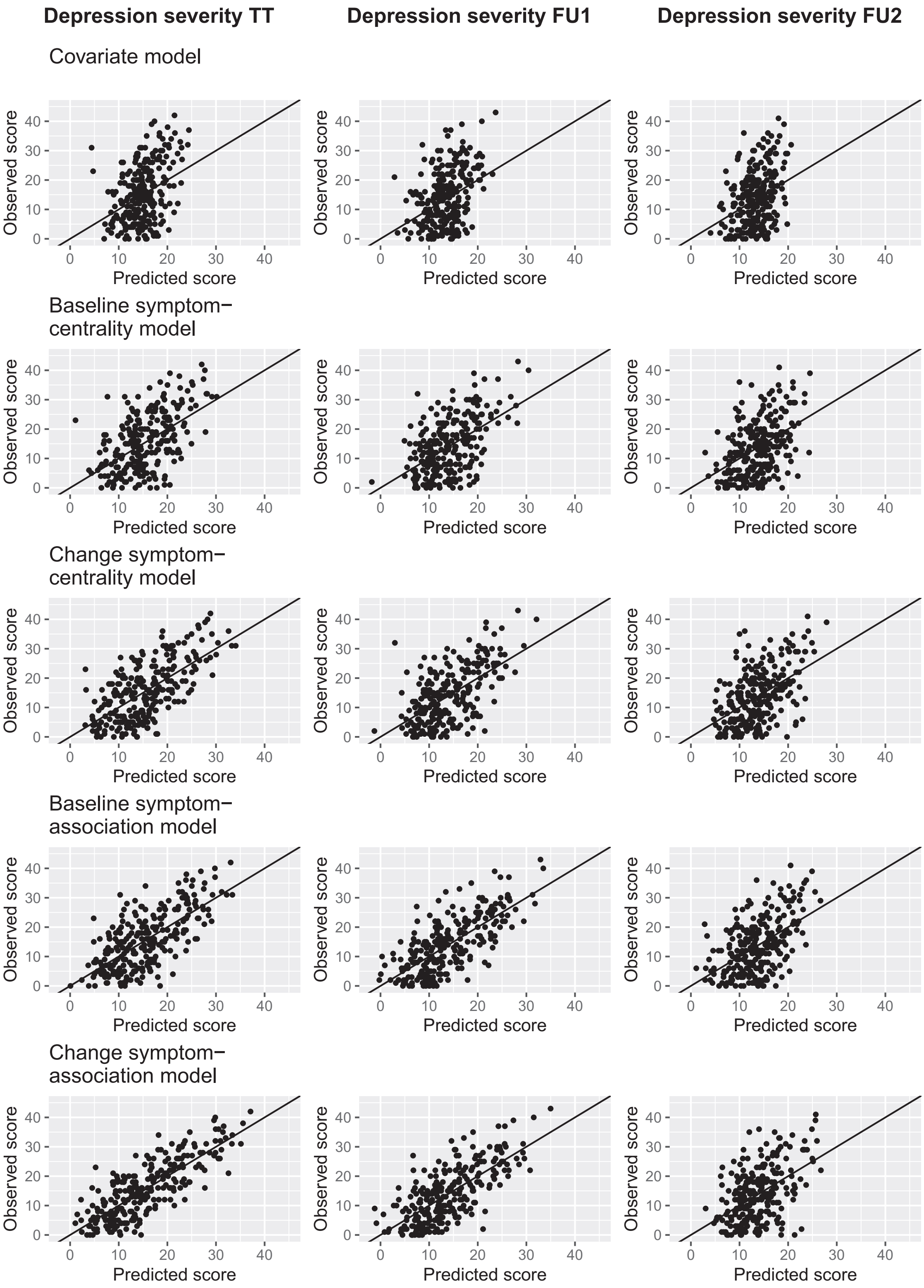

Figure 3 Calibration plots for the prediction of observer-rated depression severity. TT – treatment termination, FU1 – one year after treatment termination, FU2 – two years after treatment termination. Each point in each plot refers to the depression severity score (measured by the 24-item Hamilton Rating Scale for Depression) of a specific person. The x-axis value of each point indicates which score was predicted for a given person based on the respective model. The y-axis value indicates the observed score for a given person. The solid line indicates perfect prediction, i.e. complete overlap between predicted and observed scores for depression severity. Points above the solid line mark individuals for whom the observed values are higher than the predicted values (underestimation), while points below the line mean that the observed values are lower than the estimated values (overestimation). The points on or very close to the line indicate accurate predictions with the respective model.

Table 3 Results of sensitivity analyses

	Adjusted R^2 with 95% credible intervals		
Analyses	**Treatment termination**	**1-year follow-up**	**2-year follow-up**
1. Covariate model including the severity of each symptom at baseline	0.10 (0.02, 0.17)	0.10 (0.03, 0.18)	0.10 (0.03, 0.17)
2. Symptom-centrality models including the interaction between each symptom centrality and treatment group			
Baseline symptom-centrality model	0.24 (0.16, 0.31)	0.23 (0.15, 0.31)	0.19 (0.11, 0.26)
Change symptom-centrality model	0.36 (0.28, 0.42)	0.28 (0.20, 0.35)	0.21 (0.13, 0.28)
3. Symptom-association models including only symptom associations as possible predictors			
Baseline symptom-association model	0.41 (0.34, 0.48)	0.53 (0.47, 0.58)	0.24 (0.15, 0.31)
Change symptom-association model	0.53 (0.47, 0.58)	0.46 (0.39, 0.52)	0.25 (0.17, 0.32)
4. All models with expected influence as symptom centrality measure			
Baseline symptom-centrality model	0.23 (0.14, 0.30)	0.21 (0.13, 0.29)	0.18 (0.10, 0.26)
Change symptom-centrality model	0.40 (0.32, 0.46)	0.27 (0.19, 0.35)	0.23 (0.14, 0.30)
Baseline symptom-association model	0.39 (0.31, 0.46)	0.45 (0.38, 0.51)	0.24 (0.16, 0.32)
Change symptom-association model	0.53 (0.47, 0.58)	0.46 (0.39, 0.51)	0.25 (0.17, 0.33)
5. All models estimated with complete cases			
Covariate model	0.11 (0.04, 0.18)	0.13 (0.05, 0.22)	0.08 (0.01, 0.16)
Baseline symptom-centrality model	0.26 (0.17, 0.34)	0.28 (0.19, 0.37)	0.21 (0.12, 0.30)
Change symptom-centrality model	0.40 (0.33, 0.47)	0.34 (0.25, 0.42)	0.24 (0.14, 0.32)
Baseline symptom-association model	0.44 (0.37, 0.50)	0.47 (0.38, 0.53)	0.26 (0.17, 0.35)
Change symptom-association model	0.61 (0.55, 0.65)	0.43 (0.35, 0.50)	0.34 (0.24, 0.42)

difference was found to be negligible two years after treatment termination. Additional analyses further supported the superior prediction of treatment outcome based on symptom associations as opposed to centrality parameters.

In addition to the common covariates considered in this study, several previous investigations tested other possible predictive variables such as the number and duration of depressive episodes, the subtypes of depression, personality traits, age, and employment status[39-43]. In general, the proportion of explained variance ranged between 5 and 20% for variables collected before treatment, sometimes reaching up to 40% when data collected during treatment were used[44-49]. In this study, we did not use any input beyond the repeated measurement of individual symptoms, but still obtained a similar or higher predictive performance than models based on those variables.

When using person-specific symptom networks for treatment planning and monitoring, it is important to determine the specific network information that should be prioritized. Clinicians could focus on specific symptoms or specific symptom associations[14,17,50]. The current study suggests that a focus on specific pairwise symptom associations could be more useful than focusing on symptom-wise centrality measures, i.e. the outstrength of each symptom.

So far, treatment recommendations and evaluations mostly rely on the presence or the severity of a specific disorder. However, previous research showed that individuals with the same depression severity markedly differed in how symptoms related to each other[51]. Together with our findings, this suggests that an assessment and monitoring of symptom associations, in addition to the assessment of symptom severity, provides additional information relevant for individualized treatment planning.

If the current results are replicated and more information is gained on which specific symptom associations are important for a given population or individual, person-specific networks may open new paths for clinical practice. Clinicians could gather data on symptoms of the patient at the outset of treatment and subject these to network analyses. Subsequently, the network could be examined to determine which of the pairwise symptom associations that are known to predict outcome are present in this individual patient. If, for example, it emerges that in a given patient there is a strong association between sleep disturbance and loss of pleasure, the treatment for this patient could focus on weakening this association by training strategies to engage in pleasurable activities even in the presence of sleep disturbance. In a sense, this would be a data-enhanced version of classic functional analysis[52].

Additionally, person-specific networks might reveal patterns of interactions between behaviors, emotions, cognitions and somatic experiences that sustain the mental disorder. For example, a person-specific symptom network of an individual patient could show that his/her low self-worth leads to avoidance behaviors, which lead to loss of pleasure and depressed mood, and subsequently to even more strongly reduced self-worth. Then, treatment could be personalized to break such vicious circles of self-sustaining symptoms. In sum, person-specific symptom networks could help identify maladaptive symptom associations and potentially provide insight into the self-sustaining mechanisms of the mental disorder for a specific person and, therefore, guide individualized treatment.

A major challenge for the use of person-specific networks in clinical practice is their reliable estimation[15,53]. These networks can be estimated reliably only with a high number of repeated measures for each individual[54-56]. Alternatively, Bayesian network modelling might enable a robust estimation of person-specific networks with less data points per person, because prior information could be incorporated[57]. This information could be based on how symptom interactions are perceived by the clinician or by the patient, or stem from large group-level studies on within-person symptom interactions[58].

For the implementation of network analyses in clinical practice, a desirable solution would be a comprehensive decision support tool consisting of: a) largely automated data collection before and during treatment by easy-to-use and privacy-preserving apps; b) automated and continuously updated data analysis formally combining the collected data with data from similar patients and settings; c) a clear presentation of the results visually (e.g., network diagrams) and numerically (e.g., probabilities) with accompanying interpretations and recommendations for treatment. Such data-informed treatment planning and monitoring tools are being developed[54,59,60].

The presented findings need to be considered under the light of some limitations. First of all, this study is exploratory. Therefore, our results need to be subjected to replication efforts. This is particularly relevant because the limited sample size prevented us from cross-validating our model. We attempted to address this problem by quantifying uncertainty with Bayesian analysis and adjusting R^2 for the number of predictors, but the risk of overfitting remains. Second, the person-specific networks were estimated with data from all time points during treatment. Therefore, we used a different measure of depression severity as outcome (the observer-rated HRSD-24) than the depression measure used for creating the underlying model for the symptom networks (the self-rated IDS) and also investigated outcomes one and two years after treatment termination. Finally, the current results were obtained in a sample of people with chronic depression undergoing psychotherapy, so future research needs to show whether and to what extent the findings are relevant to other samples or settings.

Overall, we could show that person-specific networks offer valuable information that could be used for personalized treatment planning, monitoring and evaluation in persons with chronic depression. There are still various open questions, such as how person-specific networks should be estimated or constructed, or which specific network parameters should be chosen. Still, our findings suggest that individualizing treatment for depression on the basis of symptom networks might be a valuable path to follow and that machine learning approaches could be powerful tools in this respect.

Our results emphasize the importance of symptom associations and support the notion of depression as a dynamic system of interacting symptoms. Understanding what works for whom has been an essential question for decades, and approaching it from a network perspective might offer new opportunities for improving treatment effects for the individual.

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REFERENCES

1. Leichsenring F, Steinert C, Rabung S et al. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. World Psychiatry 2022;21:133-45.
2. Lambert MJ. Bergin and Garfield's handbook of psychotherapy and behavior change. Hoboken: Wiley, 2013.
3. Cuijpers P, Noma H, Karyotaki E et al. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry 2020;19:92-107.
4. Barlow DH, Nock MK. Why can't we be more idiographic in our research? Perspect Psychol Sci 2009;4:19-21.
5. Piccirillo ML, Rodebaugh TL. Foundations of idiographic methods in psychology and applications for psychotherapy. Clin Psychol Rev 2019;71:90-100.
6. Bickman L. Improving mental health services: a 50-year journey from randomized experiments to artificial intelligence and precision mental health. Adm Policy Ment Health Ment Health Serv Res 2020;47:795-843.
7. Cuijpers P, Karyotaki E, Ciharova M et al. The effects of psychotherapies for depression on response, remission, reliable change, and deterioration: a meta-analysis. Acta Psychiatr Scand 2021;144:288-99.
8. Cuijpers P, Miguel C, Harrer M et al. Cognitive behavior therapy vs. control conditions, other psychotherapies, pharmacotherapies and combined treatment for depression: a comprehensive meta-analysis including 409 trials with 52,702 patients. World Psychiatry 2023;22:105-15.
9. Molenaar PCM. A manifesto on psychology as idiographic science: bringing the person back into scientific psychology, this time forever. Meas Interdiscip Res Perspect 2004;2:201-18.
10. Delgadillo J, Lutz W. A development pathway towards precision mental health care. JAMA Psychiatry 2020;77:889-90.
11. Lutz W. Patient-focused psychotherapy research and individual treatment progress as scientific groundwork for an empirically based clinical practice. Psychother Res 2002;12:251-72.
12. Lutz W, de Jong K, Rubel JA et al. Measuring, predicting, and tracking change in psychotherapy. In: Barkham M, Lutz W, Castonguay LG (eds). Bergin handbook of psychotherapy and behavior change, 7th ed. Hoboken: Wiley, 2021:89-133.
13. Borsboom D, Cramer AOJ. Network analysis: an integrative approach to the structure of psychopathology. Annu Rev Clin Psychol 2013;9:91-121.
14. Borsboom D. A network theory of mental disorders. World Psychiatry 2017;16:5-13.
15. Bringmann LF. Person-specific networks in psychopathology: past, present, and future. Curr Opin Psychol 2021;41:59-64.
16. Rubel JA, Fisher AJ, Husen K et al. Translating person-specific network models into personalized treatments: development and demonstration of the Dynamic Assessment Treatment Algorithm for Individual Networks (DATA-IN). Psychother Psychosom 2018;87:249-51.
17. Blanchard MA, Heeren A. Ongoing and future challenges of the network approach to psychopathology: from theoretical conjectures to clinical translations. In: Asmundson GJG (ed). Comprehensive clinical psychology, 2nd ed. Amsterdam: Elsevier, 2022:32-46.
18. Spiller TR, Levi O, Neria Y et al. On the validity of the centrality hypothesis in cross-sectional between-subject networks of psychopathology. BMC Med 2020;18:297.
19. Rodebaugh TL, Tonge NA, Piccirillo ML et al. Does centrality in a cross-sectional network suggest intervention targets for social anxiety disorder? J Consult Clin Psychol 2018;86:831.
20. Lee CT, Kelley SW, Palacios J et al. Estimating the prognostic value of cross-sectional network connectivity for treatment response in depression. Psychol Med 2024;54:317-26.
21. Borsboom D, Deserno MK, Rhemtulla M et al. Network analysis of multivariate

data in psychological science. Nat Rev Methods Primer 2021;1:1-18.
22. Epskamp S, Waldorp LJ, Mõttus R et al. The Gaussian graphical model in cross-sectional and time-series data. Multivar Behav Res 2018;53:453-80.
23. Fisher AJ, Reeves JW, Lawyer G et al. Exploring the idiographic dynamics of mood and anxiety via network analysis. J Abnorm Psychol 2017;126:1044-56.
24. Bos FM, Snippe E, de Vos S et al. Can we jump from cross-sectional to dynamic interpretations of networks implications for the network perspective in psychiatry. Psychother Psychosom 2017;86:175-7.
25. Schumacher L, Burger J, Echterhoff J et al. Methodological and statistical practices of using symptom networks to evaluate mental health interventions: a review and reflections. Multivar Behav Res 2024; doi: 10.1080/00273171.2024.2335401.
26. Schumacher L, Klein JP, Elsaesser M et al. Implications of the network theory for the treatment of mental disorders: a secondary analysis of a randomized clinical trial. JAMA Psychiatry 2023;80:1160-8.
27. Lutz W, Schwartz B, Hofmann SG et al. Using network analysis for the prediction of treatment dropout in patients with mood and anxiety disorders: a methodological proof-of-concept study. Sci Rep 2018;8:7819.
28. Frumkin M, Piccirillo M, Beck ED et al. Feasibility and utility of idiographic models in the clinic: a pilot study. PsyArXiv 2019; doi:10.31234/osf.io/m34aw.
29. Bastiaansen JA, Kunkels YK, Blaauw FJ et al. Time to get personal? The impact of researchers choices on the selection of treatment targets using the experience sampling methodology. J Psychosom Res 2020;137:110211.
30. Schramm E, Hautzinger M, Zobel I et al. Comparative efficacy of the cognitive behavioral analysis system of psychotherapy versus supportive psychotherapy for early onset chronic depression: design and rationale of a multisite randomized controlled trial. BMC Psychiatry 2011;11:134.
31. Schramm E, Kriston L, Zobel I et al. Effect of disorder-specific vs nonspecific psychotherapy for chronic depression: a randomized clinical trial. JAMA Psychiatry 2017;74:233-42.
32. Schramm E, Kriston L, Elsaesser M et al. Two-year follow-up after treatment with the cognitive behavioral analysis system of psychotherapy versus supportive psychotherapy for early-onset chronic depression. Psychother Psychosom 2019;88:154-64.
33. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278-96.
34. Rush AJ, Carmody T, Reimitz PE. The Inventory of Depressive Symptomatology (IDS): Clinician (IDS-C) and Self-Report (IDS-SR) ratings of depressive symptoms. Int J Methods Psychiatr Res 2000;9:45-59.
35. Schafer JL. Analysis of incomplete multivariate data. Boca Raton: Chapman and Hall/CRC, 1997.
36. Huang A, Liu D. EBglmnet: a comprehensive R package for sparse generalized linear regression models. Bioinformatics 2021;37:1627-9.
37. Miles J. R-squared, adjusted R-squared. In: Everitt BS, Howell DC (eds). Encyclopedia of statistics in behavioral science. Hoboken: Wiley, 2005. https://doi.org/10.1002/0470013192.bsa526.
38. Bürkner PC. brms: an R package for Bayesian multilevel models using Stan. J Stat Softw 2017;80:1-28.
39. Rost N, Binder EB, Brückl TM. Predicting treatment outcome in depression: an introduction into current concepts and challenges. Eur Arch Psychiatry Clin Neurosci 2023;273:113-27.
40. Kessler RC, van Loo HM, Wardenaar KJ et al. Using patient self-reports to study heterogeneity of treatment effects in major depressive disorder. Epidemiol Psychiatr Sci 2017;26:22-36.
41. Lee Y, Ragguett RM, Mansur RB et al. Applications of machine learning algorithms to predict therapeutic outcomes in depression: a meta-analysis and systematic review. J Affect Disord 2018;241:519-32.
42. De Carlo V, Calati R, Serretti A. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: a systematic review. Psychiatry Res 2016;240:421-30.
43. Maj M, Stein DJ, Parker G et al. The clinical characterization of the adult patient with depression aimed at personalization of management. World Psychiatry 2020;19:269-3.
44. Iniesta R, Malki K, Maier W et al. Combining clinical variables to optimize prediction of antidepressant treatment outcomes. J Psychiatr Res 2016;78:94-102.
45. Schindler A, Hiller W, Witthöft M. What predicts outcome, response, and drop-out in CBT of depressive adults? A naturalistic study. Behav Cogn Psychother 2013;41:365-70.
46. Coley RY, Boggs JM, Beck A et al. Predicting outcomes of psychotherapy for depression with electronic health record data. J Affect Disord Rep 2021;6:100198.
47. Iniesta R, Hodgson K, Stahl D et al. Antidepressant drug-specific prediction of depression treatment outcomes from genetic and clinical variables. Sci Rep 2018;8:5530.
48. Buckman JEJ, Cohen ZD, O'Driscoll C et al. Predicting prognosis for adults with depression using individual symptom data: a comparison of modelling approaches. Psychol Med 2023;53:408-18.
49. Bone C, Simmonds-Buckley M, Thwaites R et al. Dynamic prediction of psychological treatment outcomes: development and validation of a prediction model using routinely collected symptom data. Lancet Digit Health 2021;3:e231-40.
50. Bringmann LF, Albers C, Bockting C et al. Psychopathological networks: theory, methods and practice. Behav Res Ther 2022;149:104011.
51. Ebrahimi OV, Borsboom D, Hoekstra RHA et al. Towards precision in the diagnostic profiling of patients: leveraging symptom dynamics as a clinical characterisation dimension in the assessment of major depressive disorder. Br J Psychiatry 2024;224:157-63.
52. Scholten S, Lischetzke T, Glombiewski JA. Integrating theory-based and data-driven methods to case conceptualization: a functional analysis approach with ecological momentary assessment. Psychother Res 2022;32:52-64.
53. Rodebaugh TL, Frumkin MR, Piccirillo ML. The long road from person-specific models to personalized mental health treatment. BMC Med 2020;18:365.
54. Bos FM, von Klipstein L, Emerencia AC et al. A web-based application for personalized ecological momentary assessment in psychiatric care: user-centered development of the PETRA application. JMIR Ment Health 2022;9:e36430.
55. Mansueto AC, Wiers RW, van Weert JCM et al. Investigating the feasibility of idiographic network models. Psychol Methods 2023;28:1052-68.
56. Klintwall L, Bellander M, Cervin M. Perceived causal problem networks: reliability, central problems, and clinical utility for depression. Assessment 2023;30:73-83.
57. Burger J, Ralph-Nearman C, Levinson CA. Integrating clinician and patient case conceptualization with momentary assessment data to construct idiographic networks: moving toward personalized treatment for eating disorders. Behav Res Ther 2022;159:104221.
58. Burger J, Epskamp S, van der Veen DC et al. A clinical PREMISE for personalized models: toward a formal integration of case formulations and statistical networks. J Psychopathol Clin Sci 2022;131:906-16.
59. Lutz W, Rubel JA, Schwartz B et al. Towards integrating personalized feedback research into clinical practice: development of the Trier Treatment Navigator (TTN). Behav Res Ther 2019;120:103438.
60. Lutz W, Rubel J, Deisenhofer AK et al. Continuous outcome measurement in modern data-informed psychotherapies. World Psychiatry 2022;21:215-6.

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Associations between physical diseases and subsequent mental disorders: a longitudinal study in a population-based cohort

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People with physical diseases are reported to be at elevated risk of subsequent mental disorders. However, previous studies have considered only a few pairs of conditions, or have reported only relative risks. This study aimed to systematically explore the associations between physical diseases and subsequent mental disorders. It examined a population-based cohort of 7,673,978 people living in Denmark between 2000 and 2021, and followed them for a total of 119.3 million person-years. The study assessed nine broad categories of physical diseases (cardiovascular, endocrine, respiratory, gastrointestinal, urogenital, musculoskeletal, hematological and neurological diseases, and cancers), encompassing 31 specific diseases, and the subsequent risk of mental disorder diagnoses, encompassing the ten ICD-10 groupings (organic, including symptomatic, mental disorders; mental disorders due to psychoactive substance use; schizophrenia and related disorders; mood disorders; neurotic, stress-related and somatoform disorders; eating disorders; personality disorders; intellectual disabilities; pervasive developmental disorders; and behavioral and emotional disorders with onset usually occurring in childhood and adolescence). Using Poisson regression, the overall and time-dependent incidence rate ratios (IRRs) for pairs of physical diseases and mental disorders were calculated, adjusting for age, sex and calendar time. Absolute risks were estimated with the Aalen-Johansen estimator. In total, 646,171 people (8.4%) were identified as having any mental disorder during follow-up. All physical diseases except cancers were associated with an elevated risk of any mental disorder. For the nine broad pairs of physical diseases and mental disorders, the median point estimate of IRR was 1.51 (range: 0.99-1.84; interquartile range: 1.29-1.59). The IRRs ranged from 0.99 (95% CI: 0.98-1.01) after cancers to 1.84 (95% CI: 1.83-1.85) after musculoskeletal diseases. Risks varied over time after the diagnosis of physical diseases. The cumulative mental disorder incidence within 15 years after diagnosis of a physical disease varied from 3.73% (95% CI: 3.67-3.80) for cancers to 10.19% (95% CI: 10.13-10.25) for respiratory diseases. These data document that most physical diseases are associated with an elevated risk of subsequent mental disorders. Clinicians treating physical diseases should constantly be alert to the possible development of secondary mental disorders.

Key words: Physical diseases, mental disorders, comorbidity, population-based cohort, absolute risk, incidence rate, respiratory diseases, musculoskeletal diseases, cancers

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People with various physical diseases – including cardiovascular, endocrine, respiratory and neurological diseases, as well as cancers – have been reported to be at higher risk of developing mental disorders than those without these diseases[1-12]. In people with both physical diseases and mental disorders, a lower quality of life[13-15] and a shorter life expectancy[16] have been observed than in those with either physical diseases or mental disorders alone.

Exploring the patterns of association between physical diseases and later mental disorders can allow the identification of groups with elevated risk. However, most studies to date have focused on specific physical diseases or mental disorders. This narrow focus may fail to reveal general associations and etiological links. Moreover, although some studies have considered the lifetime association between groups of mental disorders and physical diseases, only few of them have considered the temporal order of occurrence of the disorders of interest[1,3,4,6,9,10,17,18].

Cross-sectional studies often rely on self-reported collected data and, due to issues with potential recall bias, may underestimate past disorders. Additionally, as participants need to be alive to respond to surveys, it is likely that survey-based studies will underestimate the number of people with potentially fatal conditions (particularly those of greatest severity). Such "survival bias" could lead to lower estimates of the associations between physical diseases and mental disorders[19].

Furthermore, studies have rarely considered risks associated with multiple physical diseases, and they have generally focused on relative risks, not reporting risks in absolute terms, which provide information about the actual number of people with diseases. Thus, further research is needed to assess more comprehensively the association between a wide range of physical diseases and the subsequent development of mental disorders.

The use of Danish register-based data can address the above issues. The analysis of routinely collected health care data covering the whole population and containing dates of diagnoses offers a better chance of capturing the association between physical diseases and mental disorders in a specified direction[20], reducing the risk of selection or recall bias.

In an earlier study[21], we documented that mental disorders are associated with an increased subsequent risk of many physical diseases. However, we did not consider the reciprocal associations. While previous evidence[1,3-12] indicates that associations may be present in the opposite direction, only a study considering several physical disease - mental disorder pairs can provide a comprehensive picture.

We used Danish nationwide register data to provide temporally ordered age- and sex-specific pairwise estimates of the risks of a comprehensive range of physical diseases and subsequent mental disorders. We explored variations of associations over time. Additionally, we calculated the age- and sex-specific cumulative incidence of subsequent mental disorders among people with vs. without physical diseases (by using matched comparison cohorts), which can aid interpretation of the clinical implications of the relative risks.

This research was carried out using a well-characterized list of

31 physical diseases, developed in Denmark, with input from public health epidemiologists and clinicians, and previously used in Danish multimorbidity research[22]. By combining register data on hospital contacts and prescriptions, diagnoses or treatments for these diseases could be ascertained for all individuals. Furthermore, using previously published methods enabling extraction of person-level health-related disability from registers[23], we calculated a cumulative disability burden score summarizing the disability associated with combinations of diagnosed physical diseases, and considered its relationship to subsequent mental disorders.

METHODS

Study population and ascertainment of disorders

This population-based cohort study included all 7,673,978 people living in Denmark between January 1, 2000 and December 31, 2021 (i.e., living in Denmark on January 1, 2000, or born in or immigrating to Denmark after that date), as identified in the Danish Civil Registration System.

Information on physical diseases was collected from 1995 onward, using criteria developed for investigating multimorbidity in Danish registers[22]. These criteria included 31 physical diseases, grouped into nine broad categories: cardiovascular, endocrine, respiratory, gastrointestinal, urogenital, musculoskeletal, hematological and neurological diseases, and cancers. The data on physical diseases came from two sources: a) diagnoses made during inpatient admissions and outpatient clinic visits from the Danish National Patient Registry recorded as ICD-10 codes, and b) redeemed prescriptions for disease-specific medications (Anatomical Therapeutic Chemical Classification System codes) in the Danish National Prescription Register. The registration date of a physical disease was the date of the first hospital diagnosis or relevant repeat prescription, whichever occurred first (however, for simplicity, we refer here to "diagnosis").

Information on mental disorders was obtained from the Danish Psychiatric Central Research Register, which includes admissions to psychiatric inpatient facilities since 1969, and visits to outpatient psychiatric and emergency departments since 1995. The diagnosis date was defined as the discharge date for the first contact. We considered any mental disorder, as well as ten types of mental disorders (ICD-10 subchapter F and corresponding ICD-8 diagnoses): organic, including symptomatic, mental disorders; mental disorders due to psychoactive substance use; schizophrenia and related disorders; mood disorders; neurotic, stress-related and somatoform disorders; eating disorders; personality disorders; intellectual disabilities; pervasive developmental disorders; and behavioral and emotional disorders with onset usually occurring in childhood and adolescence.

Table 1 Baseline characteristics of the study population

Sex, N (%)	
Men	3,838,695 (50.0)
Women	3,835,283 (50.0)
Birth year, N (%)	
<1900	484 (<0.1)
1900-1909	30,102 (0.4)
1910-1919	178,562 (2.3)
1920-1929	364,596 (4.8)
1930-1939	483,548 (6.3)
1940-1949	749,288 (9.8)
1950-1959	768,167 (10.0)
1960-1969	887,277 (11.6)
1970-1979	879,585 (11.5)
1980-1989	891,834 (11.6)
1990-1999	940,511 (12.3)
2000-2009	732,669 (9.5)
2010-2021	767,355 (10.0)
Age at start of follow-up, years, median (IQR)	28 (7-49)
Age at end of follow-up, years, median (IQR)	46 (24-68)

IQR – interquartile range

Statistical analyses

Each analysis was performed separately for any mental disorder and for each mental disorder group. Follow-up started on January 1, 2000, and terminated at mental disorder diagnosis, death, emigration from Denmark, or December 31, 2021, whichever occurred first. Because we were interested in only incident mental disorders during the follow-up period, all people with a diagnosis before January 1, 2000 were considered to have prevalent mental disorders and were excluded from the analyses in which the specific mental disorder was the outcome of interest.

We estimated associations between 99 pairs of broad physical diseases and subsequent mental disorders (any mental disorder and ten types of mental disorder), as well as 341 specific physical disease - mental disorder pairs. First, we compared rates of mental disorder diagnosis between people with vs. without physical diseases (both broad categories and specific diseases) through incidence rate ratios (IRRs), estimated using Poisson regression models adjusting for sex, age (in 0.25-year intervals), and birth year. Additionally, we investigated whether these associations depended on the time after diagnosis of the physical disease (0-6 months, >6-12 months, >1-2 years, >2-5 years, >5-10 years, >10-15 years, or >15 years). Subsequently, we estimated the cumulative incidence of diagnosis of mental disorders after physical disease diagnosis using the Aalen-Johansen estimator, which accounts for competing risks (of dying or emigrating).

To compare the cumulative incidence of mental disorders among people with vs. without physical diseases, we generated matched comparison cohorts. For every index person with the physical disease, up to five age- and sex-matched individuals

Table 2 Frequencies of prevalent cases, persons at risk, and incident cases for each mental disorder, in the total cohort

	Prevalent cases before follow-up	Persons at risk at start of follow-up	New cases during follow-up
Any mental disorder			
Total	270,730	7,328,530	646,171
Males	119,132	3,681,297	302,506
Females	151,598	3,647,233	343,665
Organic disorders			
Total	24,728	4,611,275	103,856
Males	10,035	2,274,720	43,183
Females	14,693	2,336,555	60,673
Substance use disorders			
Total	71,206	6,898,341	95,864
Males	43,927	3,433,032	62,534
Females	27,279	3,465,309	33,330
Schizophrenia and related disorders			
Total	50,590	6,918,957	67,421
Males	23,824	3,453,135	35,127
Females	26,766	3,465,822	32,294
Mood disorders			
Total	79,161	6,890,386	222,564
Males	27,095	3,449,864	86,209
Females	52,066	3,440,522	136,355
Neurotic, stress-related and somatoform disorders			
Total	98,167	7,207,158	321,228
Males	34,906	3,614,529	133,145
Females	63,261	3,592,629	188,083
Eating disorders			
Total	5,329	7,593,931	27,266
Males	280	3,800,149	1,836
Females	5,049	3,793,782	25,430
Personality disorders			
Total	76,433	6,893,114	75,588
Males	30,834	3,446,125	24,516
Females	45,599	3,446,989	51,072
Intellectual disabilities			
Total	5,890	7,593,370	24,083
Males	3,290	3,797,139	14,714
Females	2,600	3,796,231	9,369
Developmental disorders			
Total	3,470	7,595,790	54,913
Males	2,723	3,797,706	38,033
Females	747	3,798,084	16,880

Table 2 Frequencies of prevalent cases, persons at risk, and incident cases for each mental disorder, in the total cohort *(continued)*

	Prevalent cases before follow-up	Persons at risk at start of follow-up	New cases during follow-up
Behavioral disorders			
Total	14,474	7,584,786	116,163
Males	9,620	3,790,809	72,104
Females	4,854	3,793,977	44,059

"Behavioral disorders" is an abbreviation for "behavioral and emotional disorders with onset usually occurring in childhood and adolescence"

(without a diagnosis of the relevant physical disease at that point) were randomly selected from the entire population. Cumulative incidence proportions were stratified by sex and age (at diagnosis of the physical disease) groups (<35, 35-<70 and ≥70 years). They provide a measure of risk in absolute terms that can be interpreted as the percentage of individuals among those with vs. without a particular physical disease who develop the mental disorder after a specified time.

To assess the effects of complex (multi)morbidity patterns, we calculated the IRR of any mental disorder diagnosis (and of each specific mental disorder diagnosis) as a function of the "disability burden score", i.e. a summary score accounting for health-related disability associated with each type of physical disease. Specifically, we used the disability weights developed by the Global Burden of Disease Study to quantify the health loss associated with combinations of diseases[24] and adapted in our previous work for the physical diseases considered in the present study[23]. This approach allowed us to determine scores for our specific list of 31 physical diseases[25]. Disability weights represent the severity of health loss associated with a given disorder. The weights are measured on a scale of 0 to 1, where 0 indicates full health, and 1 a health state equivalent to death.

For each individual, we calculated a time-varying disability burden score based on the observed diagnoses and disability weights. Calculation of the disability burden score was carried out using a specific formula (see supplementary information). Individuals with no physical diseases were assigned a disability burden score of 0. As an example, an individual with a physical disease linked to a disability weight of 0.3 was assigned a total disability burden score of 0.3, while an individual with two physical diseases, with respective disability weights of 0.3 and 0.5, had a total disability burden score of $1-(1-0.3)\times(1-0.5) = 0.65$.

To simplify the presentation of results, we focus here on the associations between any mental disorder and the nine broad physical disease categories. Results for all included pairs (i.e., all mental disorder groupings and the 31 specific physical diseases) are provided in the supplementary information and in an interactive website (see Acknowledgements).

The study was registered with the Danish Data Protection Agency via Aarhus University (no. 2016-051-000001-2587) and was approved by Statistics Denmark and the Danish Health Data Authority. According to the Danish law, informed consent or ethical approval is not required for register-based studies conducted in the country. All data were pseudonymized and not recognizable at an individual level, and were analyzed on the secured platform of Statistics Denmark via remote access. A pre-specified analysis plan was uploaded on the Open Science Framework before the analyses started[26].

Table 3 Incidence rate ratios (IRRs) for any subsequent mental disorder in people with vs. without a physical disease diagnosis

	IRR (95% CI)		
	Total	Males	Females
Cardiovascular diseases	1.58 (1.57-1.60)	1.70 (1.68-1.73)	1.49 (1.47-1.50)
Endocrine diseases	1.29 (1.28-1.31)	1.39 (1.37-1.41)	1.24 (1.22-1.25)
Respiratory diseases	1.30 (1.29-1.30)	1.27 (1.26-1.28)	1.30 (1.30-1.31)
Gastrointestinal diseases	1.59 (1.57-1.61)	1.75 (1.72-1.78)	1.47 (1.45-1.49)
Urogenital diseases	1.27 (1.25-1.29)	1.35 (1.32-1.37)	1.27 (1.21-1.33)
Musculoskeletal diseases	1.84 (1.83-1.85)	1.90 (1.88-1.92)	1.78 (1.76-1.80)
Hematological diseases	1.68 (1.65-1.71)	1.76 (1.71-1.81)	1.62 (1.59-1.66)
Cancers	0.99 (0.98-1.01)	1.03 (1.00-1.05)	0.98 (0.96-1.00)
Neurological diseases	1.51 (1.50-1.52)	1.64 (1.62-1.66)	1.42 (1.41-1.43)

RESULTS

The cohort consisted of 7,673,978 Danish residents (50.0% female), followed up for a total of 119.3 million person-years. During the follow-up, 1.19 million people died, and 0.92 million emigrated. The baseline cohort characteristics are presented in Table 1.

The number of prevalent cases (between 1969 and 1999), the population defined as being at risk at the start of follow-up, and the number of incident cases during follow-up (between 2000 and 2021) for any mental disorder and for the individual groupings of mental disorders are shown in Table 2. In total, 646,171 people (8.4%) were identified as having any mental disorder during follow-up (302,506 males and 343,665 females).

The risks of any subsequent mental disorder diagnosis in people with vs. without each physical disease are shown in Table 3 and Figure 1. For the nine broad pairs of physical diseases and mental disorders, the median point estimate of IRR was 1.51 (range: 0.99-1.84; interquartile range, IQR: 1.29-1.59). The IRRs were 1.58 (95% CI: 1.57-1.60) for cardiovascular diseases; 1.29 (95% CI: 1.28-1.31) for endocrine diseases; 1.30 (95% CI: 1.29-1.30) for respiratory diseases; 1.59 (95% CI: 1.57-1.61) for gastrointestinal diseases; 1.27 (95% CI: 1.25-1.29) for urogenital diseases; 1.84 (95% CI: 1.83-1.85) for musculoskeletal diseases; 1.68 (95% CI: 1.65-1.71) for hematological diseases; 0.99 (95% CI: 0.98-1.01) for cancers; and 1.51 (95% CI: 1.50-1.52) for neurological diseases.

The IRRs were higher for males than females for almost all broad physical diseases (see Table 3). The IRRs for broad physical diseases and specific types of mental disorders are shown in Figure 2 (see also supplementary information).

Time-dependent IRRs for receiving a diagnosis of any mental disorder, according to the time after the first diagnosis of each broad physical disease, are shown in Figure 3 (see supplementary information for all IRR values). For all nine broad physical diseases, the rate of diagnosis of any mental disorder was highest in the initial 0-6 months after a physical disease diagnosis and subsequently decreased to varying extents (e.g., relatively steep decreases were observed for cardiovascular and hematological diseases at 6-12 months).

As shown in Figure 4, the IRR of any mental disorder diagnosis generally increased with increasing disability burden score (see supplementary information for estimates concerning the various mental disorders).

The cumulative incidence of any mental disorder for people previously diagnosed with a physical disease, and for people within comparison cohorts, is presented in Table 4 and Figure 5. Within

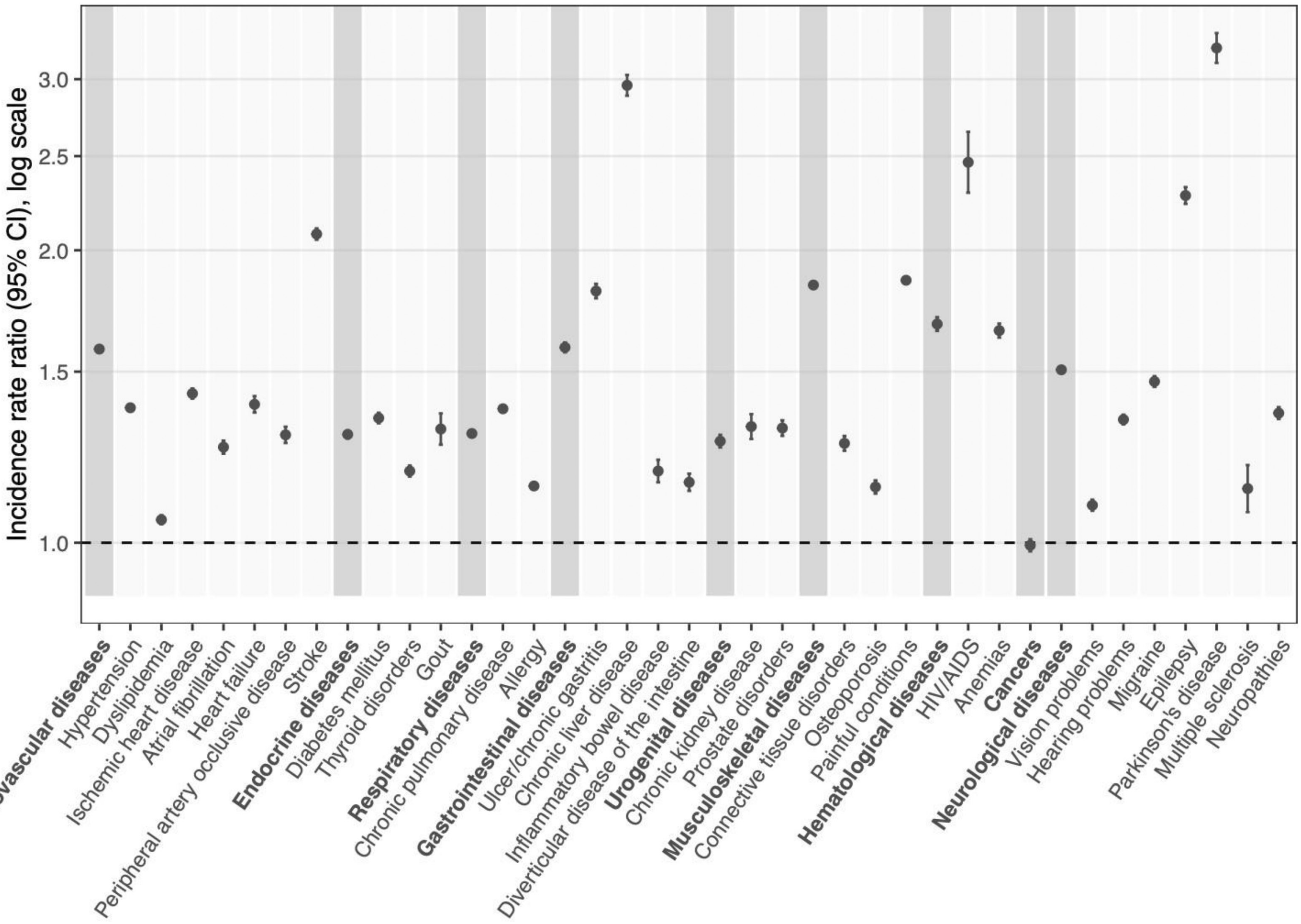

Figure 1 Incidence rate ratios for a diagnosis of any mental disorder after the diagnosis of a physical disease

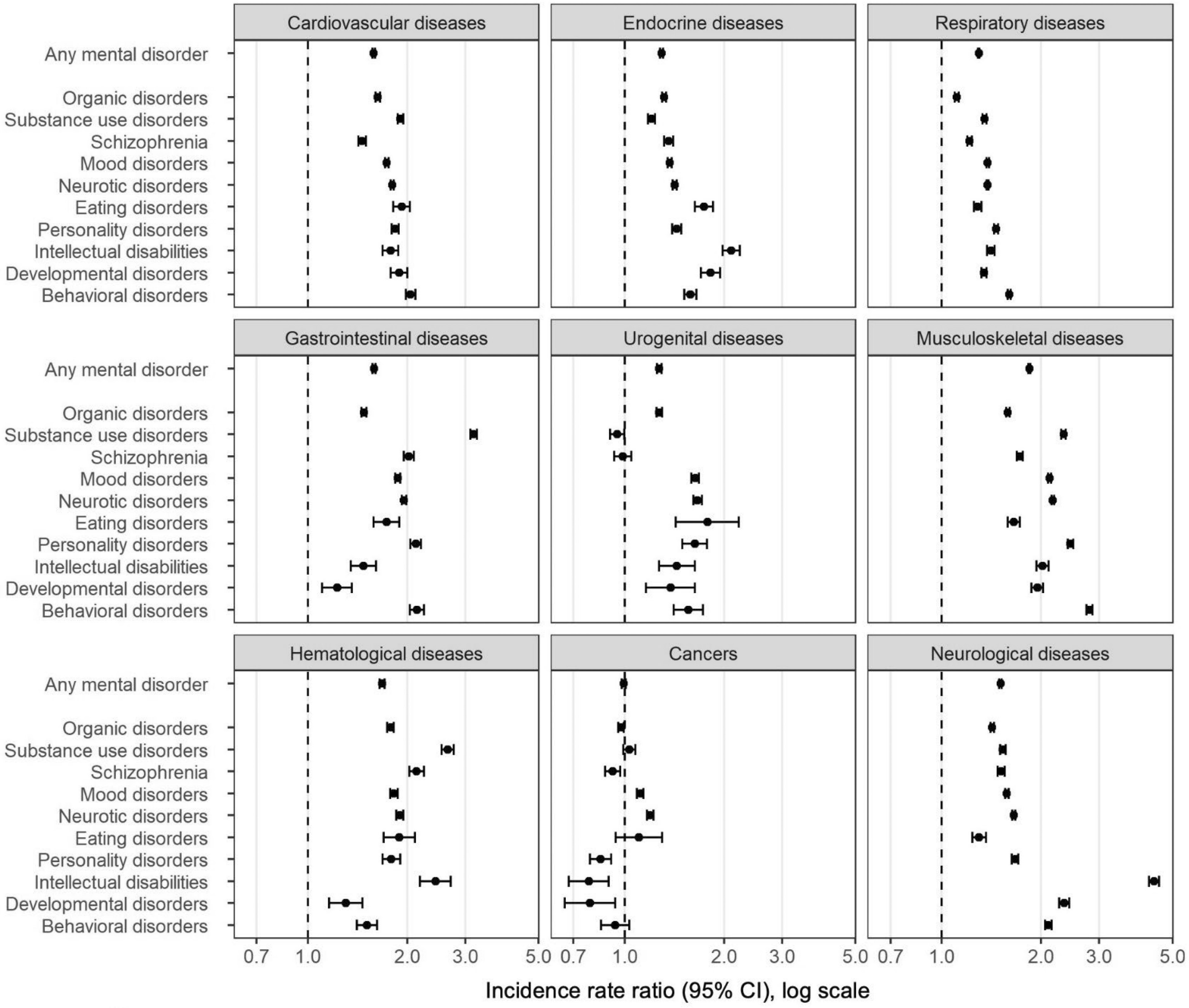

Figure 2 Incidence rate ratios for each mental disorder diagnosis after a diagnosis within each broad physical disease category. "Neurotic disorders" is an abbreviation for "neurotic, stress-related and somatoform disorders". "Behavioral disorders" is an abbreviation for "behavioral and emotional disorders with onset usually occurring in childhood and adolescence".

15 years after the physical disease diagnosis, the highest cumulative incidence of any mental disorder was observed for the broad group of respiratory diseases (10.19%, 95% CI: 10.13-10.25). For the corresponding matched comparison cohort (i.e., people without a respiratory disease diagnosed at the time of matching), the cumulative incidence within 15 years was 7.68% (95% CI: 7.66-7.71).

For almost all broad groups of physical diseases, the cumulative incidence of any mental disorder within 15 years was higher in people with the prior diagnosis of interest than in the respective matched comparison cohorts, with two exceptions. First, the incidence of any mental disorder was initially higher in people with a hematological disease than in the matched comparison group (IRR=1.68, 95% CI: 1.65-1.71); however, similar levels were seen in the two groups within 15 years after diagnosis (6.58%, 95% CI: 6.47-6.70 vs. 6.52%, 95% CI: 6.47-6.57). Second, the incidence of any mental disorder was initially similar in people with vs. without a cancer diagnosis (IRR=0.99, 95% CI: 0.98-1.01), but became higher in the comparison cohort starting approximately 2 years after diagnosis (2.33% vs. 1.87% at 5 years; 4.26% vs. 2.94% at 10 years; 5.72% vs. 3.73% at 15 years) (see supplementary information for estimates concerning the various mental disorders, also by sex and age).

DISCUSSION

This population-based study, comprising 7.7 million people, provides a detailed picture of the emergence of mental disorders in people with a broad range of prior physical diseases. For most

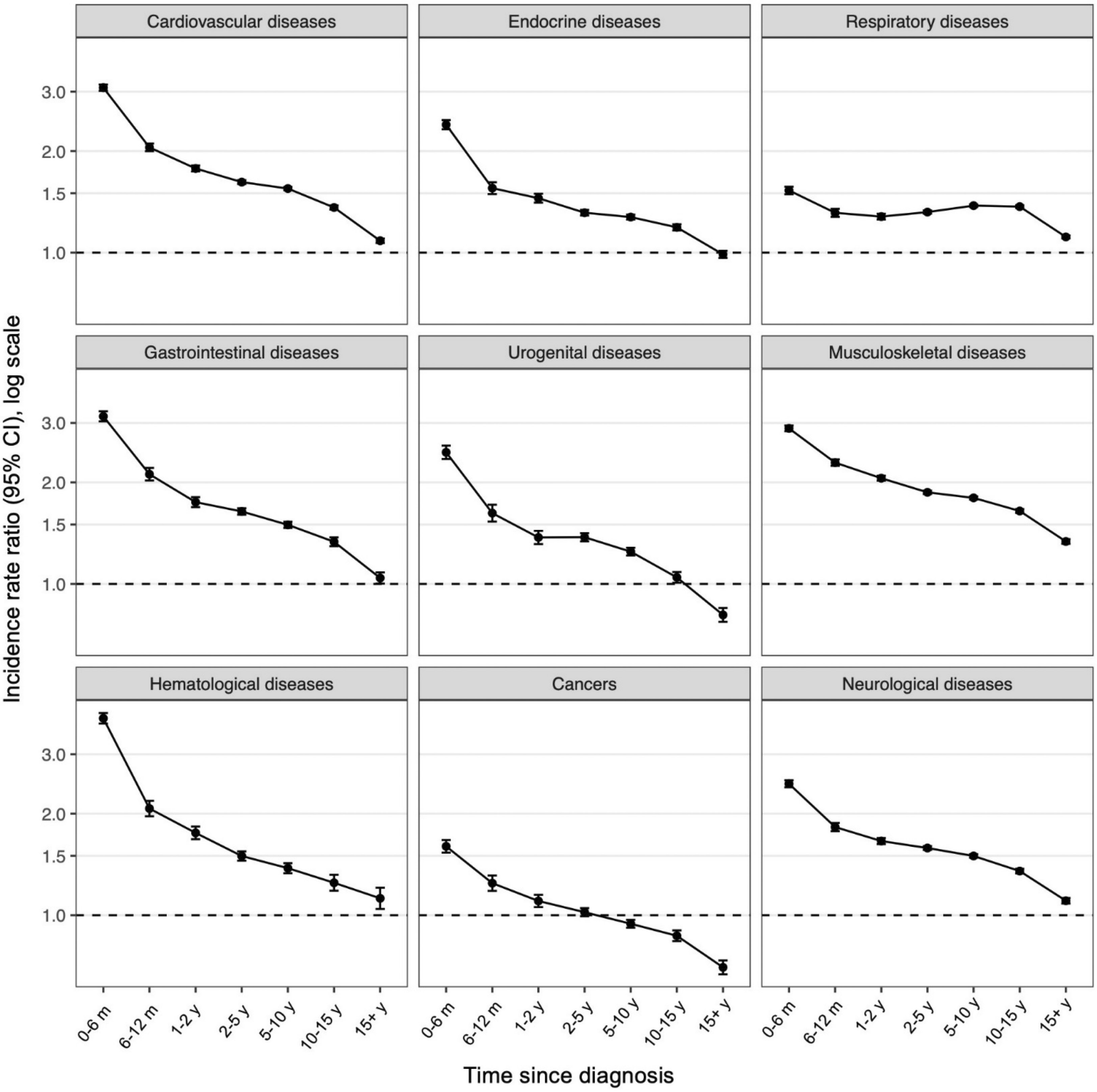

Figure 3 Incidence rate ratios for any mental disorder diagnosis after a diagnosis within a broad physical disease category, according to the timing of the physical disease diagnosis

pairs, the risk of subsequent mental disorders was higher among people with vs. without the physical disease in question. However, for some pairs, the opposite association was observed (e.g., the risk for any mental disorder and for several specific mental disorders was lower among people with vs. without a prior diagnosis of cancer).

Different pairs had different temporal patterns. For example, the risk of any mental disorder was much higher in the 0-6 months after hospital contact for a cardiovascular disease and decreased as time went on. In contrast, for any mental disorder after respiratory diseases, the association remained somewhat flat over time.

Within 15 years after most physical diseases, the proportion of people subsequently diagnosed with mental disorders was higher than among people in the comparison cohorts. However, this was not the case for any mental disorder following cancer, which was higher in the comparison cohort than among people with a prior cancer diagnosis.

Finally, we observed that the mental disorder risk was generally higher with greater disability burden from physical diseases, in line with previous findings suggesting that the overall burden of physical morbidity is associated with poor mental health with a dose-response pattern[27-29].

Our findings for cancer were a notable exception from the general pattern of increased risk of mental disorders following physical diseases. In fact, the occurrence of several mental disorders was lower among people with vs. without a prior diagnosis of cancer. We did, however, find an increased rate of mood and neurotic disorders following cancer (IRR=1.11, 95% CI: 1.09-1.14; and

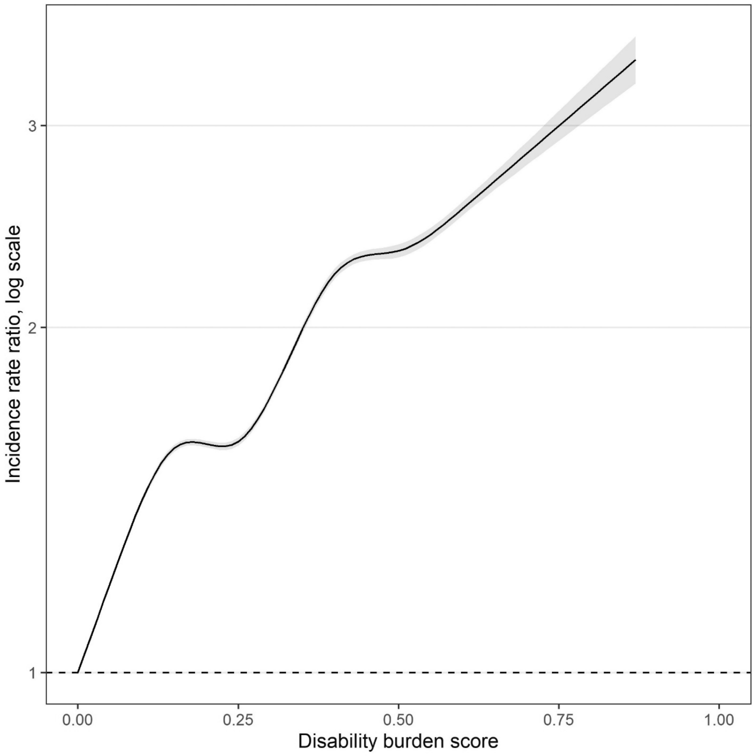

Figure 4 Incidence rate ratios for any mental disorder diagnosis as a function of the disability burden score. The gray shading indicates the 95% CIs.

IRR=1.19, 95% CI: 1.17-1.22, respectively). The observed reduced risk for certain mental disorders after cancer is likely due to the competing risk of death, as premature mortality is particularly pronounced for cancer[16].

Several mechanisms may underlie the associations observed in our study. For example, illness-related stress, pain, restriction and disability due to physical diseases[30-33] have been demonstrated to increase the risk of onset of mental disorders. Moreover, shared environmental and/or genetic risk factors may also underlie the observed findings[34]. On the other hand, detection bias (hospital contacts for physical diseases leading to referral to psychiatric services) may also be at work. In some cases, specific etiological mechanisms may link pairs of physical diseases and subsequent mental disorders. However, the increase in the risk of virtually all mental disorders after diagnosis of almost any physical disease observed herein suggests that more general mechanisms (such as those mentioned above) are likely to be involved, and should be investigated further.

This register-based study comprised a large population, and had no susceptibility to recall or self-reporting bias. Data were available for the entire population, thereby minimizing selection bias. Because Danish citizens have free and equal access to health care[35], any effects associated with the ability to afford private insurance/access to health care are likely negligible. In Denmark, all hospitals must report discharge diagnoses, and all pharmacies must report redemptions of drug prescriptions to the central registers providing data for this study. We considered a broad range of disorders, and also assessed cumulative disability due to physical diseases as a risk factor for subsequent mental disorders.

However, this study has some limitations. First, physical diseases and mental disorders might have been incompletely ascertained. Although register-based psychiatric diagnoses in Denmark have been found to be generally valid for a range of disorders[36-40], the validity varies to some extent across diagnoses. Given the lack of data on people who did not seek treatment, and on diagnoses assigned by general practitioners and other private practitioners,

Table 4 Cumulative incidence (after 15 years) of any mental disorder in people with vs. without a prior physical disease diagnosis

	Cumulative incidence, % (95% CI)	
	Physical disease cohort	Comparison cohort
Cardiovascular diseases	6.73 (6.68-6.78)	4.46 (4.44-4.48)
Endocrine diseases	7.18 (7.10-7.26)	5.59 (5.56-5.62)
Respiratory diseases	10.19 (10.13-10.25)	7.68 (7.66-7.71)
Gastrointestinal diseases	8.31 (8.20-8.42)	5.92 (5.88-5.96)
Urogenital diseases	6.14 (6.04-6.25)	5.27 (5.23-5.32)
Musculoskeletal diseases	8.23 (8.18-8.28)	4.46 (4.44-4.48)
Hematological diseases	6.58 (6.47-6.70)	6.52 (6.47-6.57)
Cancers	3.73 (3.67-3.80)	5.72 (5.69-5.76)
Neurological diseases	8.92 (8.85-8.98)	5.94 (5.92-5.97)

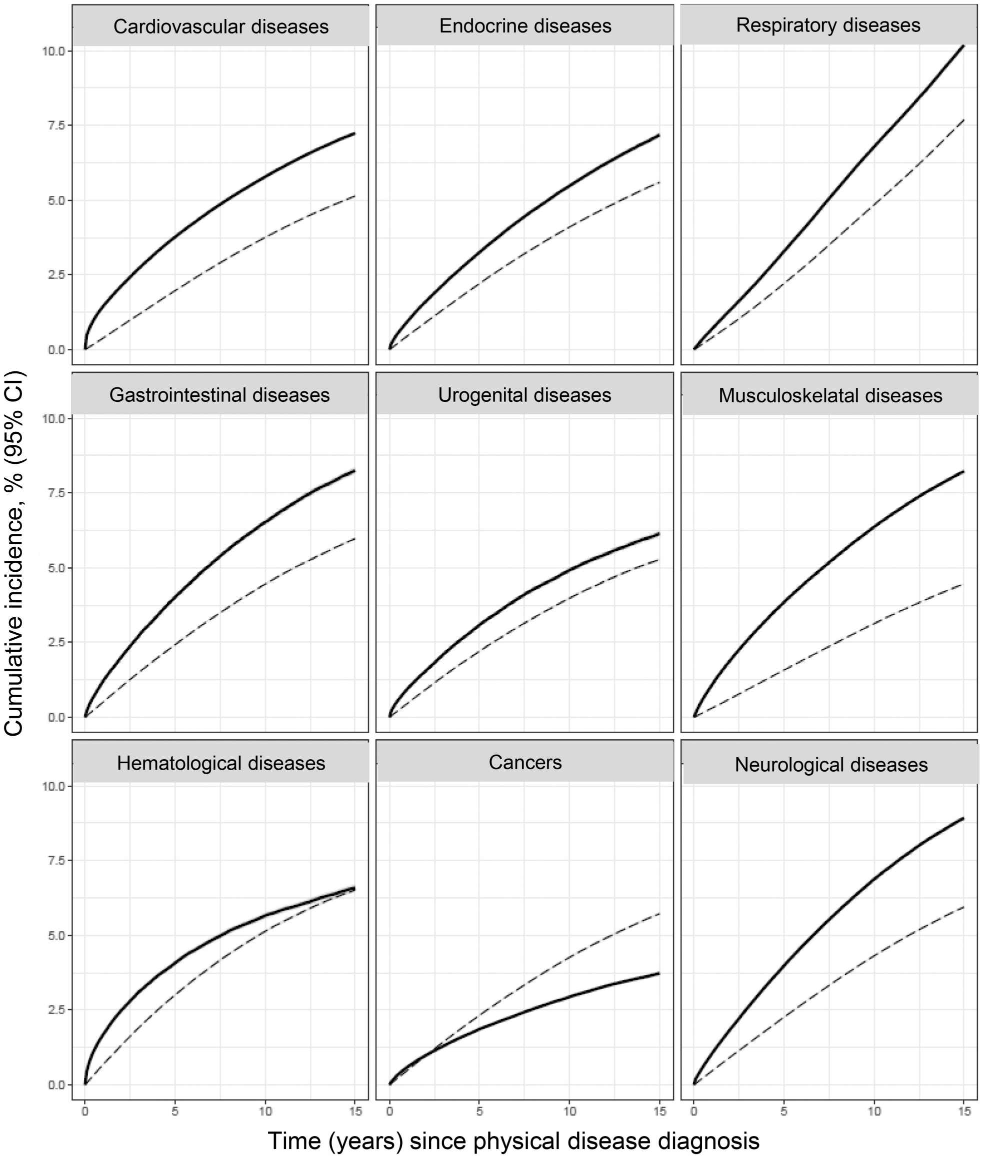

Figure 5 Cumulative incidence of any mental disorder diagnosis after the diagnosis of a broad physical disease category. The bold lines indicate the incidence in people diagnosed with a physical disease; the dashed lines indicate the incidence in matched comparison cohorts.

there may have been some underdetection. For certain physical diseases, this limitation was partially offset by the use of prescription data, in combination with hospital diagnoses; however, prescriptions were not used to identify mental disorders, because of the lack of specificity of many psychotropic medications[41]. Thus, cases of both mental and physical diseases may have been biased toward relatively high severity.

Since we were interested in only incident mental disorders during follow-up (starting on January 1, 2000), a "wash-out" period in the preceding years (1969-1999) excluded prevalent mental disorder cases from their respective analysis. However, our procedures might have not identified all prevalent mental disorders. Furthermore, details on the date of onset of illness are unavailable in the registers, and the dates of diagnosis or prescription were used as proxies. In some cases, incorrect temporal ordering of conditions might have occurred.

Studies based on health care registers are prone to surveillance and diagnostic bias; i.e., people who are in contact with the health care system and diagnosed with a physical disease might be more likely to be diagnosed with additional conditions[42]. The time-dependent analyses helped us assess the extent of this bias.

Some of the physical disease categories studied were very broad and may warrant more focused/stratified investigation. Other prior diseases/events (e.g., highly acute diseases, surgeries, infections and accidents) may also be of interest, but were outside the scope of this study. Finally, our findings may not be generalizable outside of Denmark, as patterns of morbidity and comorbidity vary across countries and may be different in those with health care systems and socioeconomic structures that differ from Denmark.

Our analyses considered many physical disease - mental disorder pairs, which were likely to be linked by different pathways, as discussed above. We hope that our findings at the more general level will, in turn, support specific hypothesis-driven research into some of these pairs.

In conclusion, our data document that most physical diseases are associated with an elevated risk of subsequent mental disorders. This risk is pervasive in both relative and absolute terms. Clinicians treating physical diseases should constantly be alert to the possible development of secondary mental disorders.

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REFERENCES

1. Tegethoff M, Stalujanis E, Belardi A et al. Chronology of onset of mental disorders and physical diseases in mental-physical comorbidity – A national representative survey of adolescents. PLoS One 2016;11:e0165196.
2. Adams JS, Chien AT, Wisk LE. Mental illness among youth with chronic physical conditions. Pediatrics 2019;144:e20181819.
3. Horsboel TA, Kjaer SK, Johansen C et al. Increased risk for depression persists for years among women treated for gynecological cancers – a register-based cohort study with up to 19 years of follow-up. Gynecol Oncol 2019;153:625-32.
4. Ording AG, Horvath-Puho E, Veres K et al. Cancer and risk of Alzheimer's disease: small association in a nationwide cohort study. Alzheimers Dement 2020; 16:953-64.
5. Krebber AM, Buffart LM, Kleijn G et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology 2014;23:121-30.
6. Secher N, Adelborg K, Szentkuti P et al. Evaluation of neurologic and psychiatric outcomes after hospital discharge among adult survivors of cardiac arrest. JAMA Netw Open 2022;5:e2213546.
7. Farooqi A, Gillies C, Sathanapally H et al. A systematic review and meta-analysis to compare the prevalence of depression between people with and without Type 1 and Type 2 diabetes. Prim Care Diabetes 2022;16:1-10.
8. Mohammad MYH, Bushulaybi NA, AlHumam AS et al. Prevalence of depression among hypothyroid patients attending the primary healthcare and endocrine clinics of King Fahad Hospital of the University (KFHU). J Family Med Prim Care 2019;8:2708-13.
9. Liu X, Plana-Ripoll O, McGrath JJ et al. Bidirectional associations between asthma and types of mental disorders. J Allergy Clin Immunol Pract 2023;11: 799-808.e14.
10. Tsai TY, Livneh H, Lu MC et al. Increased risk and related factors of depression among patients with COPD: a population-based cohort study. BMC Public Health 2013;13:976.
11. Marrie RA, Horwitz R, Cutter G et al. The burden of mental comorbidity in multiple sclerosis: frequent, underdiagnosed, and undertreated. Mult Scler 2009;15:385-92.
12. Leo RJ, Singh J. Migraine headache and bipolar disorder comorbidity: a systematic review of the literature and clinical implications. Scand J Pain 2016; 11:136-45.
13. Baumeister H, Hutter N, Bengel J et al. Quality of life in medically ill persons with comorbid mental disorders: a systematic review and meta-analysis. Psychother Psychosom 2011;80:275-86.
14. O'Mahony J, Salter A, Ciftci B et al. Physical and mental health-related quality of life trajectories among people with multiple sclerosis. Neurology 2022; 99:e1538-48.
15. Chong SA, Abdin E, Nan L et al. Prevalence and impact of mental and physical comorbidity in the adult Singapore population. Ann Acad Med Singap 2012;41:105-14.
16. Momen NC, Plana-Ripoll O, Agerbo E et al. Mortality associated with mental disorders and comorbid general medical conditions. JAMA Psychiatry 2022;79:444-53.
17. Benros ME, Nielsen PR, Nordentoft M et al. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. Am J Psychiatry 2011;168:1303-10.
18. Benros ME, Waltoft BL, Nordentoft M et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. JAMA Psychiatry 2013;70:812-20.
19. Scott KM, de Jonge P, Alonso J et al. Associations between DSM-IV mental disorders and subsequent heart disease onset: beyond depression. Int J Cardiol 2013;168:5293-9.
20. Scott KM, Lim C, Al-Hamzawi A et al. Association of mental disorders with subsequent chronic physical conditions: World Mental Health Surveys from 17 countries. JAMA Psychiatry 2016;73:150-8.
21. Momen NC, Plana-Ripoll O, Agerbo E et al. Association between mental disorders and subsequent medical conditions. N Engl J Med 2020;382:1721-31.
22. Prior A, Fenger-Gron M, Larsen KK et al. The association between perceived stress and mortality among people with multimorbidity: a prospective population-based cohort study. Am J Epidemiol 2016;184:199-210.
23. Weye N, Momen NC, Whiteford HA et al. The contribution of general medical conditions to the non-fatal burden of mental disorders: register-based cohort study in Denmark. BJPsych Open 2022;8:e180.
24. Salomon JA, Haagsma JA, Davis A et al. Disability weights for the Global Burden of Disease 2013 study. Lancet Glob Health 2015;3:e712-23.
25. Elixhauser A, Steiner C, Harris DR et al. Comorbidity measures for use with administrative data. Med Care 1998;36:8-27.
26. Momen NC, Østergaard SD, Toft Sorensen H et al. Associations between general medical conditions and subsequent mental disorders. Analysis plan - version 2. https://osf.io/p2qw8.
27. Leong IY, Farrell MJ, Helme RD et al. The relationship between medical comorbidity and self-rated pain, mood disturbance, and function in older people with chronic pain. J Gerontol A Biol Sci Med Sci 2007;62:550-5.
28. Watkins LL, Schneiderman N, Blumenthal JA et al. Cognitive and somatic symptoms of depression are associated with medical comorbidity in patients after acute myocardial infarction. Am Heart J 2003;146:48-54.
29. Hoogwegt MT, Kupper N, Jordaens L et al. Comorbidity burden is associated with poor psychological well-being and physical health status in patients with an implantable cardioverter-defibrillator. Europace 2013;15:1468-74.
30. IsHak WW, Wen RY, Naghdechi L et al. Pain and depression: a systematic review. Harv Rev Psychiatry 2018;26:352-63.
31. Tibubos AN, Burghart J, Klein EM et al. Frequency of stressful life events and associations with mental health and general subjective health in the general population. J Public Health 2021;29:1071-80.
32. Ingle VK, Pandey I, Singh AR et al. Screening of patients with chronic medical disorders in the outpatient department for depression using handheld computers as interface and Patient Health Questionnaire-9 as a tool. Int J Appl Basic Med Res 2017;7:129-33.
33. Ma Y, Xiang Q, Yan C et al. Relationship between chronic diseases and depression: the mediating effect of pain. BMC Psychiatry 2021;21:436.
34. Dragioti E, Radua J, Solmi M et al. Impact of mental disorders on clinical outcomes of physical diseases: an umbrella review assessing population attributable fraction and generalized impact fraction. World Psychiatry 2023;22:86-104.
35. Schmidt M, Schmidt SAJ, Adelborg K et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol 2019;11:563-91.
36. Bock C, Bukh JD, Vinberg M et al. Validity of the diagnosis of a single depressive episode in a case register. Clin Pract Epidemiol Ment Health 2009;5:4.
37. Kessing L. Validity of diagnoses and other clinical register data in patients with affective disorder. Eur Psychiatry 1998;13:392-8.
38. Lauritsen MB, Jorgensen M, Madsen KM et al. Validity of childhood autism in the Danish Psychiatric Central Register: findings from a cohort sample born 1990-1999. J Autism Dev Disord 2010;40:139-48.

39. Phung TK, Andersen BB, Hogh P et al. Validity of dementia diagnoses in the Danish hospital registers. Dement Geriatr Cogn Disord 2007;24:220-8.
40. Schmidt M, Schmidt SA, Sandegaard JL et al. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449-90.
41. Kohler-Forsberg O, Gasse C, Hieronymus F et al. Pre-diagnostic and post-diagnostic psychopharmacological treatment of 16 288 patients with bipolar disorder. Bipolar Disord 2021;23:357-67.
42. McGee G, Haneuse S, Coull BA et al. On the nature of informative presence bias in analyses of electronic health records. Epidemiology 2022;33:105-13.

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Sensitivity of the familial high-risk approach for the prediction of future psychosis: a total population study

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Children who have a parent with a psychotic disorder present an increased risk of developing psychosis. It is unclear to date, however, what proportion of all psychosis cases in the population are captured by a familial high-risk for psychosis (FHR-P) approach. This is essential information for prevention research and health service planning, as it tells us the total proportion of psychosis cases that this high-risk approach would prevent if an effective intervention were developed. Through a prospective cohort study including all individuals born in Finland between January 1, 1987 and December 31, 1992, we examined the absolute risk and total proportion of psychosis cases captured by FHR-P and by a transdiagnostic familial risk approach (TDFR-P) based on parental inpatient hospitalization for any mental disorder. Outcomes of non-affective psychosis (ICD-10: F20-F29) and schizophrenia (ICD-10: F20) were identified in the index children up to December 31, 2016. Of the index children (N=368,937), 1.5% (N=5,544) met FHR-P criteria and 10.3% (N=38,040) met TDFR-P criteria. By the study endpoint, 1.9% (N=6,966) of the index children had been diagnosed with non-affective psychosis and 0.5% (N=1,846) with schizophrenia. In terms of sensitivity, of all non-affective psychosis cases in the index children, 5.2% (N=355) were captured by FHR-P and 20.6% (N=1,413) by TDFR-P approaches. The absolute risk of non-affective psychosis was 6.4% in those with FHR-P, and 3.7% in those with TDFR-P. There was notable variation in the sensitivity and total proportion of FHR-P and TDFR-P cases captured based on the age at which FHR-P/TDFR-P were determined. The absolute risk for psychosis, however, was relatively time invariant. These metrics are essential to inform intervention strategies for psychosis risk requiring pragmatic decision-making.

Key words: Psychosis, schizophrenia, prediction, prevention, psychosis risk, familial high-risk approach, sensitivity, transdiagnostic approach

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A major focus of psychiatric research in the past quarter century has been the prediction and prevention of severe mental illness, in particular psychotic disorders[1-3]. In order to achieve psychosis prediction (and, ultimately, prevention), researchers have pursued a number of "high-risk" approaches, seeking to identify individuals at elevated risk of developing psychotic disorders[4-7].

The familial high-risk approach to psychosis (FHR-P) is one of the most widely used "high-risk" strategies in psychiatric research[1]. This approach involves identifying individuals at elevated risk of psychosis based on having family members (especially first-degree relatives) with a history of psychotic disorder. Several studies have demonstrated that individuals who have a first-degree relative with a history of psychotic disorder present an increased risk of going on to develop psychosis[8-16], identifying the FHR-P approach as a potential strategy for psychosis prediction and prevention. A recent systematic review with meta-analysis published in this journal[8] reported that 8% of the offspring of parents who had one or more psychotic episodes went on to themselves develop psychosis.

While it is established that the offspring of individuals with a history of psychotic disorder have an increased risk of psychosis, it is unclear to date what proportion of all psychosis cases in the population are captured by the FHR-P approach, i.e. the sensitivity of this approach to capture future cases. This is essential information for prevention research and health service planning, as it tells us the upper limit of psychosis cases that could be prevented if we were to identify an effective preventive intervention[17,18]. We therefore aimed to assess, using a prospective design, both the absolute risk of psychosis in individuals having one or both parents with a history of psychotic disorder, and the sensitivity of the FHR-P approach in terms of the total proportion of all future psychosis cases that it captures.

Given increasing evidence of transdiagnostic risk for psychosis, we also aimed to apply these questions to a transdiagnostic familial risk approach (TDFR-P)[8,19,20]. That is, we evaluated the risk of psychosis in individuals with a parent who had received inpatient treatment for any mental disorder (not just for psychotic disorders), and established the sensitivity of the TDFR-P approach to capturing future cases of psychosis.

We used total population health care register data on all people born in Finland from 1987 to 1992 in order to calculate the following: a) the absolute risk of psychosis in individuals when one or both parents had a history of psychotic disorder (FHR-P approach); b) the proportion of all cases of psychosis in the population captured by the FHR-P approach; c) the absolute risk of psychosis in individuals when one or both parents had a history of inpatient treatment for any mental disorder (not limited to psychosis, the TDFR-P approach); and d) the proportion of all cases of psychosis in the population captured by the TDFR-P approach.

We also conducted two sensitivity analyses. First, absolute risk and sensitivity for capturing future psychosis may vary depending on the age at which one determines FHR-P or TDFR-P status. Thus, we investigated the effect of various cut-off ages on the absolute risk and sensitivity for capturing future cases of psychosis in the population. Second, we examined the separate contributions of maternal history, paternal history and a history on both sides of the family to the absolute risk and sensitivity for psychosis.

METHODS

National register data

Finnish national register data were used to identify the population of interest. We linked data from the Medical Birth Register, the Care Register for Health Care, Statistics Finland (for death records), and Digital and Population Data Services (for emigration records).

The Care Register for Health Care provides information on all inpatient visits within a person's lifetime (both parents and offspring) and all outpatient visits to a secondary level health care from the year 1998 to present. Information on diagnosis (ICD-8: 1965-1986, ICD-9: 1987-1995, and ICD-10: 1996-2016), admission and discharge dates, and whether it was an inpatient or outpatient visit are recorded for all observations. The register-based data have been shown to have good diagnostic validity, especially for psychotic disorders[21,22].

Population

All individuals born in Finland between 1987 and 1992 (N= 384,551) were identified using the Medical Birth Register. Individuals who had died or emigrated prior to 2016 (N=11,957) were excluded, as were individuals for whom data linkage was unavailable in both parents (N=3,657). Reasons for lack of data linkage availability include parent not registered in the medical birth register or requested register removal. The final sample included all individuals born in Finland between 1987 and 1992 and for whom parental data linkage was possible, herein referred to as index children.

Exposure

FHR-P was defined as having at least one parent with a recorded history of non-affective psychotic disorder. TDFR-P was defined as having at least one parent with a recorded history of one or more inpatient psychiatric admissions (for any reason) up to the index child's 13th birthday.

The Care Register for Health Care was used to identify the records of mothers and fathers of the index children within the sample. For harmonization and consistency across the databases (1965-2016), both FHR-P and TDFR-P were based on primary diagnosis within inpatient records (non-affective psychotic disorder in the case of FHR-P, and psychiatric inpatient admission for any reason in the case of TDFR-P).

Harmonization of the ICD codes across versions 8, 9 and 10 was carried out according to Lahti et al[23] (see also supplementary information). All maternal and paternal records were identified separately and compiled into FHR variables.

Sensitivity and absolute risk are metrics which may vary depending on the time point that is set for capturing parental diagnoses (for example, taking parental psychiatric history by the birth of the index child versus at a later stage in the child's development). For our primary analyses, we set this threshold as the 13th birthday of the index child. For completeness and comparison, however, we also calculated the equivalent figures when the threshold was set as the index child's birth, 5th birthday, 18th birthday, and study endpoint.

Outcome

Non-affective psychosis in the index children was defined by the ICD-10 diagnostic code F20.x, F23.x, F28, F29, F22.x, F25.x or F24. This diagnosis was identified using inpatient or outpatient records. Schizophrenia was defined as a recording of ICD-10 F20.x diagnosis.

Demographic variables

We report the sex observed at birth, and mother's and father's highest attained education at the time the index child was born. Low corresponds to International Standard Classification of Education (ISCED) classes 0-2, intermediate to ISCED classes 3-5, and high to ISCED classes 6-8[24].

Analyses

We report the incidence of FHR-P and TDFR-P, as well as the incidence of non-affective psychosis and schizophrenia specifically, in the index children by the end of follow-up (index child age range: 25-29 years). Demographic descriptive statistics are provided for the overall sample and for those with FHR-P and TDFR-P.

We report the sensitivity, absolute risk and hazard ratios (HRs) with 95% confidence intervals (CIs) for both non-affective psychosis and schizophrenia. HRs were calculated using a Cox proportional hazard model, with date of entry set as the index child's 13th birthday, and date of exit specified as exposure to the outcome, death, emigration, or administrate censoring on December 31, 2016.

We examined the change in sensitivity and absolute risk across the different index child age-points when familial risk was determined. We separately examined the contributions of maternal and paternal diagnoses to sensitivity and absolute risk. We examined the duration of time between parental psychosis/inpatient admission and the index child's psychosis diagnosis. Since there was a maximum of five-year difference in the duration of follow-up between index children born in different years, and longer follow-up will result in higher incidence of psychosis in the index children, we conducted an analysis restricted to just those born in 1987 (i.e., with the longest follow-up), examining the sensitivity and absolute risk of both familial risk approaches.

RESULTS

Incidence data and demographic variables

After excluding those who had died or emigrated prior to 2016, or for whom data linkage was unavailable in both parents, 368,937 children born in Finland between 1987 and 1992 were included in our analyses ("index children"). In total, 1.5% (N=5,544) of these children had at least one parent with an inpatient psychiatric admission for a psychotic disorder, and 10.3% (N=38,040) of them had at least one parent with an inpatient psychiatric admission for any reason prior to the child's 13th birthday. Of the index children, 1.9% (N=6,966) had been diagnosed with non-affective psychosis and 0.5% (N=1,846) had been diagnosed with schizophrenia by the study endpoint.

The proportion of males in FHR-P (51.0%, N=2,827) and TDFR-P (51.3%, N=19,524) groups was similar as in the total population (51.2%, N=188,991). By the time of the child's birth, there were significant differences between FHR and non-FHR groups in maternal (FHR-P: X^2=349.47, p<0.001; TDFR-P: X^2=5.1e^3, p<0.001) and paternal (FHR-P: X^2=398.64, p<0.001; TDFR-P: X^2=4.8e^3, p<0.001) education level, as the proportion of mothers and fathers with low education was higher in FHR-P (29.6% and 31.9%) and TDFR-P (33.5% and 37.2%) than in non-FHR (20.1% and 23.9%) groups, while the proportion of mothers and fathers with tertiary education was lower in FHR-P (7.7% and 8.7%) and TDFR-P (6.5% and 7.3%) than in non-FHR (11.3% and 14.2%) groups.

Sensitivity and absolute risk data

Of all non-affective psychosis cases diagnosed after the index child's 13th birthday, 5.2% (95% CI: 4.7-5.7, N=355) were captured by the FHR-P approach. Of all schizophrenia cases diagnosed after the index child's 13th birthday, 6.2% (95% CI: 5.2-7.4, N=114) were captured by the FHR-P approach (see Table 1).

Of all non-affective psychosis cases diagnosed after the index child's 13th birthday, 20.6% (95% CI: 19.7-21.6, N=1,413) were captured by the TDFR-P approach. Of all schizophrenia cases diagnosed after the index child's 13th birthday, 21.3% (95% CI: 19.5-23.3, N=391) were captured by the TDFR-P approach.

The absolute risk of non-affective psychosis in FHR-P children was 6.4% (95% CI: 5.8-7.1, N=355; HR=3.7, 95% CI: 3.3-4.1). The absolute risk of schizophrenia in FHR-P children was 2.1% (95% CI: 1.7-2.5, N=114; HR=4.4, 95% CI: 3.6-5.3).

The absolute risk of non-affective psychosis in TDFR-P children was 3.7% (95% CI: 3.5-3.9, N=1,413; HR=2.3, 95% CI: 2.2-2.4). The absolute risk of schizophrenia in TDFR-P children was 1.0% (95% CI: 0.9-1.1, N=391; HR=2.4, 95% CI: 2.1-2.7).

Further analyses

Within our main analysis, we included parental diagnoses until the index child's 13th birthday, which resulted in 1.5% of the population meeting FHR-P criteria. By the end of the study follow-up period, however, 2.2% (N=8,273) of the index children met FHR-P criteria. The absolute risk and sensitivity of the FHR-P at selective ages of the index children are reported in Table 1. Depending upon the age at which FHR-P was determined, the absolute risk of non-affective psychosis varied from 4.6% to 7.5%, and the sensitivity ranged from 2.5% to 7.2%.

Table 1 Incidence, absolute risk, and sensitivity of the familial high-risk (FHR-P) and the transdiagnostic familial risk (TDFR-P) approaches to psychosis when stratified by age cut-off

Risk system stratified by age limit	Incidence of FHR, % (N)	Non-affective psychosis		Schizophrenia	
		Absolute risk	Sensitivity	Absolute risk	Sensitivity
FHR-P					
Birth	0.7 (2,397)	7.3%	2.5%	1.9%	2.5%
Age 5	0.9 (3,130)	7.5%	3.4%	2.3%	4.0%
Age 13	**1.5 (5,544)**	**6.4%**	**5.2%**	**2.1%**	**6.2%**
Age 18	1.9 (6,872)	4.6%	5.8%	1.8%	7.4%
Ever	2.2 (8,273)	6.1%	7.2%	2.1%	9.3%
TDFR-P					
Birth	4.7 (17,573)	4.3%	10.8%	1.2%	11.3%
Age 5	6.6 (24,574)	4.2%	14.8%	1.2%	16.0%
Age 13	**10.3 (38,040)**	**3.7%**	**20.6%**	**1.0%**	**21.3%**
Age 18	12.3 (45,982)	2.7%	23.0%	0.9%	24.5%
Ever	15.2 (56,636)	3.5%	28.7%	1.0%	29.3%

The bold prints indicate that for primary analyses the threshold was set as the 13th birthday of the index child

Compared with an age 13 years cut-off, where 10.3% of the index children were in the TDFR-P group, 15.2% (N=56,636) of the index children met TDFR-P criteria by the end of the follow-up. Depending upon the age at which TDFR-P was determined, the absolute risk of psychosis varied from 2.7% to 4.3%, and the sensitivity ranged from 10.8% to 28.7% (see Table 1).

The maternal and paternal contributions to sensitivity and absolute risk are displayed in Table 2. Broadly, in FHR-P for non-affective psychosis, mothers and fathers had equivalent contributions to both sensitivity and absolute risk. Fathers had a higher incidence of inpatient psychiatric admission (TDFR-P), and thus contributed slightly more to the sensitivity in this approach. The absolute risk of non-affective psychosis was 16.7% for individuals in whom both parents had a history of psychosis and 6.9% for individuals in whom both parents had a history of inpatient psychiatric admission (for any reason).

For individuals who developed non-affective psychosis, the median number of years between parental first psychosis diagnosis and the index child diagnosis was 14.1 years (interquartile range, IQR: 6.3-26.7, see Figure 1). For individuals who developed schizophrenia, the median number of years between parental first inpatient admission and the index child diagnosis was 13.3 years (IQR: 5.8-23.0, see supplementary information).

For individuals who developed non-affective psychosis, the median number of years between parental first inpatient admission and the index child diagnosis was 16.1 years (IQR: 6.5-26.0, see Figure 2). For individuals who developed schizophrenia, the median number of years between parental first inpatient admission and the index child diagnosis was 17.8 years (IQR: 7.9-27.4, see supplementary information).

Restricting analyses to those who had the longest follow-up period (individuals born in 1987 only) had little impact on the sensitivity and absolute risk of either approach. Of all non-affective psychosis diagnoses in the index children, 5.3% (95% CI: 4.0-6.7, N=64) were from FHR-P. Of all schizophrenia diagnoses in the index children, 4.3% (95% CI: 4.5-6.9, N=15) were from FHR-P. Of all non-affective psychosis diagnoses in the index children, 20.4% (95% CI: 18.1-22.8, N=247) were from TDFR-P. Of all schizophrenia diagnoses in the index children, 23.3% (95% CI: 19.0-28.1, N=82) were from TDFR-P (see also supplementary information).

DISCUSSION

Using total population health care register data, we identified the total proportion of future psychosis cases captured by the FHR-P approach. Following the total population born in the years 1987-1992 from age 13 to 29 years, we found that 5.2% of all psychosis cases in the index children were captured by the approach. This is the upper limit of psychosis cases that could be prevented using the approach if we had an effective preventive intervention.

We also identified the total proportion of future psychosis cases captured by taking a transdiagnostic approach to familial risk (i.e., parents with a history of psychiatric admission for any reason). In total, 20.6% of all psychosis cases were captured by this approach.

The sensitivity of the FHR-P approach for capturing future psychosis was similar to recent UK findings on the sensitivity of the clinical high risk (CHR) approach. Researchers in South London mental health services found that their CHR clinics captured 4.1% of future psychosis cases[25]. FHR-P and TDFR-P status, in contrast to the CHR approach, can be identified based on routine administrative health care data. Thus, unlike the CHR approach, the identification of risk using the FHR approach is not inherently associated with any additional costs or other types of burden for the clinician or the individual.

We also calculated the absolute risk of psychosis associated with FHR-P and TDFR-P status. We found that 6.4% of all children who had a parent with psychosis went on to be diagnosed with a psychotic disorder by age 25-29 years. The equivalent figure for the TDFR-P approach was 3.7%. In contrast to time-varying effects on sensitivity, the age at which familial risk was determined had little effect on absolute risk.

The absolute risk of psychosis associated with both FHR approaches was lower than the risk of psychosis typically reported for the CHR approach. A systematic review of studies of children and adolescents diagnosed with a CHR syndrome found that 16% went on to be diagnosed with a psychotic disorder at follow-ups of 5 years or more[26]. Within samples of adults and young people,

Table 2 Incidence, sensitivity, and absolute risk of the familial high-risk (FHR-P) and the transdiagnostic familial risk (TDFR-P) approaches to psychosis in the index children stratified by each parental contribution (threshold set as the 13th birthday of the index child)

	FHR-P			TDFR-P		
	Incidence, % (N)	**Absolute risk**	**Sensitivity**	**Incidence, % (N)**	**Absolute risk**	**Sensitivity**
Non-affective psychosis in index children						
Mother	0.8 (3,038)	7.1%	3.1%	4.2 (15,532)	4.4%	10.0%
Father	0.7 (2,608)	6.0%	2.3%	6.8 (25,248)	3.6%	13.3%
Both	0.03 (102)	16.7%	0.3%	0.7 (2,740)	6.9%	2.7%
Schizophrenia in index children						
Mother	0.8 (3,038)	2.4%	3.9%	4.2 (15,532)	1.3%	10.8%
Father	0.7 (2,608)	2.0%	2.8%	6.8 (25,248)	1.0%	14.0%
Both	0.03 (102)	9.8%	0.6%	0.7 (2,740)	2.3%	3.5%

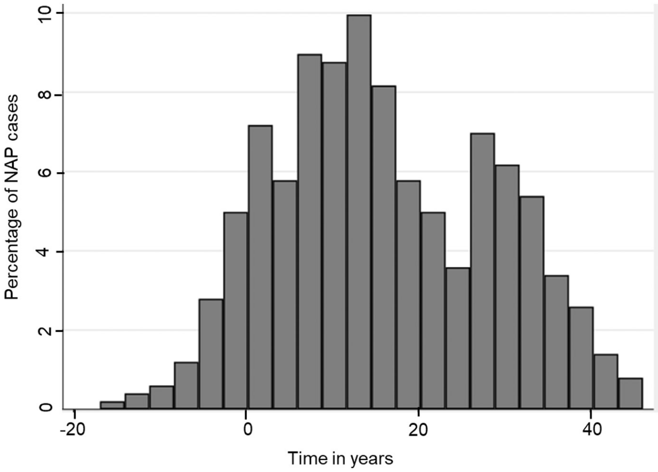

Figure 1 Time between parental first psychosis diagnosis and child's non-affective psychosis (NAP) diagnosis (median: 14.1 years, interquartile range: 6.3-26.7)

the cumulative transition risk was 28% at over 4 years[27]. The absolute risk associated with meeting FHR-P and TDFR-P criteria suggests that, similar to the CHR approach[5], additional factors are needed to stratify risk among the FHR groups.

We found little difference in the contributions of maternal versus paternal psychosis to the absolute risk and sensitivity for non-affective psychosis or schizophrenia in the index children. The absolute risk for non-affective psychosis and schizophrenia was notably higher if both parents had a history of psychosis, at 16.7%, though this event was rare. There was also little difference in the relationship between maternal versus paternal history of psychiatric admission and the absolute risk of psychosis or schizophrenia. Paternal psychiatric history, however, was more sensitive to capturing future offspring psychosis than maternal psychiatric history. This was attributable to the higher incidence of psychiatric inpatient admission in fathers.

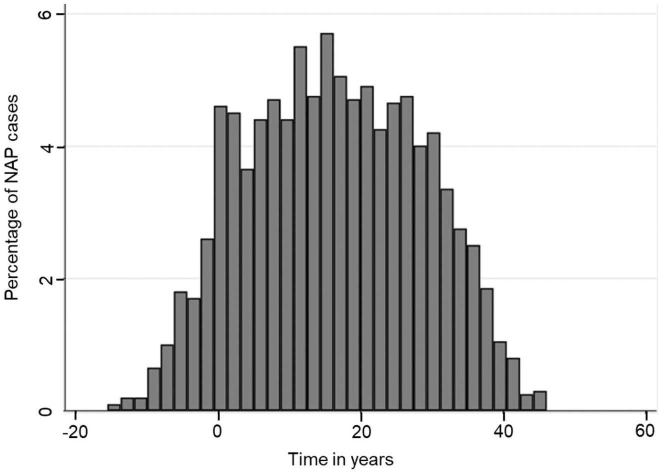

Figure 2 Time between parental first inpatient admission and child's non-affective psychosis (NAP) diagnosis (median: 16.1 years, interquartile range: 6.5-26.0)

Finally, we observed significant differences in the proportion of parent and index children cases identified when different age cut-offs were applied to the FHR systems. This clearly demonstrates that the age cut-offs for FHR systems need careful and pragmatic consideration to ensure that they: a) capture enough of the total cases of parents who qualify over their lifetime (FHR-P or TDFR-P); b) capture enough of the index children who develop psychosis; and c) allow a sufficient window for an intervention to occur between parent entering the FHR system and index child's diagnosis.

In order to prevent unnecessary stigmatization and fear, we recommend that professionals applying FHR-P approaches are explicit about the absolute risk of psychosis. Although the risk is elevated from a relative perspective, just 6.4% of all FHR-P individuals had been diagnosed with a psychotic disorder by the end of follow-up. This means that more than 93% did not develop psychosis. For individuals with transdiagnostic familial risk based on a parental history of inpatient psychiatric admission, more than 96% did not develop psychosis by the end of follow-up. Moreover, only a minority of psychosis cases arose in individuals at familial risk. This information should prevent any sense of fatalism associated with familial risk for psychosis.

This study used national register data covering the entire population of Finland born from 1987 to 1992. It had parental data linkage for both mother and father histories, with only a small proportion of cases for whom linkage was unavailable (<2%). In countries with developed-registers, these risk systems are already recorded as part of administrative health data and require no additional cost to operationalize. This weighs favorably against symptom-based risk indicators, which require lengthy and costly assessments that need to be conducted by trained medical professionals and require patient input and resourcing.

Familial risk was identified based on psychiatric inpatient records for the parents of index children. The validity of these records, specifically for psychosis, have been previously examined, with true positive accuracy ranging from 75 to 93%[21,22,28]. Of course, not all parents with mental disorders may have been hospitalized, which has likely generated a downward bias in the estimates of proportions of affected parents and offspring.

In terms of transdiagnostic familial risk, we had data on inpatient, but not outpatient, psychiatric admissions for the parents. We would hypothesize that, if we were to extend the study to include outpatient psychiatric care, this would increase the sensitivity to capture risk for future psychosis, but at the expense of a reduced absolute risk. It was not possible to test this in the current study, given the limited period for which outpatient registers have existed. However, as the duration of time for which it is possible to follow individuals in the register naturally increases over time, it may become possible to test this in the future.

CONCLUSIONS

We identified, for the first time, the sensitivity of the FHR-P approach and a novel transdiagnostic familial risk approach for capturing psychosis risk. In total, 5.2% and 20.6% of future psychosis cases were captured, respectively, by the FHR-P and TDFR-P approaches. The sensitivity of these approaches varied according to the age at which familial risk was determined. Absolute risk, on the other hand, was relatively invariant regardless of the age at which familial risk was determined. Additional factors, beyond familial risk, will be necessary to stratify risk for psychosis within these populations.

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REFERENCES

1. Fusar-Poli P, Correll CU, Arango C et al. Preventive psychiatry: a blueprint for improving the mental health of young people. World Psychiatry 2021;20:200-21.
2. Klosterkotter J, Schultze-Lutter F, Bechdolf A et al. Prediction and prevention of schizophrenia: what has been achieved and where to go next? World Psychiatry 2011;10:165-74.
3. Salazar de Pablo G, Studerus E, Vaquerizo-Serrano J et al. Implementing precision psychiatry: a systematic review of individualized prediction models for clinical practice. Schizophr Bull 2021;47:284-97.
4. Fusar-Poli P, Borgwardt S, Bechdolf A et al. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 2013;70:107-20.
5. Worthington M, Cannon TD. Prediction and prevention in the clinical high-risk for psychosis paradigm: a review of the current status and recommendations for future directions of inquiry. Front Psychiatry 2021;12:770774.
6. Shah JL, Tandon N, Keshavan MS. Psychosis prediction and clinical utility in familial high-risk studies: selective review, synthesis, and implications for early detection and intervention. Early Interv Psychiatry 2013;7:345-60.
7. Ellersgaard D, Plessen KJ, Jepsen JR et al. Psychopathology in 7-year-old children with familial high risk of developing schizophrenia spectrum psychosis or bipolar disorder – The Danish High Risk and Resilience Study - VIA 7, a population-based cohort study. World Psychiatry 2018;17:210-9.
8. Uher R, Pavlová B, Radua J et al. Transdiagnostic risk of mental disorders in offspring of affected parents: a meta-analysis of family high-risk and registry studies. World Psychiatry 2023;22:433-48.
9. Agerbo E, Sullivan PF, Vilhjálmsson BJ et al. Polygenic risk score, parental socioeconomic status, family history of psychiatric disorders, and the risk for schizophrenia. JAMA Psychiatry 2015;72:635-41.
10. Rasic D, Hajek T, Alda M et al. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. Schizophr Bull 2014;40:28-38.
11. Laursen TM, Labouriau R, Licht RW et al. Family history of psychiatric illness as a risk factor for schizoaffective disorder. Arch Gen Psychiatry 2005;62:841-8.
12. Shevlin M, McElroy E, Christoffersen MN et al. Social, familial and psychological risk factors for psychosis: a birth cohort study using the Danish Registry System. Psychosis 2016;8:95-105.
13. Käkelä J, Nordström T, Haapea M et al. Association between family history of mental disorders and outcome in psychotic disorders. Psychiatry Res 2018;270:616-21.
14. Blomström AL, Karlsson H, Gardner RM et al. Associations between maternal infection during pregnancy, childhood infections and the risk of subsequent psychotic disorder – A Swedish cohort study of nearly 2 million individuals. Schizophr Bull 2016;42:125-33.
15. Mortensen PB, Pedersen MG, Pedersen CB. Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? Psychol Med 2009;40:201-10.
16. Keskinen E, Miettunen J, Koivumaa-Honkanen H et al. Effect of parental psychosis on early risk factors and risk for psychoses in the Northern Finland 1966 Birth Cohort. Int Clin Psychopharmacol 2011;26:e158.
17. Lång U, Ramsay H, Yates K et al. Potential for prediction of psychosis and bipolar disorder in child and adolescent mental health services: a longitudinal register study of all people born in Finland in 1987. World Psychiatry 2022;21:436-43.
18. Kelleher I. Psychosis prediction 2.0: why child and adolescent mental health services should be a key focus for schizophrenia and bipolar disorder prevention research. Br J Psychiatry 2023;222:185-7.
19. Leijdesdorff S, van Doesum K, Popma A et al. Prevalence of psychopathology in children of parents with mental illness and/or addiction: an up to date narrative review. Curr Opin Psychiatry 2017;30:312-7.
20. Campbell TC, Reupert A, Sutton K et al. Prevalence of mental illness among parents of children receiving treatment within child and adolescent mental health services (CAMHS): a scoping review. Eur Child Adolesc Psychiatry 2021;30:997-1012.
21. Pihlajamaa J, Suvisaari J, Henriksson M et al. The validity of schizophrenia diagnosis in the Finnish Hospital Discharge Register: findings from a 10-year birth cohort sample. Nord J Psychiatry 2008;62:198-203.
22. Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health 2012;40:505-15.
23. Lahti M, Eriksson JG, Heinonen K et al. Late preterm birth, post-term birth, and abnormal fetal growth as risk factors for severe mental disorders from early to late adulthood. Psychol Med 2014;45:985-99.
24. UNESCO Institute for Statistics. International standard classification of education (ISCED). https://uis.unesco.org.
25. Ajnakina O, Morgan C, Gayer-Anderson C et al. Only a small proportion of patients with first episode psychosis come via prodromal services: a retrospective survey of a large UK mental health programme. BMC Psychiatry 2017;17:308.
26. Lång U, Yates K, Leacy FP et al. Systematic review and meta-analysis: psychosis risk in children and adolescents with an at-risk mental state. J Am Acad Child Adolesc Psychiatry 2022;61:615-25.
27. De Pablo GS, Radua J, Pereira J et al. Probability of transition to psychosis in individuals at clinical high risk. JAMA Psychiatry 2021;78:970-8.
28. Mäkikyrö T, Isohanni M, Moring J et al. Accuracy of register-based schizophrenia diagnoses in a genetic study. Eur Psychiatry 1998;13:57-62.

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Emotion regulation and mental health: current evidence and beyond

The concept of emotion regulation (ER) is receiving considerable attention in research on psychiatric disorders and their treatment. The popularity of the concept is largely rooted in its premise that deficits in adaptive responses toward undesired affective states contribute to the development and maintenance of most forms of psychopathology.

This appears obvious when considering psychiatric disorders that are primarily defined by an excess of undesired affective states (e.g., anxiety and mood disorders). For these conditions, it follows almost by definition that the perpetuation or escalation of undesired affective states results from the individual's inability to regulate them.

However, given that many behavioral and cognitive symptoms of other psychiatric disorders can also be conceptualized as dysfunctional ER strategies, the scope of this paradigm extends much further. Consider, for example, when avoidance is used to reduce anxiety, when alcohol is consumed to numb loneliness, when binge eating serves to distract from emotional anguish, or when appraising a situation as uncontrollable and hopeless is used to reduce the pressure to solve one's problems or to shield oneself from further disappointment. In all these scenarios, behavioral or cognitive strategies yield short-lived relief from undesired affective states. Since the immediate ameliorating effects of these maladaptive strategies reinforce their usage, individuals tend to progressively increase their adoption until criteria for an anxiety, alcohol use, eating or mood disorder, etc. are met.

Importantly, this trajectory is preventable if the individual realizes the negative mid- and long-term consequences of maladaptive strategies, and pivots to more adaptive ways of coping with undesired affective states. However, any such shift will fail to the extent that the individual lacks effective ER skills. Since all psychiatric disorders are arguably maintained by behaviors and cognitions that initially reduce negative affect, and since a distressed individual is more likely to utilize those strategies in the absence of more adaptive alternatives, it can be hypothesized that all psychiatric disorders are, to a significant degree, perpetuated by insufficient ER skills.

Drawing on this framework, it can be deduced that patients with psychiatric disorders should benefit from treatments that systematically enhance effective ER skills. Evidence-based ER frameworks, such as the Adaptive Coping with Emotions Model[1], posit that such treatments should foster the ability to modify the intensity and duration of undesired affective states, as well as the ability to accept and tolerate such states when modification is not possible.

Additionally, these treatments should foster so-called preparatory ER skills that facilitate the successful utilization of modification- and acceptance-focused ER skills. Examples of such preparatory skills include the ability to become aware of one's feelings, to adequately identify and label one's feelings, and to develop a mental model explaining how one's present feelings are maintained, preferably in a manner that validates and destigmatizes one's experience, while also proposing concrete tools to promote successful change/acceptance.

Finally, it is noteworthy that all adaptive ER strategies reviewed so far may initially increase negative affect[1,2]. Thus, treatments focusing on ER should also strengthen self-support skills that enable patients to persistently commit to adaptive strategies, despite their likely initial exacerbation of negative affect.

Regarding empirical evidence for these theoretical premises, salient deficits in ER skills have been reported for various psychiatric disorders[3]. Moreover, a significant number of longitudinal and experimental studies suggest that this association results from ER deficits impacting mental health, and not (exclusively) vice versa[3]. Regarding the importance of specific ER skills, substantial evidence supports the efficacy of *reappraisal*, *acceptance*, and *self-compassion*[4,5].

Further studies yield evidence that treatments *explicitly* focusing on enhancing ER skills (e.g., dialectical behavioral therapy) are effective in treating a wide range of psychiatric disorders. More specific evidence in the literature shows that interventions *exclusively* focusing on enhancing ER skills (e.g., affect regulation training, emotion regulation therapy) are effective treatments for several disorders[2,6]. Finally, significant mediation effects observed across these studies suggest that ER skill improvement is the main driver of symptom severity reduction[7,8].

While these findings are encouraging, ER research in the context of psychopathology remains fraught with several challenges. First of all, conceptual definition of key terms lacks sufficient clarity, beginning with the term *emotion*, which is ubiquitously used for various affective states even though more specific definitions have been proposed (i.e., *emotion* refers to a rather short-lived experience that has an identifiable trigger; *mood* is comparably more protracted, often with a vague trigger; s*tress* is an unspecific response to threats thwarting attainment of one's goals; *urges* are motivational impulses; *feelings* are the subjective experience of affective states; and *affect* is an umbrella term for all of the above).

Further ambiguity plagues the term *regulation*, which implies that actions must be undertaken to change an affective state. However, in some instances, a conscious decision *not* to regulate an emotion, but rather simply observe it and allow it to run its course, could be the most adaptive response. Thus, terms such as *adaptive/maladaptive response* toward an undesired affective state could represent useful alternatives to *regulation* when conceptual clarity is deemed crucial.

Another challenge arises when researchers try to identify the most effective ER strategies. Obviously, there is no silver bullet for successfully regulating all undesired affective states under all circumstances. The number of variables moderating the efficacy of a particular ER strategy in a specific situation is too large to allow for a systematic comparison of the efficacy of multiple ER strategies for all possible constellations of potential moderators. Nevertheless, research should develop and validate rules of thumb that take significant moderators into account (e.g., "use acceptance if your chances of modifying the emotion are slim", or "use exposure to cope with fear, but distraction to cope with anger").

A related challenge results from the likelihood that combinations of ER strategies are more effective than any single ER strategy. For example, it has been shown that encouraging patients to practice *self-compassion* prior to engaging in *reappraisal* augments the potency of the latter[9]. Thus, future studies should elucidate effective combinations of ER strategies.

Moreover, it is evident that present research tends to focus on comparatively broad skill categories. For instance, many studies demonstrate the efficacy of the general ER skill represented by *reappraisal*. However, there are many ways by which an individual can reappraise a salient problem, and these different approaches may differ significantly in their effects on undesired emotions. Thus, future research should also compare the efficacy of different *ways of applying* ER strategies from the same ER skill domain.

Regarding intervention studies, treatments focusing *exclusively* on ER skill enhancement have previously only been evaluated for a relatively limited set of mental disorders. Thus, future research should evaluate the efficacy of such ER-focused interventions for a broader range of psychiatric conditions. Since, according to preliminary evidence, ER interventions may, at best, match the effect sizes of disorder-specific treatments, researchers might choose to prioritize the evaluation of treatment formats that capitalize on the unique practical and economic advantages of ER-focused treatments – particularly their transdiagnostic applicability.

More specifically, investigators might examine the incremental effects to be achieved when disorder-specific individual therapy is augmented with transdiagnostic group-based interventions focusing exclusively on ER skill promotion. Such combinations would ensure the crucial targeting of disorder-specific maintaining factors, while also exploiting the increased ease of organizing group therapy sessions for diagnostically diverse patients.

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1. Berking M, Whitley B. Affect regulation training (ART). New York: Springer, 2014.
2. Berking M, Musa NS. In: Gross JJ, Ford BQ (eds). Handbook of emotion regulation. New York: Guilford, 2024:391-8.
3. Lukas CA, Ebert DD, Fuentes HT et al. J Clin Psychol 2018;74:1017-33.
4. Cludius B, Ehring T. In: Gross JJ, Ford BQ (eds). Handbook of emotion regulation. New York: Guilford, 2024:285-93.
5. Diedrich A, Grant M, Hofmann S et al. Behav Res Ther 2014;58:43-51.
6. Mennin DS, Fresco DM. In: Gross JJ, Ford BQ (eds). Handbook of emotion regulation. New York: Guilford, 2024:383-90.
7. Berking M, Eichler E, Naumann E et al. Br J Clin Psychol 2022;61:998-1018.
8. Berking M, Eichler E, Luhmann M et al. PLoS One 2019;14:e0220436.
9. Diedrich A, Hofmann SG, Cuijpers P et al. Behav Res Ther 2016;82:1-10.

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Emotion regulation, scaffolding and psychiatry

Discrete emotional episodes – belonging to established categories such as fear, anger and joy – both regulate and dysregulate cognition and behavior. They also need to be regulated themselves, and the term "emotion regulation" usually refers specifically to this latter process.

Although there are different definitions of emotion regulation, it is generally taken to encompass a range of strategies, such as changing our situation, shifting attention, re-evaluating things, and modifying expressions of emotion. It is also said to include both conscious and nonconscious strategies, as well as different and sometimes conflicting goals and motives[1].

In line with this, emotion dysregulation could be regarded as a matter of whether an emotion occurs at all, whether it is situationally appropriate, and whether its intensity is proportionate to an eliciting stimulus. It might concern a single occurrence of emotion, a type of emotion and/or emotionally relevant situation, or wider-ranging sets of emotional dispositions.

Conceived of in such ways, emotion regulation and dysregulation are certainly of interest to psychiatry. However, it is important not to think of them in ways that are too atomistic and individualistic. A broader, more integrated approach is required if we are to appreciate a distinctive *kind* of dysregulation often associated with psychiatric diagnoses.

I suggest that we distinguish three regulatory challenges: a) everyday emotion regulation; b) regulating emotional responses when our lives lack structure; and c) regulating temporally extended patterns of emotions that contribute to how we respond and adapt to losses of structure.

The appropriateness of our emotional responses to everyday situations depends in part on the idiosyncratic organization of our lives. Whether and how something matters to us reflects what we already care about or value – an established network of relationships, projects, commitments, pastimes, and treasured possessions. Whether or not our anger, fear, joy or relief is situationally appropriate, and also proportionate in its intensity and duration, depends on whether and how it relates to this backdrop of cares and concerns.

So, we could think of emotion regulation in terms of ensuring that our various emotions track how events and situations matter to us in relation to the dynamic structures of our lives, enabling us to respond in appropriate and effective ways. It is arguable that, in mundane situations, separate regulatory processes are seldom required for this. Instead, our emotions "auto-regulate", by initiating behaviors that alter emotion-eliciting stimuli or our relationships with them[2]. In any case, whatever we are doing here is altogether different from the task of regulating emotion when our lives lack organization, as in circumstances of upheaval.

Consider, for instance, the variety of circumstances associated with "grief" or "loss": a significant bereavement; the breakup of an interpersonal relationship; forced migration; the sudden and unexpected end of a career; the destruction of one's home; or the diagnosis of serious illness. These and other life events can undermine the cares and concerns relative to which mundane emotional experiences once arose and made sense to ourselves and others. Hence we can no longer draw upon regulatory resources that presuppose this orienting life structure.

There is also a third regulatory challenge to be discerned. Certain patterns of emotions contribute to how we respond and adapt to significant changes in the organization of our lives. Some of these are more plausibly construed as integrated, temporally extended processes than as sequences of disparate emotional episodes. This applies to the grief we experience over the death of another person, which involves – amongst other things – comprehending, responding to, and adapting to what has happened and what is now the case, often over a lengthy period of time[3].

How do we regulate such emotions while engaging with losses of regulatory structure? In considering this question, we should turn our attention to processes that are distributed between individuals and their social environments, rather than limiting ourselves to the capacities of individuals. It is plausible to maintain that we utilize external "scaffolding" even to regulate certain everyday emotions[4]. However, there is a distinction to be drawn between mundane and exceptional forms of scaffolding. The organization of our lives depends in many ways upon habitually established interactions with social environments – our home, our workplace, our family and friends. Emotional responses to upheaval engage with losses of this structure, where what is lost includes emotional scaffolding that was once taken for granted. So, the need for emotion regulation is especially apparent here, as is the lack of regulatory resources. There is thus a need for *exceptional* forms of regulation, involving exceptional forms of scaffolding. I want to suggest that this *type* of regulatory challenge is – or at least should be – of particular interest to psychiatry.

Much of the emotional scaffolding that we rely upon in both mundane and exceptional circumstances is interpersonal or social in nature. Regulatory processes draw upon – and may even be partly constituted by – relations with specific individuals, families, other people in general, and larger social and cultural environments. For example, it has been suggested that there are close links between emotion regulation and attachment[5]. When deprived of our more usual regulatory resources, we can still turn to other people in order to interpret, evaluate and alter our emotions, including those emotions that contribute to negotiating upheaval and reorienting ourselves.

Hence, an especially profound form of dysregulation would be one involving a pervasive loss or absence of life structure, combined with lack of access to interpersonal and social scaffolding – one is lost and alone. This is consistent with a number of psychiatric conditions, including post-traumatic stress disorder and some forms of depression. One might feel cut off from others, or unable to trust anyone anymore. There might be feelings of shame, guilt, fear or inadequacy. But underlying this variety is the common theme of feeling unable to experience and relate to others in *precisely* those ways that might otherwise mitigate emotional turmoil and distress.

Deprivation of certain kinds of interpersonal possibilities not only contributes to experiences of being lost or alone. It can further amount to a sense of *inescapability* or *irrevocability*. For example, first-person accounts of trauma often refer to a pervasive loss of the capacity for interpersonal trust, something that might otherwise have sustained the appreciation that there remain significant possibilities beyond one's current situation[6]. Being estranged from others without any prospect of positive change is also a prominent and consistent theme in first-person accounts of depression. There is no way of escaping from your prison or pit because what is altogether absent from your experiential world is the prospect of anyone ever throwing you a rope[7,8]. The sense of irrevocability, and with it the loss of a capacity for hope, is inseparable from one's being alone, cut off from others, estranged, or abandoned.

This form of experience can be characterized in terms of losing access to regulatory processes that might otherwise have aided in navigating loss and disorientation. Diagnoses of depression are often associated with a "felt unavailability of others as potential external co-regulators"[9]. However, the sense that nobody could intervene in ways that might have opened up new and significant life possibilities is not limited to depression. Experiences of disorientation, inescapability, disconnection, absence, lack, loss and emptiness that involve diminished access to interpersonal scaffolding are diagnostically non-specific.

What is therefore required is an overarching perspective on emotion regulation that emphasizes the relationships between emotions and the ever-changing organization of human lives, in conjunction with the importantly different ways in which mundane and exceptional forms of emotion regulation are reliant upon interpersonal and social processes.

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1. Gross JJ. In: Gross JJ (ed). Handbook of emotion regulation. New York: Guilford, 2014:3-20.
2. Kappas A. Emot Rev 2011;3:17-25.
3. Ratcliffe M. Grief worlds: a study of emotional experience. Cambridge: MIT Press, 2022.
4. Colombetti G, Krueger J. Philos Psychol 2015;28:1157-76.
5. Mikulincer M, Shaver PR, Pereg D. Motiv Emot 2003;27:77-102.
6. Brison SJ. Aftermath: violence and the remaking of a self. Princeton: Princeton University Press, 2002.
7. Ratcliffe M. Experiences of depression: a study in phenomenology. Oxford: Oxford University Press, 2015.
8. Fusar-Poli P, Estradé A, Stanghellini G et al. World Psychiatry 2023;22:352-65.
9. Varga S, Krueger J. Rev Philos Psychol 2013;4:271-92.

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Adolescent mental health and supportive relationships: 21st century challenges

It is firmly established that personal relationships play a pivotal role in adolescent mental health and well-being. During adolescence, individuals become aware of their distinctiveness and uniqueness from others, initiating the development of a personal identity. Developing a coherent sense of identity is crucial for adolescent mental health, and relationships serve as a vital source of support that aid adolescents to navigate this task[1].

Supportive relationships with parents who are sensitive and responsive to their evolving needs provide a secure base from which adolescents can confidently explore various aspects of their identity. As adolescents increasingly find independent exploration of new social contexts intriguing and rewarding, peers gain centrality in their lives, offering opportunities to learn through novel experiences with friends.

Furthermore, interactions with both parents and peers provide adolescents with self-relevant feedback that enables them to assess whether their self-perception aligns with how they are perceived by significant others. This feedback serves as a tool for them to strengthen or adjust their identity. Hence, these relationships are fundamental for adolescent mental health and well-being[2,3].

During the latter decades of the 20th century and the first decades of the 21st century, there has been a significant increase in mental health problems among adolescents worldwide. Multiple repeated cross-sectional surveys across the world, with extensive sample sizes ranging from over 100,000 to as high as 915,054 individuals, have indicated declining trends in adolescent mental health over recent decades. Although there are considerable national variations regarding the prevalence and changes over time in adolescent mental well-being, declines have been observed in 36 countries[4]. These declines are particularly noticeable in higher-income countries, especially among girls.

These declines coincide with an increase in perfectionism over the past three decades[5]. Recent generations of young people perceive higher expectations from others, and place more demands on themselves. This heightened pressure to achieve perfection partly accounts for the rise in mental health issues[4]. When perfectionism becomes maladaptive, it might complicate the development of a coherent identity, and result in worrying, rumination, indecisiveness, and negative emotions such as guilt and shame. This might explain the association between perfectionism and mental health problems.

The rise in perfectionism probably stems from a combination of various factors, including the growing prevalence of individualistic and materialistic values in society. These trends foster highly competitive settings and set unattainable standards, contributing to unrealistic expectations for youth. These macro-level societal factors not only intensify adolescents' inclination towards perfectionism and the perceived pressure to excel, but also affect adolescents' pivotal relationships. Interaction dynamics with parents and peers may be characterized by an increasing preoccupation with youth's successes and setbacks.

Puberty and the associated neurodevelopmental changes contribute to changing power dynamics in parent-adolescent relationships, that are often associated with a temporary increase in conflict. However, relationships with parents usually tend to be warm and supportive throughout adolescence around the world[6]. Research illustrates a marked decrease in authoritarian parenting practices over the last decades, transitioning towards more egalitarian practices[7].

However, the increase in warm and supportive parenting tends to coincide with heightened parental overinvolvement, anxious overcontrol, and an inclination toward overprotectiveness. Especially during adolescence, such intrusive parenting practices, despite their well-intentioned nature, might impede healthy development. Furthermore, there has been an increase in parental expectations and criticism[5], which could contribute to the increase in perfectionism and related mental health issues.

Adolescents also face increasing pressure to meet the (perceived) expectations set by their peers, resulting in burgeoning perfectionism and mental health issues. This might have been exacerbated by the widespread use of social media. However, it is important to note that, although trends in mental health problems have been related to social media use[8], the use of social media is not detrimental for adolescent mental health *per se*. Contrary to the presumption that social media undermine genuine peer communication, they primarily function as an extension of offline interactions, predominantly fostering and facilitating social connections, and often yielding positive effects on mental well-being[9]. A poignant example arose during the COVID-19 pandemic, when physical interactions among adolescents significantly decreased, and many of them felt more lonely and experienced more mental health issues. Staying connected with peers online helped alleviate some of these adverse effects of physical isolation.

Whereas social media use can be linked to fewer mental health issues when it fosters positive interactions, enhances social support, and facilitates social connectedness, it tends to be associated with more mental health problems when it becomes excessive, displaces time spent in face-to-face interactions, and involves negative interactions or social comparisons[8]. These risks primarily stem from the characteristics of adolescents or their environment, rather than directly from the use of social media itself[9]. There is also a genuine concern regarding addictive behaviors, where youth struggle to disengage from social media and neglect other crucial aspects of their lives, such as schoolwork, relationships or sleep. Social media provide opportunities for positive self-presentation, which might increase feelings of insecurity, perfectionism and depression among youth who grapple with insecurities and constantly compare themselves to seemingly more successful and socially thriving peers.

Rather than discouraging adolescents from using social media, we need to focus on understanding the individual and environmental factors that predispose youth to the adverse effects of these media. Guiding adolescents toward a healthier engagement with social media can reinforce positive social interactions and minimize potential harm for mental health.

Future research should address the repercussions of societal and technological changes on the way in which adolescents' relationships with both parents and peers are constructed. The prevailing societal trend towards heightened individualism and materialism is fostering increasingly competitive environments and unrealistic expectations. These changes not only directly impact the development of adolescents' identities and mental well-being, but might also affect the nature of their interactions with parents and peers.

Even within the context of warm and supportive parent-adolescent relationships and friendships, these societal changes are likely to influence the perceptions of these relationships, the interaction behaviors, and the interpretation of these behaviors. We need to acquire a more nuanced understanding of the interactions with parents and peers that contribute to the cultivation of perfectionism, which impedes healthy identity development and jeopardizes adolescent mental health.

Perhaps even more important is addressing the macro-level factors that contribute to a societal landscape characterized by increasing competitiveness, economic disparities, and pressure to constantly excel. This socio-cultural context creates an environment in which some youth, along with parents and peers, inadvertently cultivate conditions that breed perfectionism. Therefore, comprehensive research must aim not only to scrutinize the micro-level interactions within relationships, but also to understand the broader societal forces shaping these dynamics.

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1. Branje S, De Moor EM, Spitzer J et al. J Res Adolesc 2021;31:908-27.
2. Smetana JG, Rote WM. Annu Rev Dev Psychol 2019;1:41-68.
3. Schwartz-Mette RA, Shankman J, Dueweke AR et al. Psychol Bull 2020;146:664-700.
4. Cosma A, Stevens G, Martin G et al. J Adolesc Health 2020;66:S50-8.
5. Curran T, Hill AP. Psychol Bull 2022;148:107-28.
6. Branje S. Child Dev Perspect 2018;12:171-6.
7. Trifan TA, Stattin H, Tilton-Weaver L. J Marriage Fam 2014;76:744-61.
8. Twenge JM, Joiner TE, Rogers ML et al. Clin Psychol Sci 2018;6:3-17.
9. Odgers CL, Jensen MR. J Child Psychol Psychiatry 2020;61:336-48.

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Trends, advances and directions in cognitive-behavioral therapy for adolescent anxiety

Adolescence is a time of dramatic change in physical, behavioral, emotional, cognitive and social domains, and the context in which one matures plays a crucial role. The early 2020s provided a unique context for adolescent development, filled with unprecedented events across multiple levels of life. These contextual forces potentially impacted what we know from previously studied developmental trajectories during adolescence.

Here we briefly highlight recent research on adolescent anxiety associated with social media use and the COVID-19 pandemic, and focus on the latest trends and advances in cognitive-behavioral therapy (CBT) for treating anxiety in youth. We emphasize the importance of behavioral exposure tasks and the necessity of "flexibility within fidelity"[1] in manual-based CBT interventions. Lastly, we identify future research directions for evaluating the development, maintenance and treatment of anxiety in adolescents.

Rates of anxiety among youth – as well as depression, suicidality, and other mental health conditions – have increased in recent years. Specifically, anxiety symptoms increased during the COVID-19 pandemic, with 20% of surveyed youth experiencing these symptoms, compared to 11% before the pandemic[2]. Further, across all socioeconomic levels, about 70% of adolescents reported believing that anxiety and depression are major problems among people of their age in their community[3]. Widening disparities in anxiety prevalence have been noted among girls relative to boys, and among sexual minority youth compared to heterosexual ones[2,4].

Adolescents currently face stressors that may contribute to increases in anxiety. The COVID-19 pandemic took a toll on youth psychological well-being, including disrupted milestones, loss of peer interactions, and social isolation[2]. Adolescents are heavy consumers of digital technology and social media: this has the potential to provide benefits to youth through opportunities to strengthen social relationships. However, social media may also lead to an increase in anxiety symptoms. In a longitudinal study of adolescents aged 12-15, those spending more than three hours per day on social media were prospectively more likely to experience internalizing problems (i.e., anxiety and depression[5]). It is not a stretch to see the double-edged features of heavy adolescent social media use.

Recent research continues to bolster the large body of existing evidence demonstrating the efficacy[6] and effectiveness[7] of CBT in treating adolescent anxiety, with the latest studies parsing treatment effects according to intervention modality and emphasis on key components (e.g., psychoeducation, cognitive restructuring, exposure tasks). When comparing CBT modalities to waitlist controls based on anxiety remission at post-treatment, significant benefits for individual, group, family, and remote-based CBT were observed. Individual, family, and remote-based CBT interventions also demonstrated superior remission outcomes relative to attention controls.

Although based on a limited number of comparative efficacy studies, the various treatment modalities did not show differential benefit (e.g., individual-based CBT did not evidence significant benefit compared to other CBT modalities). Albeit comparisons were bound by similar constraints, combined treatment with individual-based CBT and selective serotonin reuptake inhibitors (SSRIs) demonstrated greater effectiveness than either isolated treatment approach[8].

Among the core components of CBT interventions, behavioral experiments (i.e., exposure tasks) are the most impactful. Reinforcing prior research examining treatment outcome associations based on exposure task completion (e.g., amount of in-session exposure tasks), recent CBT interventions have evaluated the effectiveness of treatments that emphasize exposures specifically. Youth anxiety outcomes were examined following randomization to one of two treatments focusing on different core CBT components: an exposure-focused CBT (EF-CBT) characterized by a lack of relaxation components and quicker initiation of exposure tasks, and a relaxation-based treatment[9]. Not only was EF-CBT effective in treating youth anxiety disorders, but it demonstrated greater effectiveness relative to the relaxation-based treatment. Results indicated that EF-CBT yielded "faster and more pronounced" reductions in youth anxiety. Participants randomized to EF-CBT were more likely to complete therapy relative to those receiving the relaxation-based treatment[9].

Advancements in CBT for adolescents highlight the necessity of flexibly implementing manual-based CBT to increase its use and accessibility. Flexibility personalizes treatment based on youth interests (e.g., sports, computers, arts) and needs (e.g., comorbid diagnoses, level of cognitive development). Potential environments for administering CBT also require flexibility: they can include schools, community mental health centers, telehealth and computed-based platforms, and at-home efforts.

Key features of empirically supported treatments remain required, but features can vary based on needs for pragmatic and feasible implementation. Increased provision of CBT mediated by digital devices (brought about by the COVID-19 pandemic) highlighted flexible adjustment strategies and opportunities relative to standard in-person treatment. For example, using facetime or laptop cameras, exposure tasks can occur in an adolescent's real-world environment and be conducted with therapist support[1]. Telehealth platforms make CBT interventions more accessible across geographic regions, enabling youth to both engage in exposures with peers and connect with others with similar mental health concerns.

The future is likely to witness an increasing focus on comparisons of in-person vs. telehealth administrations of treatment for adolescent anxiety. In the same vein, apps for adolescents to use when mastering their anxiety will not only be more prevalent, but will also need proper evaluation. We do not see artificial intelligence replacing a CBT service provider, but we do see telehealth having an increasing presence and impact.

Symptom reduction has been and remains an important goal for mental health service providers. However, we know that there is more to improvement than symptom reduction. Future studies will benefit from examinations of increased self-efficacy and idiographic gains in mastering personal anxiety-producing situations. Treatments for adolescents that address their need for reassurance and/or improve their social interactions will likely augment current approaches.

One can also be hopeful for computer-directed strategies to advance personalizing treatment. Currently, service providers "wing it" as they adapt their work to fit their patients. With machine learning, we can identify features of anxious youth who will respond to the various components of treatment. In other words, the findings from machine learning applied to large, homogenized data sets can inform providers of adaptations that, for the characteristics of a specific client, will likely be optimally effective.

Thus, CBT is now well established as a first-line treatment for adolescent anxiety, but efforts to personalize and augment this empirically supported therapy are likely to spread in the future and impact significantly clinical practice.

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1. Kendall PC, Ney J, Maxwell C et al. Front Psychiatry 2023;14:1067047.
2. Racine N, McArthur BA, Cooke JE et al. JAMA Pediatr 2021;175:1142-50.
3. Horowitz JM, Graf N. Most U.S. teens see anxiety and depression as a major problem among their peers. www.pewresearch.org.
4. Parodi KB, Holt MK, Green JG et al. Soc Psychiatry Psychiatr Epidemiol 2022; 57:127-37.
5. Riehm KE, Feder KA, Tormohlen KN et al. JAMA Psychiatry 2019;76:1266-73.
6. Walkup J, Albano AM, Piacentini J et al. N Engl J Med 2008;359:2753-66.
7. Villabø M, Narayanan M, Compton S et al. J Consult Clin Psychol 2018;86:751-64.
8. Sigurvinsdóttir AL, Jensínudóttir KB, Baldvinsdóttir KD et al. Nord J Psychiatry 2019;74:168-80.
9. Bilek E, Tomlinson RC, Whiteman AS et al. J Clin Child Adolesc Psychol 2022; 51:410-8.

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The Framework for AI Tool Assessment in Mental Health (FAITA - Mental Health): a scale for evaluating AI-powered mental health tools

Even within the ever-evolving landscape of digital mental health interventions, the advent of generative artificial intelligence (GAI), large language models (LLMs), and generative pre-trained transformers (GPTs) represents a paradigm shift. These technologies bring the promise of scalable and personalized diagnostics, psychoeducation and treatment that may help close a stubborn access-to-care gap[1]. At the same time, the risk to patients' health from unmonitored AI-powered care, and to users' data from insecure platforms, presents unprecedented challenges. The enthusiasm and fear that AI mental health offerings simultaneously generate make a comprehensive tool for their systematic assessment a timely necessity.

To our knowledge, no comprehensive scale exists for systematically evaluating AI interventions. Abbasian et al[2] suggested helpful metrics for assessing AI health care conversations, without explicitly tailoring them to mental health. AI scholar L. Eliot[3] advocated rating mental health chatbots by their autonomy or degree of independence from human oversight. Pfohl et al[4] put the focus squarely on evaluating equity and bias. These efforts highlight the need for a comprehensive toolbox for evaluating AI interventions in mental health – one that encompasses autonomy and equity, but also efficacy, user experience, safety and ethical integrity, among other crucial dimensions[5].

Evaluative digital mental health tools that predate the rise of AI provide valuable lessons. The now discontinued nonprofit One Mind PsyberGuide[6] offered reviews of digital mental health apps with a focus on three dimensions: credibility, user experience, and transparency. This framework seemed to fulfill an important role across several constituencies: Psihogios et al[7] praised it in their paper on pediatric mobile health apps; Nesamoney[8] endorsed it for helping app developers and designers; and Garland et al[9] described it as more comprehensive and user-friendly than other app review platforms, including that by the American Psychological Association.

In creating an assessment framework for AI-powered mental health tools, PsyberGuide is a reasonable starting point. Besides short app reviews by users and lengthier expert reviews, it offered scoring guidelines for its dimensions. Given the importance of AI tools "learning" from ongoing feedback and reviews, and of a scoring system that facilitates comparisons across AI offerings, it forms a helpful basis.

Here we introduce the Framework for AI Tool Assessment in Mental Health (FAITA - Mental Health), a structured scale developed by updating PsyberGuide's "credibility", "user experience" and "transparency" dimensions for the AI "age", and incorporating three crucial new dimensions: "user agency", "diversity and inclusivity" and "crisis management" (see supplementary information for the full structured FAITA - Mental Health form).

Our framework reflects awareness of both the potential and challenges of AI tools, and emphasizes evidence base, user-centric design, safety, personalization, cultural sensitivity, and the ethical use of technology. Ultimately, the framework aims to promote "best practices" and to guide industry development of AI technologies that benefit users while respecting their rights. Additionally, the framework seeks to be sufficiently flexible to accommodate continued evolution in the field and, with some minor modifications, adaptation to other medical disciplines impacted by AI (e.g., "FAITA - Genetics").

The framework's first dimension, "credibility", evaluates AI-powered mental health tools according to their scientific underpinnings and user goal achievement capabilities. Integrating the three subdimensions of "proposed goal", "evidence-based content" and "retention", this dimension advocates for interventions that have clear and measurable goals, are grounded in validated research and practices, and can keep users meaningfully engaged over time. Each subdimension is awarded up to 2 points, for a maximum dimension score of 6 for the most "credible" tool.

The second dimension for assessing AI mental health tools, "user experience", addresses more complex interactions than those encountered in static mental health apps. As such, PsyberGuide's "user experience" dimension – with its focus on engagement, functionality and esthetics – was found to be insufficient, and three new subdimensions were incorporated: "personalized adaptability", to evaluate the AI's ability to improve from user feedback over time; "quality of interactions", to evaluate the naturalness of exchanges; and "mechanisms for feedback", to underscore the importance of users' ability to report issues, suggest improvements, and seek assistance. Each subdimension on the "user experience" dimension is awarded up to 2 points, for a maximum dimension score of 6.

The third dimension, "user agency", is new and underlines the importance of empowering users to manage their personal data and treatment choices. It is divided into two subdimensions. The first, "user autonomy, data protection, and privacy", focuses on control over personal health data, clearly worded and user-friendly consent processes, robust data protection protocols, secure storage, and users' ability to actively manage their data. The second, "user empowerment", focuses on users' self-efficacy and capacity for self-management, gauging AI interventions' inclusion of tools that support users' independence, as well as encouraging the application of skills learned using the tool to real-life contexts in ways that prevent dependency on the tool. Each subdimension is awarded up to 2 points, for a maximum "user agency" dimension score of 4.

The fourth dimension, "equity and inclusivity", is also new and consists of two subdimensions: "cultural sensitivity and inclusivity", which assesses a tool's capability to engage with users from diverse cultural backgrounds and emphasizes the need for content recognizing cultural and other identity differences; and "bias and fairness", which addresses the tool's commitment to diversify its training material and remove biases that might impact fairness and equity. Each subdimension is awarded up to 2 points, for a maximum "equity and inclusivity" dimension score of 4.

The fifth dimension, "transparency", remains from PsyberGuide, but now extends beyond data management to include the AI's ownership, funding, business model, development processes, and primary stakeholders. It highlights the importance of providing clear and comprehensive information about operational and business practices, so that users are better equipped to make informed decisions on using such technologies. It also aims to help developers adhere to best practices by disclosing information regarding their tools' intention and governance. The "transparency" dimension carries a maximum score of 2.

Finally, the new sixth dimension of "crisis management" evaluates the safeguarding of user well-being and whether the mental health AI tool provides immediate, effective support in emergencies. It emphasizes comprehensive safety protocols and crisis management features that not only steer users to relevant local resources during crises, but also facilitate follow-through with these resources. The "crisis management" dimension carries a maximum score of 2.

Integrating GAI, LLMs and GPTs into mental health care heralds a promising but complicated new era. The promise of these technologies for delivering personalized, accessible and scalable mental health support is immense. So, unfortunately, are the challenges. We developed the FAITA - Mental Health to equip users, clinicians, researchers, and industry and public health stakeholders with a scale for comprehensively evaluating the quality, safety, integrity and user-centricity of AI-powered mental health tools.

With an overall score ranging from 0 to 24, this scale attempts to capture the complexities of AI-driven mental health care, while accommodating ongoing evolution in the field and possible adaptations to other medical disciplines. Formal research is required to empirically test its strengths, weaknesses, and most pertinent components.

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Supplementary information including the FAITA - Mental Health scale is available at https://www.FAITAmentalhealthscale.com.

1. Torous J, Blease C. World Psychiatry 2024;23:1-2.
2. Abbasian A, Khatibi E, Jain R et al. arXiv 2023;2309.12444.
3. Eliot L. Creatively judging those generative AI mental health advisement chatbots by astutely gauging their levels of AI autonomy. Forbes, December 15, 2023.
4. Pfohl SR, Cole-Lewis H, Sayres R et al. arXiv 2024;2403.12025.
5. Lawrence HR, Schneider RA, Rubin SB et al. arXiv 2024;2403.14814.
6. One Mind. PsyberGuide. https://onemind.org/psyberguide.
7. Psihogios AM, Stiles-Shields C, Neary M. J Pediatr Psychol 2022;45:1106-13.
8. Nesamoney S. International Journal of High School Research 2023;5:104-9.
9. Garland AF, Jenveja AK, Patterson JE. Fam Syst Health 2021;39:155-7.

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The problem with borderline personality disorder

In the late 1980s, the ICD-10 Working Party on Personality Disorders had little evidence on which to base its decisions and, understandably, followed the lead of the DSM, with its well-funded and popular third and subsequent editions.

When the Working Party came to the sensitive subject of individual personality disorders, it found that the evidence for "borderline personality disorder" was insufficient for it to be included. But a lobby of supporters did not allow this, and eventually two extra personality disorder groupings were included under the heading of "emotionally unstable personality disorder" (F60.3) – an "impulsive type" (F60.30), characterized by a "tendency to act unexpectedly" and to show "quarrelsome behaviour" and an "unstable and capricious mood"; and a "borderline type" (F60.31), characterized by uncertain self-image, unstable relationships, efforts to avoid abandonment, and recurrent self-harm.

We have yet to see much evidence that the impulsive type (F60.30) has been used in practice. On the contrary, the borderline type is by far the most commonly used personality disorder diagnosis, so much so that the original splitting of the "emotionally unstable personality disorder" into two groups has been forgotten entirely.

In the ICD-11 revision group, more than two decades later, the same conclusion was reached: borderline personality disorder was not considered to be a suitable diagnosis for inclusion and was ignored, as indeed were all other categories of personality disorder in the new dimensional system[1]. But, as with the ICD-10, the borderline diagnosis was not to be spurned by others. There was general dissatisfaction with its omission[2], and a strong appeal for it to be included in some form. Thus, the "borderline pattern specifier" was added as a compromise[3].

How do we explain that, after two revision groups decided to exclude this condition as unsatisfactory, borderline personality disorder continues to be supported as a diagnosis? The standard explanations are that it is useful in clinical practice, is widely used, and gives options for treatment, unlike other personality disorders. However, the same could be said, almost exactly, of the diagnosis of neurasthenia between 1870 and 1990 (it appeared apologetically in the ICD-10), which has now been recognized to be redundant, as it was vaguely defined, was so prevalent that it lacked discrimination, and became toxic through criticism and stigma.

These same concerns apply to borderline personality disorder. It is like a large bubble wrap over all personality disorders, easily recognized on the surface but obscuring the disorders that lie beneath. Personality abnormality is identifiable through traits that are persistent, exactly as normal personality traits. The features of borderline personality disorder are not traits, but symptoms and fluctuating behaviours[4], and – like many symptomatic conditions – improve steadily over time[5]. When borderline symptoms are examined in factor analytic studies, they are scattered over a range of both personality and other mental disturbance, and have no specificity[6].

All attempts to find a borderline trait have failed. While borderline symptoms appear coherent when examined in isolation, they disappear into a general personality disorder factor when modelled alongside other personality disorder symptoms[7]. Borderline personality disorder symptoms strongly align with all other personality disorder symptoms, and the borderline personality disorder diagnosis is better conceptualized as moderate to severe personality pathology in general[6]. Gunderson and Lyons-Ruth may have been on to something when they identified the core of borderline pathology as interpersonal hypersensitivity, a symptom-behaviour complex present in most personality disorders[8].

An unsatisfactory diagnosis leads to imperfect treatment. Although it appears that there are many treatments available for borderline personality disorder, their value evaporates on analysis. While the treatments are complex, often time-consuming and well-constructed, they are no more effective than good psychiatric care, which now, in our current passion for three-letter acronyms, is called SCM (structured clinical management) or GPM (general psychiatric management). There is confusion over who should receive SCM and GPM and who needs the more complex interventions of dialectic behavioural therapy (DBT), mentalization-based therapy (MBT), transference-focused psychotherapy (TFT), cognitive behavioural therapy (CBT) and cognitive analytic therapy (CAT). Wheeling out stepped care as an answer sounds good but, because the diagnosis is so defective, nobody knows where stepped care is to begin.

An argument might be made that, while criticisms of the borderline personality disorder diagnosis are valid, the term is familiar to clinicians and could be seen as a synonym for moderate to severe personality pathology and lead to appropriate treatment with structured psychotherapy. The problem with this argument is that the term is a major source of stigma. Patients identified as having borderline personality disorder are seen as more difficult to manage even when their behaviour is the same as other patients without the label[9]. Access to treatment for other psychiatric disorders – such as attention-deficit/hyperactivity disorder, substance use disorder or mood disorders – as well as for physical disorders may also become more difficult. The label borderline personality disorder devalues all other symptoms, so that they can be more easily disregarded. This, in turn, increases the sense of alienation that many patients with personality problems already feel.

We argue that the solution is to drop the borderline personality disorder diagnosis and replace it with a more transparent system of describing personality pathology. Since borderline personality disorder diagnoses are highly correlated with overall moderate to severe personality disorder, assessing the level of severity of patient dysfunction is the first step. Many patients with moderate or severe personality disorder will have features now called "borderline", such as emotional dysregulation, interpersonal hypersensitivity and impulsive behaviours, but not everyone. Some will have prominent social and emotional detachment, others perfectionism and stubbornness, or self-centeredness and a lack of empathy. These patients, with personality features described over many centuries, are largely ignored by treating personality disorders with a focus on so-called borderline features.

The new ICD-11 personality disorder classification allows this broader assessment. The dimensional classification of severity – which is divided into personality difficulty and mild, moderate and severe personality disorder – means that clinicians are encouraged to assess overall severity before focusing on specific symptoms and behaviours. The five domains (negative affectivity, detachment, dissociality, disinhibition and anankastia), similar to the Big Five in normal personality, allow a more nuanced description of these symptoms and behaviours, going beyond those encompassed within borderline personality disorder, particularly in the detachment and anankastia domains.

This should lead clinicians to consider the whole spectrum of personality pathology in their patients, rather than losing interest when the borderline personality disorder criteria have been ticked off. A sophisticated formulation would hopefully lead to a range of interventions rather than standard protocol-driven treatment given to everyone. It might also encourage research around treatment for those with non-borderline personality disorder symptoms and traits.

In conclusion, borderline personality disorder may best be seen as a transitional diagnosis which drew attention to patients suffering from moderate to severe personality disorders and encouraged structured psychotherapies to be tested. However, it has now emerged that the diagnosis is not related to specific personality traits, is overinclusive, and does not lead to specific treatments beyond structured clinical care. Its domineering presence in the field means that assessment and treatment of other personality pathology is discouraged, and the whole concept of personality dysfunction is stigmatized. It is time for borderline personality disorder to lie down and die.

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1. Tyrer P, Mulder RT, Kim YR et al. Annu Rev Clin Psychol 2019;15:481-502.
2. Herpertz SC, Huprich SK, Bohus M et al. J Pers Disord 2017;31:577-89.
3. Reed GM. World Psychiatry 2018;17:227-9.
4. Tyrer P. Personal Ment Health 2009;3:86-95.
5. Zanarini MC, Frankenburg FR, Hennen J et al. Am J Psychiatry 2003;160:274-83.
6. Mulder RT, Horwood J, Tyrer P et al. Personal Ment Health 2016;10:84-95.
7. Sharp C, Wright AG, Fowler JC et al. J Abnorm Psychol 2015;124:387-98.
8. Gunderson JG, Lyons-Ruth K. J Pers Disord 2008;22:22-41.
9. Newton-Howes G, Weaver T, Tyrer P. Aust N Z J Psychiatry 2008;42:572-7.

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The ICD-11 CDDR: benefits to health systems and clinical care

At their most basic level, classification systems provide health professionals with tools to assist them in identifying people in need of health services and deciding which treatments are most likely to be effective. Moreover, the World Health Organization (WHO) expects the ICD-11 chapter on mental, behavioural and neurodevelopment disorders to provide its member states with a tool to help them reduce the disease burden associated with these disorders.

The development of the Clinical Descriptions and Diagnostic Requirements for ICD-11 Mental, Behavioural and Neurodevelopmental Disorders (CDDR)[1] was guided by current scientific evidence and best clinical practices. An overarching goal was to enhance the capability of the tool to serve as a global common language to facilitate communication among: a) health workers, who not only make decisions about the nature of mental health problems and what treatment to offer, but also consult and refer to one another; b) service users and caregivers, to help them be informed about the nature of their conditions and engage in decisions about their care; and c) member states, who need to collect and collate data from health encounters in the form of health statistics that are crucial for evidence-based health policy and planning.

To perform these functions, the CDDR must be valid, reliable, and fit for purpose, that is, have clinical utility. Even though advances in neurogenetics and psychophysiology have not provided sufficient basis for new characterizations of mental health conditions, the diagnostic validity of those conditions – that is, the evidence to affirm that the constructs are what they purport to be – has nevertheless been supported by empirical studies of responsiveness to treatment and patterns of clinical outcomes[2]. In retaining or including new diagnostic categories for the CDDR, this evidence was comprehensively reviewed and drawn upon to establish validity. The reliability of the diagnosis of highly burdensome conditions was evaluated by clinician raters of differing levels of experience across diverse country settings.

The WHO also devoted major effort to ensuring that the categories and diagnostic guidance contained in the ICD-11 and CDDR had adequate and demonstrable clinical utility[3]. Drawing on previous work[4], the WHO used a more elaborate definition of clinical utility that included: a) conceptualization (the extent to which the construct or category helps in understanding the patient's health condition); b) goodness of fit (the extent to which the guidelines accurately capture patients' symptomatic presentations and help the clinician to select interventions and make relevant clinical management decisions); and c) ease of use (the feasibility of using the guidelines, especially in clinical settings where, typically, clinicians are often pressed for time).

To facilitate the global use of the CDDR, their applicability across diverse cultures was also a key consideration. First, given its reliance on empirical sources, psychiatric nosology is influenced by where the data come from. A classification that is limited in the sources of data for its development will be constrained in its breadth of applicability. The diversification of sources of data is therefore an important requirement for global applicability. Equally important is an effort to ensure that multiple perspectives are brought to bear in delineating the boundary between normative experiences and clinically significant deviations[5]. Second, an international classification must have flexibility for cultural responsiveness and sensitivity, given that cultures influence the pattern, form and presentation of most mental health conditions.

Diversification of the sources of data was ensured through conducting clinic-based studies in a network of international field study centers. These studies evaluated the clinical utility and usability of the proposed CDDR in natural conditions, as well as the reliability of diagnoses that most commonly bring people to seek care. The settings for the field studies were in 13 countries across all WHO global regions, with the studies conducted in the local language of each country. Complementarily, the WHO established the Global Clinical Practice Network (GCPN), which participated directly in the development of the ICD-11 CDDR through Internet-based field studies.

Irrespective of the quality of the data derived from these studies and the existing scientific literature, judgements still had to be made in defining what constitutes a mental health condition. That is, given the lack of sensitive and specific biomarkers to provide precise delineation of most mental disorders, it is hardly possible that decisions on the classification of these disorders can be made on the sole basis of the strength of the available research evidence. It was therefore imperative that, to enhance the relevance and global applicability of the CDDR, the decisions guiding the classification were made through consensus judgements in which diverse stakeholder groups were involved. Inclusiveness means that these stakeholder groups provided perspectives on what constitutes a deviation from normality[5].

This consideration led the formation of multidisciplinary ICD-11 working groups, with each specifically composed to include representatives from all WHO regions – Africa, the Americas, Europe, the Eastern Mediterranean, Southeast Asia, and the Western Pacific. As in the selection of the field study sites – which included those based in Brazil, China, India, Mexico and Nigeria, countries representing about 43% of the world's population – each of the working groups also had a substantial proportion of experts from low- and middle-income countries.

As noted, cultural factors influence the presentation of mental health conditions, as well as how treatment options are negotiated and accepted by service users. Consideration of cultural factors improves decision-making during the clinical encounter and facilitates the delivery of holistic person-centred care. Attention was therefore given to how to enhance the relevance of the CDDR to the diverse cultural contexts in which they would be used.

Developing a culturally sensitive classification without detracting from the central goal of facilitating global communication required careful attention. The WHO constituted a Working Group on Cultural Considerations[6], which conducted an extensive review of existing evidence about cultural influences on diagnosis and psychopathology for each diagnostic category, including relevant cultural formulations in the ICD-10 and DSM-5. The result is a section on "culture-related features" for each diagnostic category in the CDDR. Designed to be practical and actionable, this section seeks to highlight contextually relevant cultural issues that can support clinicians in making informed decisions about the patient's condition and lived experience, as well as negotiating appropriate intervention options. It does this without detracting from the ability to communicate clinical findings and decisions among providers within and outside the particular cultural setting.

At the beginning of its work, the WHO International Advisory Group – mandated to organize the program of revision activities – noted that, to facilitate access to appropriate mental health services, the identification and treatment of health conditions for which people seek care need to be supported by a classification system that is precise, valid and clinically useful[7]. The results of the field studies show that common and high-burden disorders were diagnosed reliably using the CDDR, and that the requirements can be interpreted consistently across a wide range of countries[8]. Importantly, the CDDR's approach of describing the essential features of each disorder – to reflect real-life patterns of clinical decision-making and avoiding the reification of arbitrary cutoffs or symptom counts – was found to have high clinical utility[9].

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1. World Health Organization. Clinical descriptions and diagnostic requirements for ICD-11 mental, behavioural and neurodevelopmental disorders. https://www.who.int/publications/i/item/9789240077263.
2. Stein DJ, Shoptaw SJ, Vigo DV et al. World Psychiatry 2022;21:393-414.
3. Keeley JW, Reed GM, Roberts MC et al. Am Psychol 2016;71:3-16.
4. First MB, Pincus HA, Levine JB et al. Am J Psychiatry 2004;161:946-54.
5. Gureje O, Stein DJ. Int Rev Psychiatry 2012;24:606-12.
6. Gureje O, Lewis-Fernandez R, Hall BJ et al. BMC Med 2020;18:25.
7. International Advisory Group for the Revision of ICD-11 Mental and Behavioural Disorders. World Psychiatry 2011;10:86-92.
8. Reed GM, Sharan P, Rebello TJ et al. World Psychiatry 2018;17:174-86.
9. Reed GM, Keeley JW, Rebello TJ et al. World Psychiatry 2018;17:306-15.

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Implementation of the ICD-11 CDDR in China

Since 2007, China has been actively collaborating with the World Health Organization (WHO) and international colleagues in the revision, field testing, training, and implementation of the ICD-11 chapter on mental, behavioural and neurodevelopmental disorders, and the related Clinical Descriptions and Diagnostic Requirements (CDDR)[1]. In 2018, the National Health Commission clearly highlighted the importance of the ICD-11 and requested all health care providers in China to use the ICD-11 in their clinical practice[2]. The ICD-11 CDDR are particularly instrumental to achieving this goal in mental health systems in China, as a vast country with over 30 provincial-level administrative regions and a population of more than 1.4 billion.

The Shanghai Mental Health Center (SMHC), as a WHO Collaborating Centre for Research and Training in Mental Health and a National Center for Mental Disorders, has led the field testing and implementation of the ICD-11 CDDR in China[3]. Together with other WHO Collaborating Centers in China, National Centers for Mental Disorders, and prestigious institutions across the country, the SMHC has built a core team for ICD-11 CDDR implementation with over 60 national mental health leaders, including heads of leading mental health institutions and presidents of scientific and professional mental health associations. The implementation of the CDDR in China involves an interrelated and growing set of activities including translation, field testing, research, advocacy and training.

Translation is the cornerstone of implementing the ICD-11 CDDR in China. The translation process started in 2016, and was a collective effort by experts from Shanghai, Beijing and Changsha, coordinated by the SMHC. It was an iterative process involving eight rounds of review and revision over eight years, with 24 translators and 12 reviewers contributing to the work. The final Chinese version of the ICD-11 CDDR is now available for all mental health professionals in China.

In conjunction with the translation process, China conducted field testing of the ICD-11 CDDR from 2016 to 2021, following the protocols provided by the WHO. The SMHC was designated as an International Field Study Centre by the WHO, and the president of the SMHC, Min Zhao, was selected as chair of the ICD-11 International Advisory Group on Training and Implementation.

The Chinese field-testing work involved 2,224 patients, 59 clinical raters, 59 referring clinicians, and 23 research assistants from 10 field testing sites nationwide. The field testing was conducted through a rigorous, multidisciplinary and participatory approach, and the results were submitted to the WHO in 2021 to support the ICD-11 CDDR validation and finalization.

In June 2018, after most of the content in the CDDR had been finalized, the SMHC coordinated efforts with various government and professional agencies to discuss a national training plan. In November 2018, the SMHC launched an official training program, strategically designed to disseminate information in a graduated manner by involving a group of psychiatrists representing various regions in China. These psychiatrists were trained and then coached to become trainers at their institutions.

This training program continues to function, and aims to build a network of trainers and a system to disseminate information to clinicians throughout our vast and populous country cost-effectively. Experts continue to provide more specialized training at academic conferences and educational events. Through various methods and channels, and in collaboration with national associations, societies and other specialized institutions, the SMHC has trained over 5,000 psychiatrists to date.

In addition to the above-mentioned work, a series of research and advocacy activities focusing on the ICD-11 CDDR have been organized in China to facilitate better dissemination and implementation. The SMHC has organized and published a series of papers on the CDDR in the *Chinese Journal of Psychiatry*, the most reputable Chinese psychiatric journal. The series consists of two papers to introduce the CDDR themselves, the progress of their development, and updates on their implementation in China[4,5], and ten papers to introduce significant changes in the diagnosis of major disorders in the ICD-11 CDDR, including anxiety disorders, mood disorders, personality disorders, schizophrenia and other primary psychotic disorders, neurodevelopmental disorders, and disorders due to substance use.

Notably, the series also includes one paper discussing the research progress and controversy related to gaming disorder as a new mental disorder in the ICD-11[6]. Moreover, as knowledge and expertise on gaming disorder are currently lacking in China, the SMHC has led studies and developed a screening tool in Chinese, provided public health recommendations[7], contributed to the WHO collaborative project on the development of new international screening and diagnostic instruments for the disorder[8], and organized webinars to enhance the capacity for evaluating and treating the disorder, in collaboration with the WHO and other important partners.

Over more than 15 years of work, several factors have contributed to China's successful implementation of the CDDR. First, China's government plays a crucial role in setting and promoting international standards in national health care. Strong government endorsement for the ICD-11 provides an excellent climate for implementing and disseminating the CDDR. Second, identifying and empowering a local champion for implementing the CDDR in China is essential for providing leadership, overall coordination, resource mobilization, training, quality assurance, change management, and sustainability. Entrusted by the WHO, the SMHC has led implementation efforts and played a vital role in dealing with the immense challenges of implementing a new classification system. Third, public awareness campaigns and stakeholder engagement initiatives have raised knowledge of the benefits of ICD-11 CDDR implementation. Involving stakeholders such as the WHO, the National Health Commission, professional associations, leading research centers, health care professionals, and patient advocacy groups can help foster sustainable momentum and gain essential support for the implementation, contributing to its success.

In the future, we will continue promoting the utilization and dissemination of the ICD-11 CDDR in China, ultimately aiming to scale up mental health care in the country[9]. First, we will continue to deliver nation-wide training on the ICD-11 CDDR for mental health professionals, including psychiatrists, psychologists, general doctors, nurses, social workers, as well as health managers and policy makers. Second, an interactive network for adoption of the ICD-11 CDDR will be developed to advance research, training and clinical initiatives, thereby enhancing the quality of mental health care in the country. Third, further activities – such as developing new auxiliary diagnostic tools, screening tools, and teaching curricula based on the ICD-11 – will be undertaken to facilitate the local adaptation and application of the ICD-11 and the CDDR. Finally, China will continue strengthening international cooperation with international psychiatric experts and organizations to enhance mental health globally.

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1. World Health Organization. Clinical descriptions and diagnostic requirements for ICD-11 mental, behavioural and neurodevelopmental disorders. https://www.who.int/publications/i/item/9789240077263.
2. National Health Commission of the People's Republic of China. Notice on Issuing the Chinese Version of the Eleventh Revision of the International Classification of Diseases (ICD-11). Beijing: National Health Commission of the People's Republic of China, 2018.
3. GCP Network. Network perspectives: ICD-11 implementation in China: interview with Dr. Min Zhao and Dr. Jiang Long. https://gcp.network.
4. Dai Y, Xiao Z, Zhao M et al. Chinese J Psychiatry 2015;48:126-7.
5. Huang J, Zhao M, Xiao Z et al. Chinese J Psychiatry 2017;50:340-4.
6. Zhong N, Du J, Poznyak V et al. Chinese J Psychiatry 2018;51:149-52.
7. Zhao M, Hao W. Gen Psychiatr 2019;32:e100086.
8. Carragher N, Billieux J, Bowden-Jones H et al. Addiction 2022;117:2119-21.
9. Long J, Chen J, Xie B et al. Lancet 2022;400:732.

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How the ICD-11 and the CDDR address the public health dimensions of substance use

The use of psychoactive substances is highly prevalent and contributes substantially to risk behaviours, morbidity and mortality. The United Nations Office on Drugs and Crime World Drug Report[1] estimated that, in 2021, one in every 17 people aged 15-64 in the world had used an illicit drug in the year before. Users increased from 240 million in 2011 to 296 million in 2021, substantially more than accounted for by population growth.

Cannabis continued to be the most used illicit drug (219 million users, 4.3% of the global adult population); 36 million people had used amphetamines, 22 million cocaine, and 20 million methylenedioxymethamphetamine (MDMA or "ecstasy") or related drugs in the previous year. An estimated 60 million people engaged in non-medical opioid use, 31.5 million of whom used opiates (i.e., non-synthetic opioids; mainly heroin).

Globally, there is very limited implementation of efficient and effective prevention strategies for substance use[2], and there is a substantial treatment gap for disorders due to this use[3]. Global evidence has called attention to the need for a new and comprehensive conceptualization of substance use disorders that incorporates the full range of relevant conditions, from risky consumption to mental disorders linked to harmful drug use[4].

In response to these challenges, the World Health Organization (WHO) adopted a public health approach to the development of the classification of disorders due to substance use in the ICD-11. By public health approach, we refer to a broader perspective that integrates health and social aspects, aiming to benefit affected individuals and their community, and focusing on population well-being[5].

From a public health perspective, it is essential to identify persons who exhibit a hazardous use of substances that increases the risk of harmful psychological or medical consequences, but whose symptoms do not meet the diagnostic requirements for substance use disorders. These individuals can benefit from education, prevention, and community interventions. People with diagnosable disorders need harm reduction and treatment services of differing intensities and settings, depending on the nature of their condition and the substance involved. Those who suffer physical or psychological harm due to others' substance use should also be identified and may require services[6].

In line with this perspective, the range of psychoactive substances classified in the ICD-11 section on disorders due to substance use has been expanded, reflecting changes in the substances associated with public health impact in different parts of the world. An extended set of substance classes will help track patterns more accurately, in order to formulate appropriate clinical and social policy responses nationally and globally. For example, a new set of categories for disorders due to synthetic cannabinoids has been added. Synthetic cannabinoids are sprayed on natural herb mixtures to mimic the euphoric effect of cannabis, and can produce respiratory depression[7]. Their use is reported in high-income countries, but little information is available for low- and middle-income countries[1].

As described in the Clinical Descriptions and Diagnostic Requirements for ICD-11 Mental, Behavioural and Neurodevelopmental Disorders (CDDR)[8], four primary conditions are identified for each class of psychoactive substances, which are hierarchically and mutually exclusive from one another: a) *hazardous substance use*, which is conceptualized as a pattern of substance use that is sufficient in frequency or quantity to increase the risk of harmful physical or mental health consequences to the user or to others; since it involves incremental risk for harm that has not yet occurred, it is not considered a mental disorder (rather, it appears in the ICD-11 chapter on "Factors influencing health status or contact with health services", facilitating early attention and advice from health professionals); b) *episode of harmful substance use*, which refers to an episode that has already caused harm to a person's physical or mental health or has resulted in behaviour leading to harm to the health of others, but in the absence of a known pattern of substance use; c) *harmful pattern of substance use*, a sub-dependence diagnosis, characterized by a persistent and repetitive pattern of substance use that has directly caused harm to the person or to someone else through the person's behaviour; and d) *substance dependence*, when a disorder of substance use regulation has arisen from repeated or continuous use of a substance, typically accompanied by a strong internal drive to use it.

In the ICD-11, the substance dependence diagnosis has been simplified with respect to the ICD-10. It is based on the presence of at least two of three key features: a) impaired control over substance use, b) increasing priority given to substance use over other activities, and c) physiological features of tolerance or withdrawal. Physical and mental harm is very commonly seen in substance dependence, but is not a required feature.

The CDDR indicate that clinicians may assign other substance use diagnoses in addition to one of the four primary diagnoses, depending on the specific clinical situation, including substance intoxication, substance withdrawal, and a range of substance-induced mental disorders (delirium; psychotic, mood, anxiety, obsessive-compulsive, and impulse control disorders)[8]. Additional medical diagnoses can be assigned as appropriate to describe the consequences of substance use. Clinicians can also apply a range of specifiers offering more precision in diagnosis according to the severity, course, or other manifestations of the primary and additional diagnoses.

The classification of conditions related to substance use in the ICD-11 clearly corresponds to different types of intervention needs, consistent with the WHO services pyramid framework describing the optimal mix of services for mental health[9]. Hazardous use is an appropriate target for brief interventions as well as for public health programs and primary prevention. Harmful use can be responded to in generalist settings, such as primary care, using mild or more intensive interventions depending on whether the problem is a single episode or a harmful pattern of use, and on the substance involved. The most severe cases of substance dependence are appropriately treated in more intensive specialized settings, but they represent only a small portion of the overall disease burden related to substance use. Accordingly, the ICD-11 and the CDDR will help clinicians conceptualize and communicate the most appropriate forms of treatment for specific disorders, and support public health interventions for more common but less severe presentations.

Overall, the ICD-11 and the CDDR are valuable tools for helping to reduce the gap between those who need treatment and those who receive it. They will also support improvements in drug and health policies through better characterization of different groups of people affected by substance use, who experience different types of harm and have different needs. This includes improvements in the treatment system to provide more effective alternatives for severe alcohol and drug dependence.

Implementing the new diagnostic requirements can also support a better referral system that matches the needs of different users to the services provided. It can also support improved epidemiological studies and generate more valuable data for WHO member states by providing better categories that accurately reflect substance use outcomes. Finally, and importantly, the new classification supports implementing a public health model rather than focusing only on punishment and incarceration.

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1. UN Office on Drugs and Crime. World drug report 2023. www.unodc.org.
2. UN Office on Drugs and Crime and World Health Organization. International standards on drug use prevention, 2nd ed. Vienna: UN Office on Drugs and Crime and World Health Organization, 2018.
3. Poznyak V, Reed GM, Medina-Mora ME. Epidemiol Psychiatr Sci 2018;27:212-8.
4. Reed GM, First MB, Kogan CS et al. World Psychiatry 2019;18:3-19.
5. Crépault JF, Russell C, Watson TM et al. Int J Drug Policy 2023;112:103958.
6. Lund IO, Bukten A. Subst Abuse 2015;9(Suppl. 2):33-8.
7. Alves VL, Gonçalves JL, Aguiar J et al. Crit Rev Toxicol 2020;50:359-82.
8. World Health Organization. Clinical descriptions and diagnostic requirements for ICD-11 mental, behavioural and neurodevelopmental disorders. https://www.who.int/publications/i/item/9789240077263.
9. World Health Organization. Improving health systems and services for mental health. Geneva: World Health Organization, 2009.

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Effects of cannabidiol on symptoms in people at clinical high risk for psychosis

There is an unmet treatment need for people at clinical high risk (CHR) for psychosis[1]. As only a minority of them go on to develop a psychotic disorder, interventions need to be particularly safe and well tolerated.

Cannabidiol (CBD), a non-intoxicating constituent of cannabis, has potential anxiolytic and antipsychotic properties[2] and a good safety profile. In two out of three clinical trials in patients with established psychosis, evidence of its antipsychotic efficacy has been reported[3-5]. However, there have not been trials of a period of treatment with CBD in CHR individuals. We assessed the clinical effects of a course of CBD treatment in people with a CHR state following a protocol approved by the National Research Ethics Service Committee London (Camberwell, St. Giles) (ISRCTN46322781).

The study was conducted on antipsychotic-naïve subjects attending early detection services in the UK who met one or more criteria for CHR state for psychosis: a) attenuated psychotic symptoms; b) brief limited intermittent psychosis (i.e., a psychotic episode lasting <1 week which remitted without treatment); c) recent functional decline and either schizotypal personality disorder or first-degree relative with psychosis. Key exclusion criteria were history of previous psychotic disorder or manic episode, neurological disorder, or current DSM-IV diagnosis of substance dependence.

Thirty-three subjects were recruited after they provided written informed consent. They were advised to refrain from using cannabis for 96 hours, alcohol for a minimum of 24 hours, nicotine for 6 hours, and any other recreational drugs for 2 weeks before entering the study, and to continue to refrain from using cannabis or other recreational drugs during the course of the study. Baseline assessments included the Comprehensive Assessment of At-Risk Mental States (CAARMS)[6]; the Spielberger State-Trait Anxiety Inventory, State Subscale (STAI-S)[7]; and the Positive and Negative Syndrome Scale (PANSS)[8].

Using a parallel group, double-blind, placebo-controlled design, participants were randomly allocated to either CBD (N=16) or placebo (N=17). They received either a CBD capsule or an identical-looking placebo capsule as a single daily oral dose, which they continued for 21 days. The dose of CBD (99.9% pure) was 600 mg/day, found to be effective and well-tolerated previously[4,9]. All clinical assessments were repeated after 7 and 21 days of treatment, except for the CAARMS, which was administered at baseline and at the end of treatment. Blood samples were collected before and after taking the study drug on days 1 and 21 to assay CBD plasma levels. The effects of treatment on symptoms were examined using analyses of variance with treatment (CBD vs. placebo) as the between-subject factor after controlling for baseline scores.

At baseline, the two treatment groups were comparable in demographic and clinical variables (see supplementary information). None of the participants received any psychotropic medication other than CBD or placebo during the course of the study. Two participants dropped out from the placebo arm. Following 21-day treatment (intention-to-treat, last observation carried forward analysis), CBD-treated participants had a lower total CAARMS score ($F_{1,30}$=7.168, p=0.012) than those receiving placebo, after controlling for baseline score. There were no significant differences between the treatment groups in the incidence of treatment-emergent side effects (see also supplementary information).

The CBD group also reported less distress associated with psychotic symptoms ($F_{1,30}$=4.66, p=0.039) and had a lower PANSS total score (p=0.042), after controlling for the respective baseline values. There was a greater reduction in the CAARMS negative symptoms (p=0.045), but not in the CAARMS positive symptoms (p=0.144), in CBD-treated patients. State anxiety levels following treatment were not different between the two groups (p=0.862).

When the analyses were restricted to participants with complete data for the respective measures, the CBD-treated group again had a lower total CAARMS score (p=0.033), with a trend for less distress associated with psychotic symptoms (p=0.072) and a lower total PANSS score (p=0.056). There were no group differences in the mean number of pills missed (p=0.85) or the proportion of patients who missed at least one pill (p=1.00). CBD levels were detectable in all except one out of 15 CBD participants with available data (see also supplementary information).

These data provide the first evidence that CBD can ameliorate symptoms in the CHR population. We found that treatment with CBD for three weeks was accompanied by a reduction in the severity of CHR symptoms and the distress associated with psychotic experiences. As we did not find an effect of CBD on the STAI-S score, these effects were unlikely to be driven by a reduction in state anxiety.

Recent meta-analyses suggest that existing pharmacological and psychological treatments have little effect on symptoms or the incidence of psychosis in CHR subjects[1], and there is currently no licensed treatment for this population. Consistent with previous evidence[3-5], the incidence of adverse effects in the CBD-treated group was not different from the placebo-treated group, making CBD a good candidate treatment for CHR subjects. No subject dropped out of the CBD arm.

A limitation of the study is the small sample size, underscoring the preliminary nature of the evidence. Because treatment was limited to 21 days, we were not able to examine the effect of treatment on the risk of later transition to psychosis. As some clinical outcome data were missing, we analyzed effects on clinical outcomes using a last observation carried forward method of imputation. However, when we subsequently repeated the analyses but restricted inclusion to participants with complete data for the respective measures, the main results remained unchanged.

Our findings indicate that short-term treatment with CBD can ameliorate the symptoms of CHR state for psychosis, and is well tolerated. These results highlight the potential of CBD as a novel treatment for psychosis, and the need for large-scale efficacy studies to further evaluate its clinical utility.

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1. Davies C, Cipriani A, Ioannidis JPA et al. World Psychiatry 2018;17:196-209.
2. Davies C, Bhattacharyya S. Ther Adv Psychopharmacol 2019;9:2045125319881916.
3. Boggs DL, Surti T, Gupta A et al. Psychopharmacology 2018;235:1923-32.
4. Leweke FM, Piomelli D, Pahlisch F et al. Transl Psychiatry 2012;2:e94.
5. McGuire P, Robson P, Cubala WJ et al. Am J Psychiatry 2018;175:225-31.
6. Yung AR, Yuen HP, McGorry PD et al. Aust N Z J Psychiatry 2005;39:964-71.
7. Spielberger C. Manual of the State-Trait Anxiety Inventory. Palo Alto: Consulting Psychologists Press, 1983.
8. Kay SR, Fiszbein A, Opler LA. Schizophr Bull 1987;13:261-76.
9. Bhattacharyya S, Morrison PD, Fusar-Poli P et al. Neuropsychopharmacology 2010;35:764-74.

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Impact of pre-trauma recreational drug use on mental health outcomes among survivors of the Israeli Nova Festival terrorist attack

On October 7, 2023, about 4,000 civilians attending the Nova open-air music festival in southern Israel were the victims of a sudden terrorist attack. They had to swiftly react to the attack by running and hiding for extended periods of time to protect their lives.

At the time of the attack, a significant proportion of these people were under the influence of various recreational drugs. We hypothesized that the pre-trauma use of psychostimulants or hallucinogens would be significantly associated with the severity of peri-traumatic dissociation, anxiety, depression, and acute stress disorder (ASD) symptoms in survivors of the attack.

Two hundred thirty-two survivors sought assistance at the Chaim Sheba Medical Center and underwent clinical evaluation. They were considered for this study if they had no severe physical injuries; no first-degree family member killed during the attack; and no history of mental disorders, including post-traumatic stress disorder (PTSD).

Of the 232 survivors screened for the study, 126 met the above criteria and provided informed consent to participate. However, two of them who reported using hallucinogenic mushrooms, and one who reported using ketamine prior to the traumatic event, were excluded from the analysis, due to the small sample size for these drugs, leaving a sample of 123 participants. Their mean age (±SE) was 28.4±0.7 years; 75 of them (60.9%) were male; 68.9% were never married, and 68.2% were holding a high-school degree or equivalent.

Seventy-one of them (57.7%) reported using psychoactive drugs at the festival – 12 only alcohol, nine only lysergic acid (LSD), seven only 3,4-methylenedioxymethamphetamine (MDMA), six only cannabis, three only methylmethcathinone (MMC), 15 various drug combinations including alcohol, and 19 various drug combinations excluding alcohol.

All participants completed several questionnaires, assessing peri-traumatic dissociation (Peritraumatic Dissociative Experiences Questionnaire, PDEQ), post-traumatic anxiety (Generalized Anxiety Disorder-7, GAD-7; and Visual Analog Scale for Anxiety, VAS-A), depression (Patient Health Questionnaire-9, PHQ-9), and ASD symptoms (Posttraumatic Diagnostic Scale, PDS-5).

Both the GAD-7 scores and the PDS-5 hyperarousal scores were significantly higher in the drug-user than in the drug-free group ($p<0.05$ and $p<0.008$, respectively). The scores of most participants were above the clinical threshold for these instruments (>10 for GAD-7 in 70.4%, and >28 for PDS-5 in 81.3% of the participants), indicating a very high level of anxiety- and hyperarousal-related symptoms in both groups. Both the PDEQ and PHQ-9 scores were higher in the drug-user than in the drug-free group, but the differences were not significant. No significant differences were found between the groups in the VAS-A, total PDS-5, and PDS-5 subscales. The VAS-A scores of 51.9% of the participants were higher than 6, which is the clinical threshold for this instrument.

A multiple regression analysis was performed on the scores of the PDEQ, PHQ-9, GAD-7, PDS-5 (total and subscales), and VAS-A questionnaires, employing nine sets of independent variables related to drug use, gender and age (see supplementary information).

The multiple regression model for the PDEQ scores was statistically significant ($p=0.018$). The severity of peri-traumatic dissociation was significantly correlated with alcohol consumption prior to the event ($\beta=0.25$, $p<0.008$), but not with the consumption of any other drug. Consuming alcohol prior to the traumatic event, as compared with consuming other drugs, significantly increased the likelihood of experiencing peri-traumatic dissociation (PDEQ score = 24.8±2.0 vs. 19.3±1.0, $p<0.015$).

The model for the PHQ-9 scores was statistically significant ($p=0.02$). The severity of depressive symptoms was significantly correlated with alcohol consumption prior to the event ($\beta=0.32$, $p<0.001$), but not with the consumption of any other drug. Consuming alcohol prior to the event, as compared with consuming other drugs, significantly increased the likelihood of depressive symptoms (PHQ-9 score = 18.7±1.8 vs. 13.8±0.6, $p<0.0015$).

The model for the GAD-7 scores was statistically significant ($p=0.04$). The severity of anxiety symptoms was significantly correlated with alcohol consumption prior to the event ($\beta=0.29$, $p<0.002$). Consuming alcohol, as compared with consuming other drugs prior to the event, significantly increased the likelihood of anxiety (GAD-7 score = 16.3±1.0 vs. 12.7±0.6, $p<0.004$). None of the other drugs consumed prior to the event significantly affected symptoms of anxiety.

The model for the PDS-5 arousal-hyperactivity scores was statistically significant ($p=0.03$). The severity of arousal and hyperactivity symptoms was significantly correlated with alcohol ($\beta=0.24$, $p<0.011$) and MMC ($\beta=0.24$, $p<0.011$) consumption prior to the traumatic event. Both alcohol and MMC consumption significantly increased the likelihood of experiencing arousal and hyperactivity symptoms, as compared with the consumption of other drugs.

The multiple regression analysis of the PDEQ dissociation score with VAS-A, GAD-7, PHQ-9, and PDS-5 subscale scores, including gender and age, was statistically significant ($p=0.0001$). Experiencing peri-traumatic dissociation was significantly correlated with the VAS-A score ($\beta=0.31$, $p<0.02$) and with the PDS-5 mood score ($\beta=0.28$, $p<0.045$).

A mediation analysis showed that pre-trauma alcohol consumption positively predicted PDS-5 mood scores ($\beta=0.15$, $p=0.03$), PDS-5 arousal scores ($\beta=0.16$, $p=0.015$), PDS-5 intrusive scores ($\beta=0.23$, $p=0.001$), GAD-7 anxiety scores ($\beta=0.20$, $p=0.0015$), PHQ-9 depression scores ($\beta=0.24$, $p=0.00025$), and PDEQ peri-traumatic dissociation scores ($\beta=0.20$, $p=0.01$). With the introduction of the peri-traumatic dissociation variable into the model as a potential mediator, the association between alcohol consumption and PDS-5 mood, PDS-5 intrusive, GAD-7 anxiety and PHQ-9 depressive scores became less significant ($p<0.04$, $p<0.015$, $p<0.015$ and $p<0.02$, respectively). This finding suggests that peri-traumatic dissociation partially mediated the association between alcohol consumption and mood, intrusion, anxiety and depressive symptoms.

So, in marked contrast to our expectations, we found that only pre-trauma alcohol consumption, with or without other drugs, significantly increased the risk of peri-traumatic dissociation, anxiety, depression, and ASD symptoms.

Alcohol consumption exerts various effects on brain functions and behavior, ranging from anxiolytic and mild disinhibitory effects to sedation, motor incoordination, altered memory and emotional processing[1,2]. Therefore, pre-trauma alcohol consumption may have interfered with the cognitive, emotional and physiological processes necessary to cope with the traumatic event. The previously available evidence on the effect of pre-trauma alcohol use on the development of post-traumatic symptomatology was mixed[3-7].

Importantly, the traumatic event was prolonged (participants had to run and hide for 8-20 hours until they were rescued). Therefore, the survivors may have experienced a hangover, which could have increased their anxiety and traumatic stress[8].

We also found that peri-traumatic dissociation significantly increased the likelihood of subsequent anxiety and mood symptoms in participants who consumed alcohol. Peri-traumatic dissociation can potentially disrupt the processing and integration of traumatic memories, which may impede recovery and increase the probability of developing post-traumatic disorders, because trauma-related memories persist in a fragmented and unprocessed state[9].

The Nova massacre provides a unique opportunity to study how pre-trauma drug consumption affects post-trauma mental health outcomes. Yet, our study is not devoid of limitations. First, as in all naturalistic studies, the sample size is constrained. Second, we relied only on the reports of the participants on their consumption of drugs, rather than on measurements of blood concentrations and data regarding the actual quantities of the consumed substances, which hampers a more nuanced understanding of the correlation between drug consumption and the observed outcomes.

Nonetheless, this study presents novel insights into the relationship between pre-trauma alcohol consumption and increased vulnerability to peri-traumatic dissociation, anxiety, depression, and ASD symptoms. Given the widespread prevalence of alcohol consumption in social gatherings – and the increasing occurrence of sexual assaults, physical assaults and vehicular accidents – these findings can have a social and clinical interest. Moreover, since alcohol is a compound with a known pharmacology and mode of action, they can be relevant to the elucidation of the biology of response to traumatic experiences.

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1. Fairbairn CE, Kang D, Federmeier KD. Biol Psychiatry 2021;89:990-1000.
2. Harrison NL, Skelly MJ, Grosserode EK et al. Neuropharmacology 2017;122:36-45.
3. Maes M, Delmeire L, Mylle J et al. J Affect Disord 2001;63:113-21.
4. Mellman TA, Ramos J, David D et al. Depress Anxiety 1998;7:145.
5. Blanchard RJ, Magee L, Veniegas R et al. Prog Neuropsychopharmacol Biol Psychiatry 1993;17:171-82.
6. Zatzick DF, Kang SM, Müller HG et al. Am J Psychiatry 2002;159:941-6.
7. Richmond TS, Kauder D. J Trauma Stress 2000;13:681-92.
8. Verster JC, Scholey A, van de Loo A et al. J Clin Med 2020;9:823.
9. Thompson-Hollands J, Jun JJ, Sloan DM. J Trauma Stress 2017;30:190-4.

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Prevention, treatment and care of substance use disorders among adolescents. Statement by the UNODC-WHO Informal Scientific Network, 2024

Since 2014, the United Nations Office on Drugs and Crime (UNODC) - World Health Organization (WHO) Informal Scientific Network (ISN) has brought the voice of science to international drug policy discussions at the Commission on Narcotic Drugs, the drug-control policy-making body of the United Nations (UN). The public health dimensions of substance use, including prevention and treatment of substance use disorders, have become prominent in policy debates within the UN system.

Adolescence, which is the focus of this ISN statement, has been defined as individuals aged between 10 and 19 years[1]. While no global data on substance use within this full age range could be located, global data among more limited subsets are available. Alcohol is the most commonly used substance among all people 15+ years of age[2]: 155 million, i.e. more than a quarter (26.5%) of all those aged 15-19, are current drinkers. In addition, the 15-19 age group exhibits higher rates of heavy episodic drinking when compared to the total population of drinkers[3]. Cannabis is the internationally controlled substance most widely used by adolescents, and its use among 15-16-year-olds varies by region, from less than 3% annual prevalence in Asia to over 17% in Oceania. In most geographical areas, the proportion of adolescents using cannabis is higher than in the general population aged 15-64[3].

Consistent with Sustainable Development Goals[4] and other international commitments[5], UN Member States called for comprehensive, evidence-based prevention of substance use, including early prevention[6] and available, accessible, diverse, evidence-based treatment and care for children and young people with substance use disorders[7]. There is a joint responsibility for policy makers, scientists, service providers, and communities to implement effective demand-reduction strategies and to adequately address prevention, treatment and recovery support, as well as measures to reduce the negative health and social consequences of substance use disorders among adolescents.

The UNODC-WHO ISN makes the following recommendations:

- Expand the availability and use of evidence-based prevention, treatment and care strategies and interventions for adolescents, and ensure sustainable funding for their implementation.
- Facilitate the availability of evidence-based prevention programs in the public domain with reimbursement schemes, thus allowing for preventive interventions to be inclusive and to address the needs of socio-economically disadvantaged groups, ensuring that minoritized populations, Indigenous groups; and lesbian, gay, bisexual, transgender, queer and questioning (LGBTQ+) people are included.
- Promote population-based and environmental prevention measures, such as enforcing restrictions on commercial or public availability of legally available psychoactive substances; restricting advertising, sponsorship and promotion of such substances; and addressing the role of social and commercial determinants of health and their impact on substance use.
- Strengthen the meaningful engagement of priority groups in prevention initiatives and overcome barriers to participation, such as stigmatization. As an important youth-empowerment strategy, include adolescents not only as recipients but also as trained actors leading prevention initiatives.
- Incentivize the deployment of effective, evidence-based preventive interventions in different settings, including health care, educational systems, communities, and juvenile justice settings.
- Widely implement screening for mental health conditions among adolescents to help prevent and treat associated substance use disorders and improve overall health outcomes.
- Implement evidence-based treatment interventions for adolescents along a continuum of care that includes screening,

brief interventions, and treatments such as family therapy, contingency management, and cognitive behavioral therapies. These interventions may address mental health conditions and pharmacological treatment options in appropriate cases.
- Ensure that, when engaging with treatment and care services, adolescents are reassured that they will receive quality treatment and safe support without fear of discrimination or negative repercussions, as it should be for any other health condition.
- Adolescents with a history of substance use and substance use disorders face an increased risk of contact with the criminal justice system and, in some contexts, might be more vulnerable to exploitation by organized crime groups. Therefore, strengthen interventions aimed at fostering safer living environments, proven to protect against organized crime involvement.
- Implement evidence-based and ethically sound digital interventions that are continuously monitored for outcomes and unintended negative consequences, while being mindful of the digital gap and associated inequalities.
- Ensure that humanitarian emergency preparedness and response plans consider how to address substance use and substance use disorders, including among adolescents, to strengthen the resilience of support systems during these emergencies, including in conflicts, war settings, natural disasters, forced migration, and other situations of displacement.
- Expand and improve capacities to ensure a qualified and diverse workforce to deliver health interventions for adolescents with substance use disorders, and thus improve service coverage and reduce health disparities. Apply online and remote learning elements to strengthen the prevention and treatment workforce.
- Ensure sufficient resource allocation to develop or maintain comprehensive and differential (e.g., age and gender disaggregated) data collection systems to analyze adolescent substance use trends and evaluate the effectiveness of prevention and treatment programs.
- Invest in evidence-based prevention and treatment of substance use disorders among adolescents, and in related research to enhance the understanding of these disorders among adolescents (including biopsychosocial risk and protective factors), to inform effective prevention and treatment strategies for adolescents in different circumstances.

Children and young people, including adolescents, are a precious asset for all countries and must be protected from the health and social effects of substance use disorders. Scientists, policy makers, practitioners and communities must work together to implement the most effective prevention and treatment strategies, policies and interventions, such as those outlined in the UNODC-WHO International Standards for Drug Use Prevention and the UNODC-WHO International Standards for Treatment of Drug Use Disorders. The ISN recommends that policy makers put evidence-based and ethical policies for adolescent substance use and substance use disorders into practice, with the necessary resources, so that every adolescent can attain the highest level of health.

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1. United Nations Children's Fund. Investing in a safe, healthy and productive transition from childhood to adulthood is critical. https://data.unicef.org/topic/adolescents/overview.
2. World Health Organization. Global status report on alcohol and health. Geneva: World Health Organization, 2018.
3. United Nations Office on Drugs and Crime. World drug report. Vienna: United Nations Office on Drugs and Crime, 2023.
4. United Nations Department of Economic and Social Affairs. Sustainable development: the 17 goals. https://sdgs.un.org/goals.
5. United Nations Office on Drugs and Crime. Our joint commitment to effectively addressing and countering the world drug problem. Vienna: United Nations Office on Drugs and Crime, 2016.
6. United Nations Office on Drugs and Crime. Promoting comprehensive and scientific evidence-based early prevention. Vienna: United Nations Office on Drugs and Crime, 2021.
7. United Nations Office on Drugs and Crime. Supporting the availability, accessibility and diversity of scientific evidence-based treatment and care for children and young people with substance use disorders. Vienna: United Nations Office on Drugs and Crime, 2015.

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An update from the WPA Section on Anxiety and Obsessive-Compulsive Disorders

The WPA Section on Anxiety and Obsessive-Compulsive Disorders focuses its activities on a broad range of common and burdensome psychiatric conditions encompassing anxiety and fear-related disorders, obsessive-compulsive and related disorders, and behavioural addiction disorders, including problematic Internet use. This is an exciting area of developing clinical practice, as anxiety and obsessive-compulsive symptoms are increasingly played out in the digital environment.

The Section provides a forum for clinician scientists and academics to exchange experiences and research advances. It organizes activities at WPA meetings, produces scientific publications and develops guidance on relevant topics, in collaboration with key stakeholder groups such as the World Health Organization (WHO), the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS) (www.icocs.org), the Anxiety Disorders and Obsessive-Compulsive Research Networks of the European College of Neuropsychopharmacology (ECNP) (www.ecnp.eu), and the European Network for Problematic Usage of the Internet (www.internetandme.eu). Here we review some of the Section's recent initiatives and its ambitions for the next five years.

The ICD-11 has refined and expanded the classification of anxiety disorders, and created two new groupings, one for Obsessive-Compulsive and Related Disorders and another for Disorders due to Addictive Behaviours, including several new diagnoses.

The ICD-11 grouping of Anxiety or Fear-Related Disorders differentiates fear-related disorders (i.e., phobias related to discrete aversive situations) from anxiety disorders related to a sustained expectation that diffuse aversive events will occur. Separation anxiety disorder and selective mutism have been moved into this grouping.

Obsessive-compulsive and related disorders often present late for treatment, resulting in poor clinical outcomes. To improve recognition and diagnosis, some members of our Section worked with the WHO to reclassify disparate diagnoses into a single Obsessive-Compulsive and Related Disorders grouping. A seminal field study demonstrated that health care practitioners make more accurate diagnoses of these disorders using the ICD-11 vs. ICD-10[1]. Moreover, this new classification has advanced research heuristics establishing compulsivity as a transdiagnostic neuropsychological domain.

Another new ICD-11 grouping was created for Disorders due to Addictive Behaviours. This includes two new disorders – gaming disorder and gambling disorder (on- or off-line) – and a residual category for possible diagnosis of other forms of problematic behaviour with addictive, impulsive and/or compulsive features, including buying or shopping, pornography use, social media use, cyberchondria, digital hoarding, and online streaming.

Evidence of overlap between compulsive and addictive mechanisms and disorders has led to the establishment of the European Network for Problematic Usage of the Internet, bringing together experts in compulsivity, impulsivity and addiction. Seminal consensus papers on diagnosis, underpinning mechanisms, and assessment were published[2], culminating in a festival of science and arts, a string of educational webinars, a textbook published in the WPA Global Mental Health in Practice Series[3], and a popular e-book, *Learning to Deal with Problematic Usage of the Internet*, translated into five languages and downloaded freely hundreds of times (www.icocs.org).

Interest in anxiety and obsessive-compulsive disorders and in problematic Internet use was sharpened into focus by the COVID-19 pandemic and its aftermath. For those with the above disorders, dangers of infection inherent during the pandemic directly impacted clinical care by increasing social avoidance and preventing engagement in critical therapeutic activities. Inflexible thinking and obsessive health concerns led to public health challenges such as vaccine hesitancy and difficulties emerging from COVID-19 lockdown.

Increased use of digital communication initiated by the pandemic brought many benefits but also new challenges and risks for individuals and civil society. These included problems in balancing time spent on- and off-line, dissemination of abuse and misinformation, and societal fragmentation. Problematic Internet use, an umbrella category representing various forms of maladaptive Internet use involving loss of control or hazardous use patterns, has far-reaching harmful consequences for health and well-being in the individual and society[2,4]. Adolescents whose cognitive control is not yet developed and those with certain mental health issues are disproportionately affected by this condition, which can be conceptualized as a marker of disrupted self-management. Critically, during the COVID-19 pandemic, global rates of problematic Internet use increased, reaching 7.9% in a meta-analysis and over 30% in some low- and middle-income countries[5].

In response to the above scenario, members of our Section published open-access consensus guidance for treating anxiety and obsessive-compulsive disorders and for preventing problematic Internet use during and after the pandemic[6,7].

Responding to the "hidden pandemic" of problematic Internet use, Section members expanded the relevant European Network into a 5-year research programme, Boosting Societal Adaptation and Mental Health in a Rapidly Digitalizing, Post-Pandemic Europe (BootStRaP). This includes partners in >20 countries and a global advisory panel. It aims to reduce the harmful effects of digitalization on mental health by creating an evidence-based suite of digital behavioural health interventions addressing vulnerability to problematic Internet use in young people, whose effectiveness will be tested in a series of randomized controlled trials. The project will also develop a health and social policy toolkit, and standards to promote digital human rights and safeguard vulnerable groups from exploitation.

Advances in the neurobiology and treatment of the Anxiety or

Fear-Related Disorders and Obsessive-Compulsive and Related Disorders has resulted in an expanding armamentarium of interventions, reaching beyond traditional models to include techniques such as neuromodulation, immunotherapy and neurosurgery. Section members contributed to a revision of the World Federation of Societies of Biological Psychiatry treatment guidelines[8,9]. Another collaboration with the Canadian Network for Mood and Anxiety Treatments and the ICOCS is developing a user-friendly set of international guidelines for obsessive-compulsive disorder for release in 2024.

Addressing a critical knowledge gap, Section members were among a group of experts applying a Delphi method-based consensus approach to produce internationally agreed, consistent and clinically useful criteria for treatment-resistant anxiety disorders, to support future trial design and advance evidence-based stepped-care treatment algorithms[10]. Following this initiative, Section members, in collaboration with the ECNP Obsessive-Compulsive Research Network and the ICOCS, will use a similar approach to develop clinically useful criteria for treatment-resistant obsessive-compulsive and related disorders.

Given the global burden of problematic Internet use, its impact on youth, and the need for large-scale public health approaches to address it, Section members have embarked on a Lancet Psychiatry Commission with broad international representation that will focus on particularly vulnerable populations to provide globally relevant recommendations for health and social policy changes.

Contemporary challenges in mental health demand cutting-edge solutions. Theoretical frameworks that take an integrative and transdiagnostic approach, and practical initiatives that are inclusive and have transcultural impact, are needed.

The WPA Section on Anxiety and Obsessive-Compulsive Disorders has embraced the responsibility of contributing to such frameworks and initiatives, focusing on disorders that collectively impact a large proportion of the population. Given the high prevalences and limited resources, there is a pressing need for novel technologies in prevention, diagnosis and treatment.

Our Section has considerable potential to empower clinicians, mental health providers and researchers to advance the field. Colleagues who share our vision and interest are warmly invited to join us and contribute to our shared goals.

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1. Kogan CS, Stein DJ, Rebello TJ et al. J Affect Disord 2020;273:328-40.
2. Fineberg NA, Menchón JM, Hall N et al. Compr Psychiatry 2022;118:152346.
3. Stein DJ, Fineberg NA, Chamberlain SR (eds). Mental health in a digital world. London: Academic Press, 2022.
4. Reed GM, First MB, Billieux J et al. World Psychiatry 2022;21:189-213.
5. Burkauskas J, Pellegrini L, Mozuraityte K et al. Neuropsychopharmacol Hung 2023;25:131-41.
6. Fineberg NA, Van Ameringen M, Drummond L et al. Compr Psychiatry 2020;100:152174.
7. Király O, Potenza MN, Stein DJ et al. Compr Psychiatry 2020;100:152180.
8. Bandelow B, Allgulander C, Baldwin DS et al. World J Biol Psychiatry 2022;24:118-34.
9. Bandelow B, Allgulander C, Baldwin DS et al. World J Biol Psychiatry 2022;24:79-117.
10. Domschke K, Seuling PD, Schiele MA et al. World Psychiatry 2024;23:113-23.

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A report from the WPA Working Group on Providing Mental Health Care for Migrants and Refugees

International migration is not a single "event". In many cases, migration is a voluntary decision, due to social, economic and political contexts in the home country, or perceived opportunities in the destination country. Nearly one billion people (12.5% of the world's population) now live in a country other than the one in which they were born. In other cases, migration is involuntary or forced, i.e., aimed to escape persecution, harassment or danger, or due to displacement or expulsion. At mid-2023, there were 110 million refugees, asylum seekers, and people who were internally displaced. Up to 80% of these refugees live in low- and middle-income countries, which have limited capacity to provide housing, education, and general health and mental health services[1].

Some migrants and most refugees moving across international borders face adverse conditions before, during and after migration[2]. Prior to migration, these conditions include deprivation, persecution, violence, imprisonment, and human rights violations such as sexual harassment and torture[2]. Forced migration, greater exposure to pre-migration traumatic experiences, and the travel phase of the migration journey are associated with depression, post-traumatic stress disorder (PTSD) and anxiety among migrants and refugees[2].

Post-migration stress factors may have an even greater impact on mental health than pre-migration ones, for example on risk of psychosis and depression[3]. These include family separation, language difficulties, limited educational opportunities, limited social integration and acculturative stress, social exclusion, unemployment, stigma and discrimination. Many of these factors continue to impact mental disorder risk in the offspring of migrants. The post-migration environment, acculturation difficulties and a lack of social support can contribute to worsening mental health[3,4]. On the other hand, social-group participation is crucial for enhancing ethnic-minority and migrant mental health[3,4].

The prevalence of mental disorders may be twice as high in refugees than among economic migrants[5]. There is an increased incidence of non-affective psychotic disorders among migrants from developing countries[3,4]. While the lifetime risk of affective or non-affective psychosis in Europeans is about 1-2%, this risk could be as high as 3-6% in migrants from outside Europe. The lifetime prevalence of PTSD (31%) and depression (31.5%) in refugees and asylum seekers is much higher than in the general population (respectively, 3.9% and 12%)[6], and this increased prevalence persists for many years post-displacement[7].

Large-scale interventions are urgently needed to address psychiatric disorders in refugees and forcibly displaced persons[7]. Cultural competence, a key component of good clinical practice, emphasizes clinician skills for understanding the cultural values, attitudes and behaviors of patients, respecting and bridging differences and making sure that these differences do not negatively impact the diagnostic and therapeutic process[8]. Anti-racism and diversity training are also sometimes offered.

Attention to patients' cultural concepts of distress in clinical care can clarify the social construction of psychopathology, reduce overmedicalization, help trace a path from distress to resilience, guide research on mechanisms and markers of morbidity, guide cultural epidemiology by identifying those most at risk, and clarify cultural conflicts feeding social inequities[9].

Most psychiatric medications have been developed in the West. Despite their global use, there is limited research on their pharmacodynamic and pharmacokinetic profiles across diverse ethnic groups. In addition to ethno-biological determinants of drug response, there are significant cultural factors, including the concurrent use of pluralistic health systems, alternative therapies, and folk remedies that might support, hinder or complicate pharmacotherapy efficacy and adherence.

The WPA Working Group on Providing Mental Health Care for Migrants and Refugees was tasked with the following objectives: a) to identify issues relevant to provision of mental health care for forcibly displaced people, refugees and migrants across the world, and to develop recommendations for WPA's involvement in forcibly displaced people, refugee and migrant mental health research, education, and mental health system development; b) to identify Member Societies, institutions and individuals interested and willing to participate in WPA's programs of forcibly displaced people, refugee and migrant mental health research, education, and mental health system development; c) to liaise with the other WPA Action Plan Working Groups[9-11] with a view to promoting the inclusion of forcibly displaced people, refugee and migrant mental health in the work of those groups.

In pursuit of these objectives, the Working Group has conducted several scientific and training initiatives at the international level. These included symposia on "Racism and Mental Health" at the World Congress of Psychiatry in 2021, and on "Racism and Mental Health of Vulnerable Groups and the Role of Mental Health Professionals" at the World Congress of Psychiatry in 2022. We also organized a webinar on "Racism and Discrimination in Mental Health Care of Migrants, Refugees and Forcibly Displaced People", with the participation of experts in the field. Further symposia dealt with "Transcultural Aspects of Mental Health" and "Transcultural Psychiatry and Mental Health of Migrants, Refugees and Forcibly Displaced People". Additionally, we were invited to participate in a panel discussion on "Migration, Refugees, and Mental Health".

At the World Congress of Psychiatry in 2023, we ran a course on "Forced Displacement, Refugees, and Mental Health". We also prepared educational course materials in six languages on "Transcultural Psychiatry and Mental Health of Migrants, Refugees and Forcibly Displaced People".

A further webinar organized by the Working Group was entitled "Working with Migrants and Refugees – Why Do We Need Cultural Competence?". In this event, experts highlighted the importance of cultural competence in providing appropriate care for migrants and refugees, overcoming socio-cultural differences and other systemic challenges to reduce inequalities in mental health care.

The fact that the COVID-19 pandemic has had a greater impact on mental health of vulnerable groups of migrants, refugees and asylum seekers than many other populations has been a focus of the Working Group. A State-of-the-Art Symposium reported on "Understanding the Variation and Complexity of the Suicidal Process during the COVID-19 Pandemic" at the World Congress of Psychiatry in 2021. At the World Congress of Psychiatry in 2022, we presented a State-of-the-Art Symposium on "COVID-19 and its Impact on the Mental Health of Migrants, Refugees and Asylum Seekers", and joined the Presidential Symposium on the same topic. To take up the handling of the pandemic, the Working Group developed a position statement on "COVID-19 Pandemic and Mental Health of Migrants and Refugees".

Addressing a topical issue, the Working Group invited experts to a webinar on "War in Europe and Mental Health of Refugees and Forcibly Displaced People from Ukraine". Europe is once again confronted with a dramatic emergency, which has already caused many civilian victims and mass displacement, and worsened the economic and energy crisis. Finally, a meta-analysis and systematic review on "Psychotherapy Interventions in Migrants and Refugees" is in progress.

Mental health education and interventions that are adapted to the linguistic, cultural and social circumstances of marginalized groups are crucial. The capacity of mental health professionals to provide quality services to migrant and refugee patients and communities must be substantially improved. It is essential to ensure effective and equitable professional help and humanitarian assistance to migrants and refugees who make up an ever-increasing proportion of the world's population.

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1. United Nations High Commissioner for Refugees. Refugee data finder. www.unhcr.org.
2. Jesuthasan J, Sönmez E, Abels I et al. BMC Med 2018;16:15.
3. Henssler J, Brandt L, Müller M et al. Eur Arch Psychiatry Clin Neurosci 2020;270:325-35.
4. Selten JP, van der Ven E, Termorshuizen F. Psychol Med 2020;50:303-13.
5. Lindert J, Ehrenstein OS, Priebe S et al. Soc Sci Med 2009;69:246-57.
6. Koenen KC, Ratanatharathorn A, Ng L et al. Psychol Med 2017;47:2260-74.
7. Blackmore R, Boyle JA, Fazel M et al. PLoS Med 2020;17:e1003337.
8. Schouler-Ocak M, Graef-Calliess IT, Tarricone I et al. Eur Psychiatry 2015;30:431-40.
9. Javed A. World Psychiatry 2022;21:325-6.
10. Javed A. World Psychiatry 2023;22:165-6.
11. Javed A. World Psychiatry 2023;22:341-2.

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Addictive disorders through the lens of the WPA Section on Addiction Psychiatry

The practice of addiction psychiatry and the relevant training vary among different world regions and countries. Despite the challenges that the subspecialty has been facing, the past decade has witnessed new insights and advances in the field. In particular, the rapid development of technologies has contributed to a better understanding of addiction and its mechanisms and to the development of new therapeutics, but has also facilitated the emergence of new forms of behavioral addiction as well as the accessibility and dissemination of a variety of substances of abuse.

The WPA Section on Addiction Psychiatry was established to provide a global platform to discuss national, regional and international challenges and solutions for substance use and other forms of addictive disorders among psychiatrists and their colleagues in the related clinical disciplines.

During the World Congress of Psychiatry held in Vienna in 2023, the renovated section was officially launched. The Section chair, A. Baldacchino, shared the Section's vision based on the values of collegiality, democracy, transparency, inclusion, diversity and global representativeness. The key aim is to establish collaboration with other WPA Sections, scientific societies and organizations. The Section, therefore, plans to support global surveys, discussion panels, advocacy initiatives, and development of intersectional guidelines, consensus statements, best practices and policy documents to support such a vision. New members are being actively attracted.

The Section has strived to identify pressing topics for the next triennium action plan. It acknowledged various areas of needs, including regional drug situations, behavioral addictions, forced displacement in light of the current geopolitical disputes, as well as the impact of the COVID-19 pandemic[1,2]. However, in order to ensure a wider scope that covers advances, challenges, recent trends and training needs, we finally identified four main themes to focus on.

First, there is an ongoing effort to develop mechanism-informed therapeutics and preventive tools for substance use disorders[3]. The approval or clearance by the US Food and Drug Administration (FDA) of neuromodulatory interventions – including auricular vagus nerve stimulation to reduce the symptoms of opioid withdrawal, and deep transcranial magnetic stimulation of prefrontal cortex for smoking cessation – opened up doors for efforts to identify and target addiction neurocircuits to develop new treatments. Repurposing medications based on mechanistic understanding has shown promises to contribute to addiction recovery by targeting N-methyl-D-aspartate (NMDA), orexin, kappa opioid, and other receptors.

The next generation of mechanism-informed therapeutics for substance use disorders and their comorbidities will include neuroimaging-informed individualized neuromodulation, biomarker-informed digital therapeutics, mechanism-informed pharmacotherapeutics, neuroscience-informed behavioral interventions, and neuroscience-based individualized preventive strategies.

The Section is interested in supporting global contribution to these technological advances, while discussing how patients and addiction psychiatrists around the world may have equal access to these new advancements. The Section is working to shape international working groups and consortiums to support these efforts[4].

Second, the rise of telemedicine and its rapid development with the COVID-19 pandemic has extended to addiction psychiatry. The Section is interested in exploring this field, focusing on the development and implementation of innovative digital solutions to meet the needs of people facing addiction. This will be pursued through creating a network of shared knowledge and a design philosophy based on person centredness and inclusive communication.

The essence of this effort is to add value to the opportunities arising from digital platforms and to promote accessibility by marginalized populations. The process will not only aim to improve inclusion, but also to embrace complexity and facilitate systems change[5].

Third, neurodiversity has been a topic of growing interest over the past few years. In the field of addiction psychiatry, emerging evidence is indicating a link between substance use disorders and a variety of neurodevelopmental disorders. Attention-deficit/hyperactivity disorder (ADHD) and autism have been associated with increased risk of substance misuse[6], as well as of behavioral addictions such as gaming disorder[7].

The fourth identified priority is training in addiction psychiatry. The training gap is currently a major challenge in addressing addiction as a global public health problem. Several countries have taken initiatives in this area. However, the lack of standardization and human resources are limiting scaling up of training programmes. A recent global survey by the International Society of Addiction Medicine (ISAM) among early career addiction medicine professionals highlighted these issues. The ISAM also developed a training need assessment tool and conducted a survey to assess training needs. The close collaboration between the ISAM and the WPA will foster developments in this area.

The WPA has developed training modules for various psychiatric disorders, including addiction disorders, which have potential to contribute to the reduction of this gap[8-11]. A working group will implement the Section's collaboration with different stakeholders to formulate a global strategy in this respect[12].

Discussions with other WPA Sections, national and international associations and scientific societies are also ongoing to explore further areas of potential collaborations. The Section is looking forward to a fruitful triennium with activities aiming at improving practice, bridging gaps, and fostering an inclusive and diverse learning environment for all generations of professionals.

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1. Elkholy H. BJPsych Int 2022;19:57-8.
2. Elkholy H, Tay Wee Teck J, Arunogiri S et al. Curr Addict Rep 2023;10:341-2.
3. Ekhtiari H, Zare-Bidoky M, Verdejo-Garcia A. In: el-Guebaly N, Carrà G, Galanter M et al (eds). Textbook of addiction treatment. Cham: Springer, 2021:1159-76.
4. Ekhtiari H, Verdejo-Garcia A, Moeller SJ et al. Front Psychiatry 2020;11:590030.
5. Tay Wee Teck J, Gittins R, Zlatkute G et al. JMIR Ment Health 2023;10:e47186.
6. French B, Daley D, Groom M et al. J Atten Disord 2023;27:1393-410.
7. Koncz P, Demetrovics Z, Takacs ZK et al. Clin Psychol Rev 2023;106:102343.
8. Javed A. World Psychiatry 2023;22:165-6.
9. Javed A. World Psychiatry 2023;22:341-2.
10. Ng RMK. World Psychiatry 2022;21:478-9.
11. Ng RMK. World Psychiatry 2023;22:346-7.
12. Bhad R, Achab S, Rafei P et al. Glob Ment Health 2023;10:e44.

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Advancements, challenges and future horizons in personalized psychiatry

Personalized psychiatry has recently become an important component of the overall shift towards personalized medicine, aiming to address unmet medical needs in the field of mental health.

Mental disorders, particularly depression and anxiety disorders, are major contributors to the global health burden. Although various treatment options are available, they often lead to unsatisfactory outcomes. This is mainly because it is difficult to find the most effective treatment for each patient. While there are evidence-based guidelines for clinical practice, treatment recommendations are often based on the average response observed in clinical populations that participated in randomized clinical trials and do not consider specific individual characteristics.

The realization that people sharing a given diagnosis differ in several respects that are relevant to treatment response has led to a necessary move away from a one-size-fits-all approach to clinical care. Personalized psychiatry strives to integrate various patient-specific characteristics – symptoms, clinical features, neurobiological markers, genetics, epigenetics, brain imaging, environmental factors, and lifestyle – to predict susceptibility, aid diagnosis and optimize treatment to maximize efficacy and minimize adverse effects.

Recent technological innovations offer significant potential to advance the goals of personalized psychiatry. The introduction of electronic medical records simplifies the creation of extensive databases (big data). Real-time data collection via smart, wearable devices enables the recording of mental states as well as behavioral and physiological signals (digital phenotyping). In addition, the development of advanced artificial intelligence tools, such as machine learning methods, allows the recognition of intricate patterns in huge and complex data sets and thus predictions that go beyond human capabilities[1].

However, despite the promising potential, the development of a personalized approach in psychiatry has been slow, mainly due to several daunting challenges. These arise from the intricate and diverse nature of psychiatric disorders, which are characterized by considerable phenomenological complexity and heterogeneity. In addition, there are no established and clear pathophysiological pathways, and psychiatric disorders exhibit multilevel dynamics that encompass biological, psychological, behavioral, social and cultural dimensions. Thus, despite the emergence of numerous predictive models with potential utility for psychiatric clinical practice, minimal progress has been made in their real-world clinical application over the past two decades[2], underscoring the need for additional research and large-scale efforts.

Within this framework, the WPA launched in 2014 an innovative Scientific Section on Personalized Psychiatry, under the leadership of G. Perna, C.B. Nemeroff and A.F. Schatzberg. This pioneering initiative has attracted distinguished international experts who are active in the field as committee members, members, and speakers. Central to the Section's mandate is a commitment to harnessing advances in neuroscience, brain imaging, genetics and technology to promote the adoption of personalized approaches in all areas of mental health care.

By fostering interdisciplinary networks and collaborative research, the Section aims to unravel the complex interplay of genetic, environmental and neurobiological factors that underlie mental illness. Ultimately, the overarching goal is to equip clinicians with the tools necessary to deliver targeted psychiatric clinical interventions that benefit both professionals and patients.

Section members have conducted valuable research that contributes to this goal. Examples include identifying potential brain circuit-based biotypes for personalized treatment selection in mood disorders; translating individual-level brain circuit function into predictive markers for clinical practice[3]; and providing evidence that pharmacogenomics may be promising, but currently has no utility for treatment selection in major depressive disorder[4]. In addition, the immune system has emerged as a promising therapeutic target for certain sub-populations of people with major depression. Research is actively exploring features of immunometabolic depression as potential predictors of antidepressant treatment outcomes[5], as well as proposed peripheral inflammatory biomarkers aimed at defining biotypes of unipolar and bipolar depression. An initial proposal for an evidence-based personalized therapy for panic disorder that takes into account individual phenomenological profiles and physiological patterns has been presented[6], with ongoing clinical research projects actively exploring this area.

Artificial intelligence, a remarkably burgeoning field in all branches of medicine, has the capacity to assess the myriad of factors that have been found to contribute to treatment response in common mental disorders, leading to the development of reliable prediction models. Expert panels have recently published consensus guidelines for the definition of treatment resistance in anxiety disorders[7] and major depressive disorder[8]. However, the effectiveness of these definitions for clinical decision making and health outcomes is still limited, and improvements in the therapeutic management of these disorders are needed[9].

Through the promotion of international symposia, workshops and publications, our Section aims to promote knowledge exchange and collaboration among experts worldwide. In addition, it aims to collect and disseminate scientific knowledge in the field of personalized psychiatric care. These efforts have resulted in significant contributions to various scientific books. Notable works include *Anxiety Disorders. Rethinking and Understanding Recent Discoveries* (edited by Y.-K. Kim); *Precision Psychiatry. Using Neuroscience Insights to Inform Personally Tailored, Measurement-Based Care* (edited by L.M. Williams and L.M. Hack); *The American Psychiatric Association Publishing Textbook of Psychopharmacology, 6th edition* (edited by A.F. Schatzberg and C.B. Nemeroff); and *Personalized Integrative Treatment for Depression* (edited by Y.-K. Kim).

Since 2017, C.B. Nemeroff and G. Perna have been co-editors of the scientific journal *Personalized Medicine in Psychiatry*, a platform that grew out of their vision to create an editorial forum that allows mental health clinicians and researchers to contribute to and stay abreast of the latest advances in personalized approaches to mental health care.

In summary, by acknowledging the inherent heterogeneity and complexity of mental illness and advocating personalized approaches, this Section has attempted to lay the groundwork for a future in which each individual receives tailored treatment that addresses his/her individual needs.

However, it is clear that much more work is needed to achieve this goal. The Section will continue to advance this mission and further raise awareness of the importance of personalized approaches in the broader psychiatric community, aiming to promote implementation in practice and thus actively shaping the future landscape of psychiatric care.

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1. Perna G, Grassi M, Caldirola D et al. Psychol Med 2018;48:705-13.
2. Meehan AJ, Lewis SJ, Fazel S et al. Mol Psychiatry 2022;27:2700-8.
3. Song EJ, Tozzi L, Williams LM. Biol Psychiatry 2024; doi: 10.1016/j.biopsych.2024.03.016.
4. Baum ML, Widge AS, Carpenter LL et al. Am J Psychiatry (in press).
5. Vreijling SR, Chin Fatt CR, Williams LM et al. Br J Psychiatry 2024;224:89-97.
6. Caldirola D, Perna G. Neuropsychiatr Dis Treat 2019;15:1957-70.
7. Domschke K, Seuling PD, Schiele MA et al. World Psychiatry 2024;23:113-23.
8. Sforzini L, Worrell C, Kose M et al. Mol Psychiatry 2022;27:1286-99.
9. McIntyre RS, Alsuwaidan M, Baune BT et al. World Psychiatry 2023;22:394-412.

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Improving education in psychiatry in an evolving scenario: the activities of the WPA Section on Education in Psychiatry

Education of mental health professionals should reflect the changes occurring at scientific, clinical and sociocultural levels, and thus it should be continuously updated. However, in many parts of the world, psychiatric education is still based on a knowledge formed in the last century, and the most recent knowledge on the structure and functioning of the brain, human behaviors and social relationships is missing.

Moreover, the mission of psychiatrists has evolved over time, from the diagnosis and management of full-blown mental disorders to the identification of a series of mental health problems which are associated with high levels of personal and societal burden. The involvement of experts by experience in policy, clinical and research activities is now acknowledged as a priority[1,2], and the need for a clinical characterization of individual patients beyond diagnosis in order to personalize treatment is widely recognized[3,4]. These changes should be taken into account by current educational curricula, but this is not always the case.

The WPA Section on Education in Psychiatry is committed to improve training and education worldwide, with a special attention to low- and middle-income countries (LMICs), since the future of psychiatry as a discipline strongly depends on the education of the new generations of professionals.

The Section is updating the type of educational materials available for mental health professionals, and is keen to disseminate them worldwide[5]. In the last triennium, it has contributed to several educational activities, including the development of informational packages for the general public to decrease misconceptions on people with mental disorders, the update of training curricula for undergraduate medical students, and the organization of educational workshops and meetings for psychiatrists and other mental health professionals.

In the triennium 2020-2023, following the COVID-19 pandemic – which has represented an unprecedent traumatic event with a detrimental impact on education, training and practice worldwide – the Section has been particularly active in developing and producing new tools to improve education in mental health worldwide[6-8].

The Chair of the Section, in collaboration with the WPA Past-President, has promoted a survey targeting the WPA Zonal Representatives, to identify the educational needs and interests of professionals associated with the WPA[9]. The main finding has been that these professionals are mostly concerned with public mental health activities and with primary prevention of mental disorders. The main unmet need is the development, implementation and dissemination of educational activities in languages other than English, in order to broaden their accessibility.

Moreover, the Section has collected experiences on education and training from researchers and scholars working in different parts of the world, with a special focus on the quality of training in LMICs. These contributions have been collected in a special issue of the journal *Asia-Pacific Psychiatry*[10]. This issue also includes the views of early career psychiatrists on the difficulties and advantages of being trained in psychiatry in LMICs, the neglect of education on addiction psychiatry, the impact of the COVID-19 pandemic on psychiatric training and education, and the relevance of using digital resources and online platforms for facilitating and improving the dissemination of educational programs and activities worldwide.

Moreover, the Chair of the Section has worked closely with the WPA Past-President to highlight the importance of physical health in patients with severe mental disorders, by participating in the Working Group on Physical Activities and Comorbidities[11] and in several educational initiatives organized during WPA Congresses and other major conferences.

Based on these activities, together with Profs. N. Sartorius and A. Javed, the Chair of the Section is editing a new WPA educational book on *Comorbidity between Mental and Physical Disorders: Identification, Management and Treatment*, that will be published during 2024.

Along these lines, the Section has been involved in the preparation of the WPA Action Plan 2023-2026 by the current WPA President, and has actively contributed to the production of educational materials for the Healthy Lifestyles Hub, a dedicated webpage collecting videos and informative packages on nutrition and physical activity. The aim is to further contribute to the creation of a library of resources accessible to colleagues worldwide that can be downloaded for inspiration and application in daily psychiatric practice[12-14].

In March 2021, the Section organized a successful virtual Train the Trainers workshop, which was attended by around 130 participants, including psychiatrists, psychiatric trainees, and other mental health care professionals from 45 countries. The interactive structure of the workshop allowed participants to exchange educational and professional experiences, ask questions and receive advice from experts. Among the keynote speakers, Profs. A. Javed and N. Sartorius shared their experience on how to find innovative solutions for improving training and education in psychiatry, with a specific focus on leadership and communication skills. The success of this workshop confirmed that online interactive educational activities can represent a useful tool in order to reduce organizational and logistic costs.

The Section has been continuously reinforcing collaboration with international organizations committed to improve education and training in psychiatry, such as the Committee on Education of the European Psychiatric Association (EPA) and the European Union of Medical Specialists (UEMS). Moreover, the Chair of the Section has actively participated in meetings held at the European Parliament in Brussels, sharing ideas on educational opportunities in mental health, in collaboration with representatives from UEMS and the World Health Organization.

The number of members of the Section has been expanding regularly, with the recruitment of several early career psychiatrists and the involvement of colleagues from a vast range of countries. We look forward to further opportunities of interaction with all colleagues and other stakeholders interested in upgrading psychiatric education worldwide.

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1. Fusar-Poli P, Estradé A, Stanghellini G et al. World Psychiatry 2022;21:168-88.
2. Fusar-Poli P, Estradé A, Stanghellini G et al. World Psychiatry 2022;22:352-65.
3. Stein DJ, Shoptaw DV, Vigo DV et al. World Psychiatry 2022;21:393-414.
4. McIntyre RS, Alda M, Baldessarini RJ et al. World Psychiatry 2022;21:364-87.
5. Fiorillo A, Sampogna G, Elkholy H et al. World Psychiatry 2021;20:149-50.
6. Ng RMK. World Psychiatry 2022;21:478-9.
7. Ng RMK. World Psychiatry 2023;22:346-7.
8. Thomson S, Chumakov E, Van Hoof J et al. World Psychiatry 2022;21:161-2.
9. Sampogna G, Fiorillo A, Wasserman D. Asia Pac Psychiatry 2021;13:e12497.
10. Fiorillo A, Javed A. Asia Pac Psychiatry 2021;13:e12500.
11. Fiorillo A, de Girolamo G, Simunovic IF et al. World Psychiatry 2023;22:169-70.
12. Wasserman D, Arango C, Fiorillo A et al. World Psychiatry 2023;22:170-1.
13. Wasserman D, Arango C, Fiorillo A et al. World Psychiatry 2023;22:488-9.
14. Wasserman D. World Psychiatry 2023;22:343-4.

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The contribution of the WPA to the development of the ICD-11 CDDR

The WPA has been actively supporting the World Health Organization (WHO) in the development and scientific validation of the Clinical Descriptions and Diagnostic Requirements for ICD-11 Mental, Behavioural and Neurodevelopmental Disorders (CDDR).

Several WPA officers and experts served as chairpersons or members of the ICD-11 Working Groups that produced the drafts of the various sections of the CDDR. The chairpersons included W. Gaebel (Working Group on Psychotic Disorders), M. Maj (Working Group on Mood and Anxiety Disorders), P. Tyrer (Working Group on Personality Disorders), L. Salvador-Carulla (Working Group on Intellectual Disabilities), O. Gureje (Working Group on Somatic Distress and Dissociative Disorders) and D. Stein (Working Group on Obsessive-Compulsive and Related Disorders). Prof. M. Maj has represented the WPA in the ICD-11 International Advisory Board.

WPA Member Societies have participated in the WPA/WHO Global Survey of Psychiatrists' Attitudes Towards Mental Disorders Classification, whose results have significantly informed the process of development of the ICD-11 CDDR. The survey involved 4,887 psychiatrists from 44 countries, representing the largest and most broadly international survey ever conducted of psychiatrists' attitudes towards the classification of mental disorders. Through the survey, psychiatrists provided strong endorsement of a focus on clinical utility, which was indeed the main objective of the process of development of the CDDR. More than two thirds of the participants indicated that they would prefer a system of flexible guidance allowing for cultural variation and clinical judgement, as opposed to a system based on strict operational criteria, a preference which has been actually reflected in the structure of the CDDR.

Several WPA Member Societies and experts have been involved in the CDDR field trials, including the so-called formative field studies (aimed to guide decisions about the basic structure and content of the ICD-11 by exploring clinicians' conceptualization of the interrelationships among categories of mental disorders); the Internet-based field studies (which used vignette methodologies to examine clinical decision-making in relationship to the proposed CDDR); and the clinic-based field studies (conducted to assess the reliability and clinical utility of the CDDR with real patients). The results of the largest clinic-based CDDR field trial – conducted among 1,806 patients in 13 countries, and focusing on schizophrenia and other primary psychotic disorders, mood disorders, anxiety and fear-related disorders, and disorders specifically associated with stress – have been published in *World Psychiatry*, the official WPA journal.

World Psychiatry has also been one of the main channels through which WPA Member Societies and the international psychiatric community have been informed about the development of the ICD-11 CDDR. In particular, the journal has hosted some of the main papers summarizing the philosophy of the entire process and the structure of the diagnostic system, and many articles dealing with specific sections of the classification, as well as individual papers or forums on general topics of classification in psychiatry. Several examples can be found in recent issues of the journal[1-13]. All these contributions are freely downloadable from the WPA website (www.wpanet.org).

Educational courses focusing on various sections of the ICD-11 chapter on mental, behavioural and neurodevelopmental disorders have been held in connection with several WPA meetings, including the 18th, 19th and 20th World Congresses of Psychiatry (Mexico City, Mexico, September 27-30, 2018; Lisbon, Portugal, August 21-24, 2019; Bangkok, Thailand, March 10-13, 2021), and the Regional Congresses on "Interdisciplinary Understanding of Co-morbidity in Psychiatry: from Science to Integrated Care" (St. Petersburg, Russia, May 16-18, 2021) and "Psychopathology in Periods of Transition" (Kyiv, Ukraine, July 7-9, 2021). These courses have represented a unique opportunity for psychiatrists from many countries to directly familiarize with the CDDR and exercise in their application.

A comprehensive online 20-hr training course in the use of the CDDR has been organized by the Naples WHO Collaborating Centre on Research and Training in Mental Health and the European Psychiatric Association from 9 to 30 April, 2021. The course has been coordinated by G.M. Reed and M. Maj, and has covered all the main sections of the CDDR. W. Gaebel, M. Cloitre, M. Maj, C.S. Kogan, P. Monteleone, M. Swales, J.B. Saunders and N.A. Fineberg composed the Faculty. The live course has been attended by 120 psychiatrists, selected from almost 500 applicants, representing 78 different countries. A further group of 250 psychiatrists have had access to the course on demand. A training course co-organized by the WPA and the Global Mental Health Academy, with a structure similar to the course organized by the Naples WHO Collaborating Centre and the European Psychiatric Association, but with access also to psychologists and primary care practitioners, took place online from 8 to 29 November, 2021.

A number of lectures and symposia on various issues related to the ICD-11 CDDR have been held at several World Congresses of Psychiatry. In particular, at the 19th World Congress of Psychiatry, held in Lisbon in August 2019, a plenary session dealt with the implementation of the ICD-11. G. Reed and M. Maj, who chaired the session, summarized some lessons that should be learned from the implementation of previously developed classification systems.

A WHO International Advisory Group on Training and Implementation of the ICD-11 CDDR has been established to develop and evaluate educational, training and implementation processes related to the CDDR in various countries. WPA former officers who contributed to the development of the CDDR – such as M. Maj, W. Gaebel and D. Stein – are members of this Advisory Group.

The strong collaboration between the WHO and various WPA components in all the steps of the development and testing of the

ICD-11 CDDR is now expected to continue in the phase of implementation of the diagnostic system at the international level.

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1. Reed GM, First MB, Billieux J et al. World Psychiatry 2022;21:189-213.
2. Watson D, Levin-Aspenson HF, Waszczuk MA et al. World Psychiatry 2022;21:26-54.
3. McIntyre RS, Alda M, Baldessarini RJ et al. World Psychiatry 2022;21:364-87.
4. Stein DJ, Shoptaw SJ, Vigo DV et al. World Psychiatry 2022;21:393-414.
5. Borsboom D, Haslbeck JMB, Robinaugh DJ. World Psychiatry 2022;21:420-2.
6. Epskamp S, Isvoranu A-M. World Psychiatry 2022;463-4.
7. Parker G, Tavella G. World Psychiatry 2022;21:467-8.
8. Zachar P. World Psychiatry 2023;22:154-5.
9. Volkow ND, Blanco C. World Psychiatry 2023;22:203-29.
10. McIntyre RS, Alsuwaidan M, Baune BT et al. World Psychiatry 2023;22:394-412.
11. Karatzias T, Bohus M, Shevlin M et al. World Psychiatry 2023;22:484-6.
12. Fabrazzo M. World Psychiatry 2022;21:163-4.
13. Di Vincenzo M. World Psychiatry 2023;22:171-2.

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