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The WPA is an association of national psychiatric societies aimed to increase knowledge and skills necessary for work in the field of mental health and the care for the mentally ill. Its member societies are presently 147, spanning 123 different countries and representing more than 250,000 psychiatrists.

The WPA organizes the World Congress of Psychiatry every year. It also organizes international and regional congresses and meetings, and thematic conferences. It has 66 scientific sections, aimed to disseminate information and promote collaborative work in specific domains of psychiatry. It has produced several educational programmes and series of books. It has developed ethical guidelines for psychiatric practice, including the Madrid Declaration (1996).

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2. McRae TW. The impact of computers on accounting. London: Wiley, 1964.
3. Fraeijs de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). *Stress analysis*. London: Wiley, 1965:145-97.

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How concerns about the naming and the diagnostic concept of “schizophrenia” subtly reinforce each other, and what could be done in this respect

The term “schizophrenia” is increasingly avoided by both clinicians and researchers in many settings, to an extent that cannot be ignored anymore (in order not to foster what is apparently a gradual schism between official classifications and actual clinical and research practice). In a survey carried out in Italy¹, 49.1% of psychiatrists reported that they do not use the term “schizophrenia” when communicating with their patients, and 75.3% of those not using that term stated that “psychosis” is the term they use instead. In this issue of the journal, an outstanding scholar² broadly quotes the evidence concerning the etiology and pathogenesis of “schizophrenia”, but uses the term “psychosis” in both the title and the text of his paper; and the authors of another major contribution³, providing an evidence-based atlas of risk and protective factors, explicitly merge the evidence concerning “any ICD or DSM non-organic psychotic disorder”.

In the above survey¹, 51.2% of psychiatrists mentioned “concern about stigma” as the reason for not using the term “schizophrenia” (with an additional 14.5% mentioning the need to avoid “pessimism regarding prognosis”, and a further 2.3% of respondents indicating “fear of increasing patient’s distress”), while no psychiatrist mentioned concerns about the validity of the diagnostic concept itself, arguably because the adopted questionnaire did not include this option. In the two above-mentioned major papers^{2,3}, a certain degree of both dissatisfaction with the term “schizophrenia” and reservations about the utility of the distinction between “schizophrenia” and other “non-organic” psychoses, at least as far as etiology and pathogenesis are involved, seem to coexist (which is indeed a remarkable fact, given the scientific standing of the authors). Actually, there are other eminent scholars who have explicitly questioned, on different occasions, both the naming and the diagnostic concept of “schizophrenia” e.g.,^{4,5}.

Overall, on the basis of these examples and a reflection on the recent relevant literature, it is difficult to resist the impression that the widespread concern about the stigmatizing and even derogatory nature of the term “schizophrenia”, on the one hand, and the persisting doubts about the validity of the corresponding diagnostic concept, on the other, are to some extent related to and reinforcing each other. Renaming “schizophrenia”, as now extensively proposed, may therefore have an impact on the future of the diagnostic concept itself.

What we currently call “schizophrenia” has been described – with important variations but with some remarkable degree of consistency – for more than a century. However, “schizophrenia” is virtually unique among the disorders included in the DSM-5-TR in that its diagnosis is essentially based on the exclusion of other diagnoses rather than on its own symptomatologic features, as if the disorder did not have – contrary to virtually all the other diagnostic entities – a distinctive symptomatologic “character”. In fact, while “schizophrenia” is usually described as consisting of

“positive”, “negative”, “disorganization”, and possibly cognitive and psychomotor symptoms, it is a fact that the DSM-5-TR criteria allow diagnosing the disorder also if delusions and hallucinations of any type are the only symptoms, provided that they cannot be ascribed to a mood disorder, or to the physiological effects of a substance or another medical condition.

So, the presence of “negative” symptoms is actually not required for the diagnosis of “schizophrenia” (indeed, the prevalence of these symptoms in patients receiving the diagnosis varies extensively, with the lower end of the range being 50% in first-episode patients⁶), and the diagnostic essence of the disorder consequently appears to be that of a “primary psychosis”. This probably explains, and in part justifies, the current tendency – in both clinical practice and research – to replace the perceivedly stigmatizing term “schizophrenia” with “psychosis” or “primary psychosis”^{1-3,7}. However, this is likely to generate a discrepancy between how “schizophrenia” is usually conceptualized (and E. Bleuler described it) and the way samples of patients with this diagnosis are composed, with a possible impact on research findings.

Notably, “positive and negative symptoms disorder” has been recently proposed as an option for renaming “schizophrenia”⁸, although a major objection to this proposal would be that “positive and negative symptoms” have been indeed described – following an approach dating back to H. Spencer and J.H. Jackson – also in other conditions, such as Parkinson’s disease^{e.g., 9}. “Bleuler’s syndrome” has also been proposed as an alternative to “schizophrenia”, supported by some groups of experts by experience¹⁰, but this option has been dismissed on the basis of a prescription by the World Health Organization not to use “people’s names” in diagnostic terms⁸, although this prescription seems to apply only to “new diseases that have never been recognized before in humans”¹¹.

Those who believe that what we currently call “schizophrenia” represents “a broad syndrome with non-negligible internal cohesion”¹² – although probably not a discrete disease entity – should regard the revision of the diagnostic criteria for the disorder as a more crucial issue than its possible renaming. In line with the strategy – currently suggested within the development of the DSM-6¹³ – to identify different “levels of specificity” of diagnoses, it could be proposed to explicitly describe a first diagnostic level of “psychosis” (just requiring the occurrence of delusions and/or hallucinations), a second diagnostic level of “primary psychosis” (requiring the presence of delusions and hallucinations that cannot be attributed to a mood disorder, or to the effects of a substance or another medical condition), and a third diagnostic level of “primary psychosis with negative symptoms” (framing requirements for symptom duration and social functioning consistently in DSM and ICD, because our field cannot afford the current discrepancies between the two diagnostic systems in this respect). The presence

of passivity experiences, cognitive impairment, and psychomotor symptoms could be accounted for by using dimensional specifiers. Using the term “schizophrenia” could be kept as an option anchored to the third diagnostic level.

If this approach is adopted, researchers will have to clarify the “level of specificity” to which they refer in their reports (in order to avoid comparisons between patient samples which may be more diverse than currently assumed), and clinicians will have to use the term “psychosis” keeping in mind what it really means, and the differential diagnostic steps it further entails, rather than regarding it as a less stigmatizing synonym for “schizophrenia”. The issue of renaming “schizophrenia” will have to be considered in all its complexity, with the need to preserve and promote diagnostic clarity – without ambiguities – as the absolute priority.

Mario Maj

Department of Psychiatry, University of Campania “L. Vanvitelli”, Naples, Italy

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The frontal cortex in mental disorders

The evolutionary expansion of the primate cortical mantle, including most prominently the large regions of the anterior cerebral cortex that we call prefrontal cortex (PFC), while contributing to our enormous cognitive advance, is probably at least in part responsible for the high incidence and profound diversity of human psychopathology.

Almost every psychiatric, and many neurological, disorders are associated with PFC dysfunction. Consequently, understanding the brain mechanisms underlying its contribution to cognition and emotion in health and disorder has become a central goal for science in general, as well as neuroscience and psychiatry¹.

A number of PFC features are relevant to its role in mental disorders. First, it comprises many (at least 20) sub-regions (or Brodmann areas) that have been defined simply on the basis of cytoarchitectonics, i.e. the composition of the different types of the densely branching and highly interconnected neurons and other cells, which presumably enable different types of computation, leading to different outputs and functions¹.

A general distinction is often made between ventromedial and orbitofrontal PFC regions, which are implicated in emotional and motivational behavior, versus the lateral PFC regions, which are associated with cognitive functions, such as working memory, cognitive flexibility and behavioral inhibition, reflecting executive or cognitive control activities² and crucial components of several forms of decision-making. Cerebral asymmetries in PFC function allow for further specialization – for example, in language production and comprehension (Broca’s region).

The very most anterior part of the PFC, the frontal pole, which most distinguishes us from other primates, has even more sophisticated functions, such as planning elaborate sequences, multi-tasking and creative thought. In general, a consistent recent theme has been that of gradients of function, with progressively more complex forms of basic executive functions advancing along the

caudal-to-rostral axis of the PFC. Even in the relatively primitive mouse PFC, recent research has discovered analogous gradients of cells and molecular gene expression (transcriptomics) corresponding to behavioral functions relevant to psychiatry^{1,3,4}.

Another important organizational feature is the control that the PFC exerts over other regions of the brain, being connected anatomically to all other major brain systems, including the sensory and associative regions of the posterior cerebral cortex, the motor cortex, the limbic structures of the hippocampus and amygdala, the hypothalamus and the pituitary-adrenal axis, and the ascending neurotransmitter systems of the brain stem and midbrain that modulate states of stress and awareness, such as the cholinergic and monoaminergic (dopaminergic, noradrenergic and serotonergic) systems. The anterior cingulate cortex is intimately associated with the more “granular” PFC and is usually considered as an important relay of the fronto-executive network, especially as it contains some specialized giant neurons otherwise unique to PFC.

Some functional networks override anatomical analyses of PFC function, such as the so-called default mode network (DMN), discovered in functional magnetic resonance imaging (fMRI) studies, and including structures of the medial prefrontal cortex linked with the posterior cingulate cortex and precuneus. The DMN has important roles in such introspective functions as autobiographical memory, the concept of self, and “mind-wandering”, that are obvious meta-cognitive contributors to symptoms of psychosis, depressive rumination, and attentional deficit in attention-deficit/hyperactivity disorder (ADHD)⁵.

A critical emergent question is how the various nodes of networks actually contribute to their outputs and, additionally, how the various networks interact. A related question for the PFC is how its diverse sub-regions dynamically interact to produce behavior. This is a very difficult question to address using conventional neuroimaging methods, and would need technologies with exquisite tem-

poral resolution, such as magnetoencephalography in humans. Alternatively, for non-human primates, which have many homologous PFC sub-regions in common with humans, modern electrophysiological, optogenetic and chemogenetic techniques can be deployed. A recent salient example used chemogenetic manipulations to track selective functional effects in the PFC of the New World marmoset, of relevance to human depression⁶.

With this background in mind, it becomes more obvious why the PFC has such a prominent role in human mental disorders such as schizophrenia, depression, addiction, autism, ADHD, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and fronto-temporal dementia. The complex symptoms shown in these conditions are mainly cognitive or emotional in nature, and there is intense research into understanding how cognitive functions are negatively affected by illness – for example, in ADHD and OCD, impulsive and compulsive symptoms, respectively, may be explained in part by failures of PFC-exerted cognitive control².

Nosology is often complicated by comorbidities and apparent contradictions of categorical systems such as the DSM-5, suggesting a more dimensional approach to diagnosis that instead conceives disorders in terms of sub-types and spectra. In this age of machine learning and artificial intelligence, perhaps it will eventually be feasible to render mental disorders and their predisposing conditions in terms of complex algorithms with contributory components from several distinct functional neural networks, governed by different PFC sub-region influences. This computational approach may surmount the problems of integrating sub-typing along genetic, proteomic, immunological, cellular, neurochemical, neural network and behavioral (e.g., specific executive functions) factors, combined with clinical criteria such as symptoms and responses to treatment.

The late maturation of the PFC may result in instability of control that makes early mental life especially vulnerable to psychiatric disorder, for example by depriving the brain of adaptive coping mechanisms for stress. A specific feature of many psychiatric disorders, such as OCD and depression, is that they may implicate overactive PFC sub-regions that lead to functional impairments just as evident as those following underactive or lesioned states. Overactivity would be caused by imbalances between excitatory (glutamate) neurons and inhibitory (GABA) local interneurons – and consequent changes, for example, in deep attractor networks that may lead to psychiatric symptoms such as obsessions and ru-

minations. PFC maturation is likely controlled by multiple genetic as well as environmental factors. At the other end of the life-span, the high metabolic requirements of the PFC almost certainly render it especially susceptible to neurodegenerative disorders, such as fronto-temporal dementia.

In terms of aetiology, PFC impairments may directly cause symptoms, or instead amplify their expression. Recent studies have implicated a common neural network underlying mental disorders with much in common with fronto-executive function, leading to postulated psychopathological (“p”) or neuropsychopathological (“NP”) factors⁷. This could account for some transdiagnostic symptoms in common (and hence comorbidity), but also reflect more generally stressful effects of experiencing mental illness.

Many current psychopharmacological treatments (as well as cognitive therapies) for psychiatric disorders probably work by affecting PFC networks. For example, psychedelics such as psilocybin may achieve re-wiring of the DMN⁸. In future, high neural network specificity of treatments will be necessary, which can potentially be provided by the improving neuromodulatory techniques⁹ (exerting, where appropriate, inhibition as well as stimulation), such as deep brain stimulation and, perhaps eventually, chemogenetic stimulation, as well as methods based on non-invasive transcranial magnetic stimulation, focused ultra-sound, and temporal interference⁹.

Meeting these exciting challenges will continue to keep the PFC in the forefront of future neuropsychiatric research.

Trevor W. Robbins

Department of Psychology, University of Cambridge, Cambridge, UK; Behavioral and Cognitive Neuroscience Center; Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China

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Optimizing adolescent brain development

Adolescence – the transition from puberty to adult status – is a period of profound contradiction. It is marked by peaks in strength, agility, and resilience to illness. Yet, morbidity and mortality increase two- to three-fold¹. It is also a time of great leaps in cognition and behavioral competence, yet the period during which 75% of mental disorders emerge².

These phenomena are two sides of the same neurodevelopmental coin³. The adolescent brain does not mature by becoming larger, but by becoming more interconnected and more special-

ized. Increased connectivity is driven by ongoing myelination, a process by which axons are wrapped with a cellular insulation that markedly increases communication efficiency (100x conduction speed, 30x faster reset time), unlocking the wide range of capabilities that emerge during adolescence. Specialization proceeds by a one-two punch of overproduction followed by selective elimination according to the demands of the environment. This is the engine of evolution and the way by which almost all of complexity in nature arises.

The connectivity and specialization are inextricably bound. As myelination progresses, it releases inhibitory molecules, such as Nogo-A, that constrain the brain's adaptability⁴. This creates a trade-off between a rapid maturation of fixed skills versus a prolonged maturation maintaining "plasticity" useful for adaptation to novel environments. *Homo sapiens* evolution has led to the most extreme choice of the second path in all of nature, including compared to our fellow human species, the Neanderthals⁵. Protracted neuroplasticity is both the strength and vulnerability of our species.

Metaphorically, brain maturation resembles a sculpture more than a painting. While individuals may come into the world as different "blocks of granite", understanding the sculpting process helps reveal the "masterpiece" within. This has been a central goal of adolescent neuroscience. Large scale investigations, such as the Adolescent Brain Cognitive Development (ABCD) study, integrate imaging, genetic, environmental and behavioral measures to explore what factors guide the sculpting process in healthy or unhealthy ways.

The ABCD project, following about 12,000 9-10-year-olds through the second decade of life, now generates approximately one publication per day. Findings consistently indicate that development is not driven by a single dominant factor, but by the interaction of many. Hundreds of variables have been identified as having influence, including activities, diet, sleep, social connections, and screen time. Within this complex landscape, several domains emerge as especially tractable targets for intervention and policy, including socioeconomic factors, education, use of digital media, and expectations.

Many ABCD study associations between biological and behavioral variables are substantially attenuated when socioeconomic factors are taken into account, underscoring the pervasive role of social determinants of health⁶. Youth in disadvantaged environments experience higher rates of trauma and chronic stress, greater exposure to environmental toxins such as lead, reduced access to health care, and fewer opportunities for cognitive and educational enrichment. Addressing these intergenerational conditions – through improvements in housing, nutrition, education, and access to care – offers one of the most promising and scalable approaches to improving adolescent outcomes.

Education can be understood as the process of creating environments to which the brain adapts in ways that serve both immediate and future functioning. Schools are the predominant environment of adolescents, where crucial opportunities are available to influence brain development. Advances in artificial intelligence (AI) offer the potential for increasingly personalized learning, while emerging technologies provide new ways to assess learning readiness and engagement. Classroom-based sensing approaches can integrate remote motion detection to estimate heart rate, heart rate variability, and breathing. Natural language processing and environmental sensors capturing temperature, lighting, humidity, smells, air quality, and other contextual features provide a comprehensive picture of the learning environment. These technologies also enable simultaneous assessment of multiple individuals, allowing study of synchrony between teachers and students – a

key component of social neuroscience and effective learning.

Data science and AI are well suited to integrating these complex data streams in real time to optimize educational experiences. These same technologies facilitate earlier identification of mental illness, which affects approximately one in seven adolescents. Tragically, the average time between onset of illness and any form of treatment is ten years⁷, which is especially concerning given the greater effectiveness of interventions in younger, more plastic brains. Despite challenges related to implementation, privacy and ethics, these advances hold significant promise for improving both educational and mental health outcomes.

The digital revolution has dramatically transformed the way teens learn, play and interact⁸. Within this broader upheaval, the effects of social media on adolescent health have become a lightning rod of public concern, with Australia becoming the first country to implement nationwide limits on social media use for those under 16 years. As part of debates regarding the optimal amount of screen time, it is commonly asserted that use of digital media is "unnatural", because it was not part of our evolution. Setting aside that, by that definition, reading is not natural either, the allure of digital media is actually highly aligned with deep-rooted evolutionary traits of adolescence – specifically, the drive for social connectedness, appetite for novelty, and desire for data⁹. Like fire or any powerful tool, digital technologies can be used, misused or abused. The question is no longer whether they will impact adolescent lives, but whether we will apply the best available science to shape policy governing their design, incentives and safety.

Adolescents are frequently portrayed negatively, despite decades of well-replicated research demonstrating that, in many respects, they function far better than their stereotype suggests. The vast majority of adolescents traverse this period without marked disturbance. Regrettably, negative perceptions are often internalized by adolescents themselves. This has implications far beyond fairness, because expectations influence behavior, sometimes in powerful ways. This impact is particularly consequential during adolescence, when teens are forming their identities, values, competencies, aspirations, and sense of purpose. The influence is so pervasive that it often goes unnoticed, and is perpetuated not out of malice, but out of habit. On the positive side, it is also one of the most actionable influences. By examining and revising our assumptions, we can all contribute to optimizing adolescent development by allowing for some missteps during a time of tumultuous biological adaptations, while maintaining appropriately high expectations.

The adolescent brain is not a defective adult brain. It has been forged by evolution to have distinct features from those of a child or an adult – not simply a smooth average in between. Our protracted plasticity has ensured our survival as a species. Adolescence is not a time to be managed, but a time whose potential has to be maximized. As we navigate the path from plasticity to policy, optimizing adolescent brain development will require coordinated evidence-based action across multiple domains. This includes intensifying efforts to mitigate the intergenerational effects of socioeconomic factors; leveraging advances in AI and emerging technologies to transform educational environments; actively shaping public pol-

icy and research to enhance the benefits and reduce the risks of digital technologies; and re-examining societal and personal expectations of adolescence to promote a more balanced and evidence-based view of youth.

Jay N. Giedd

Department of Psychiatry, University of California, San Diego, CA, USA

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An etiological approach to psychosis: potential benefits for treatment, research and prevention

Robin M. Murray^{1,2}, Dominic Oliver^{1,3}, Aikaterini Dima^{1,2,4,5}, Luis Alameda^{1,2}

¹Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; ²NIHR Biomedical Research Centre, South London and Maudsley NHS Foundation Trust, London, UK; ³Department of Psychiatry, University of Oxford, Oxford, UK; ⁴NIHR Oxford Health Biomedical Research Centre, Oxford, UK; ⁵Oxleas NHS Foundation Trust, London, UK

Current treatment of psychosis focuses on antipsychotic medication, and rarely addresses the factors that have contributed to the onset and persistence of the disorder. We suggest that the most useful way of facilitating treatment, research and prevention is to identify the causal risk factors to which psychotic patients have been exposed. Operating on a background of genetic vulnerability, the main types of environmental risk factors for psychosis comprise impaired neurodevelopment, substance abuse, and social adversity. In most patients with psychosis, striatal dopamine dysfunction, often mediated by disrupted gamma-aminobutyric acid (GABA)ergic and glutamatergic signaling in the hippocampus, appears to be the final common pathway from those distal risk factors to positive symptoms. There are clinical and biological differences among individuals who develop psychosis following exposure to the different risk factors. For example, those with impaired neurodevelopment are more likely to show minor physical anomalies or soft neurological signs, cognitive deficits, and brain structural abnormalities. Individualized interventions need to be offered to those patients who have been exposed to particular risk factors. For example, in addition to antipsychotic medication, patients who continue to use cannabis should be offered cognitive behavioral/motivational therapy to decrease their substance consumption, while patients who were exposed to child abuse could be offered trauma-based therapy, and antidepressants as appropriate. Of course, many patients have been exposed to more than one type of risk factor. Such patients deserve therapeutic action directed to each of those risk pathways. In addition to promoting individualized treatment, attention to etiology could benefit research, allowing the study of psychological and biological characteristics of patients whose psychosis appears to have resulted predominantly from one particular risk factor, and could open the door to universal and selective preventive strategies to decrease psychosis incidence through reducing exposure to risk factors.

Key words: Psychosis, genetic vulnerability, environmental risk factors, neurodevelopmental impairment, substance abuse, social adversity, striatal dopamine dysfunction, individualized interventions, preventive strategies

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Current treatment for psychosis focuses on blocking or modulating the dopamine D2 receptor¹. As Maj et al² have pointed out, “the reality in many clinical contexts worldwide is that the patient will just receive an antipsychotic medication plus some psychosocial support”. Antipsychotics do, of course, help most psychotic patients, but meta-analyses show that only about 20–40% achieve long-term recovery from a first episode³, and up to 30% come to be regarded as treatment resistant⁴. Thus, an approach simply focusing on excess dopamine signaling is not sufficient.

When we compare psychiatry with general medicine, we see that, while psychiatric disorders continue to be diagnosed on the basis of signs and symptoms, many somatic diseases have been delineated by cause. The futility of relying purely on symptomatology became apparent when conditions such as tuberculosis and syphilis were shown to present a wide range of manifestations which were unified by having a single identifiable cause.

Many of the diseases that affect society today are multifactorial in cause. If we take coronary artery disease (CAD) as an example, immediate treatment addresses the thrombosis in the coronary artery, the final common pathway which mediates the cardiac muscle damage. However, this does not mean that cardiologists are disinterested in the causes of the thrombosis. On the contrary, they know that hyperlipidaemia, hypertension, diabetes mellitus, cigarette smoking, obesity, and lack of exercise all increase risk of CAD, and research has traced the mechanistic pathways leading from those distal causes to the thrombosis in the coronary artery. Furthermore, in clinical practice, once they have resolved the immediate life-threatening problems, cardiologists seek out the external and internal risk factor(s) which have led to that endpoint in

the individual patient, and attempt to address these too⁵.

In psychiatry, attention is rarely paid to the different causal factors which contribute to the onset and persistence of a disorder. In this paper, we suggest that the best way to optimize research into psychosis and improve its treatment is to attend to these causal risk factors. Such an approach may help to elucidate the underlying mechanistic pathways which link distal causes to the individual patient's symptoms, and thus contribute to personalized treatment. Moreover, focusing on causal factors opens up an avenue towards prevention.

A FINAL COMMON PATHWAY TO PSYCHOSIS?

Is there a final common pathway to psychosis equivalent to the coronary artery thrombosis in CAD? The best candidate is striatal dopamine dysfunction. In 2007, Di Forti et al⁶ published a paper entitled “Risk factors for schizophrenia – all roads lead to dopamine”, in which they suggested that susceptibility genes, obstetric complications, substance abuse, and trauma could all induce dopamine dysfunction. Howes and Kapur⁷ developed this further and argued that increased presynaptic striatal dopamine is the “final common pathway” leading to aberrant salience and schizophrenia.

Since 2009, we have learned that the striatal dopamine abnormalities are often mediated by disrupted gamma-aminobutyric acid (GABA)ergic and glutamatergic signaling in the hippocampus^{8–10}. This has led to the influential hypothesis that imbalance between inhibitory and excitatory signaling causes an increased activity in midbrain dopaminergic neurons that project to the

striatum^{10,11}. The resultant increased striatal dopamine signaling leads to discrepancies between expected and perceived stimuli^{12,13}. These prediction errors are hypothesized to lead to false associations and perceptions, and in turn to delusions and hallucinations¹⁴. This is in line with the evidence that pharmacological treatments for the positive symptoms of psychosis reduce activity at the dopamine D2 receptor, and that high dopamine synthesis capacity predicts good response of positive symptoms to D2 receptor blockers^{15,16}.

Unfortunately, as yet the presence of striatal dopamine excess synthesis cannot be ascertained in a clinical setting, since positron emission tomography (PET) scans are expensive and only available in a small number of centres. There is an urgent need for a more practical means of estimating striatal dopamine. A possible candidate for this is neuromelanin-sensitive magnetic resonance imaging (MRI)¹⁷, whose cost is similar to that of structural MRI.

While excess dopamine synthesis in the striatum appears to be the final common pathway underlying positive symptoms in most patients with psychosis, it does not explain negative symptoms or cognitive impairment. Dysfunction of other neurotransmitter systems has been involved in this respect, including glutamate, GABAergic and cholinergic dysfunction. Evidence points particularly to glutamate, since phencyclidine (PCP) and ketamine, antagonists of the glutamatergic N-methyl-D-aspartate receptor, can induce negative and cognitive symptoms in healthy individuals¹⁸⁻²⁰. Furthermore, patients deemed resistant to antipsychotics do not show the expected striatal dopaminergic excess, and some evidence suggests that they exhibit glutamatergic abnormality^{21,22}.

As with the risk factors for CAD, we now have relatively good knowledge of the causal risk factors, sometimes termed component causes, which drive onset of psychosis. However, as yet, we have a limited understanding of the neurochemical pathways between the distal causal factors and the patients' symptoms. Understanding the mechanistic pathways which link the former to the latter would allow psychiatrists to better tailor effective treatments to the individual patient.

GENETIC RISK

Similarly to CAD, the genetic vulnerability to psychosis is mostly polygenic²³, with a significant overlap of polygenic risk between schizophrenia and bipolar disorder (approximately two thirds of genes overlap)²⁴. A recent study has shown that genetic liability which is unique to schizophrenia and not shared with bipolar disorder is associated with poor cognition, while genetic liability unique to bipolar disorder is associated with better cognition²⁵. This confirms our proposal two decades ago that – on a background of shared genetic predisposition to psychosis – schizophrenia, but not bipolar disorder, is linked to additional genes or early insults which impair neurodevelopment²⁶. Owen et al²⁷ cited the occurrence of copy number variants in schizophrenia as the most obvious example of this, as the implicated variants are associated with a range of developmental disorders, from learning disability through epilepsy to schizophrenia.

Genome-wide association studies (GWAS) of schizophrenia particularly implicate genes involved in neurodevelopment and in synaptic function, and those with high expression in excitatory glutamatergic neurons from cerebral cortex and hippocampus, as well as cortical inhibitory GABA interneurons²³. As previously mentioned, GABAergic and glutamatergic systems have important effects on dopaminergic function, thus indicating that genetic variants in these systems may alter the regulation of dopamine signaling in psychosis. Recently, Sportelli et al²⁸ identified a set of genes which show dopaminergic selectivity. A higher polygenic risk score on this set of genes predicted greater dopamine synthesis in the striatum and greater striatal activation during reward anticipation.

The most common copy number variant found in people with schizophrenia is the 22q11.2 deletion, with up to 25% of carriers developing psychosis. In contrast, individuals with 22q11.2 duplication are protected from risk of schizophrenia. Interestingly, non-psychotic individuals who carry the deletion show an excess of striatal dopamine, while those with the duplication have lower striatal dopamine than normal subjects²⁹.

ENVIRONMENTAL RISK FACTORS

In this issue of the journal, Aymerich et al³⁰ provide an umbrella review of meta-analyses concerning environmental risk factors for psychosis, classified by the extent of supportive evidence. For the purposes of this paper, we have compressed the risk factors which they consider to have convincing, highly suggestive, or suggestive evidence into three overall types: a) those indicating an impaired neurodevelopment (e.g., minor physical anomalies, low premorbid IQ, birthweight under 2,000 g, being small for gestational age, soft neurological signs, smoking during pregnancy, maternal infection during pregnancy, winter season of birth); b) substance abuse (especially cannabis use 5 to 7 days per week); and c) social adversity (e.g., childhood adversities, being a first- or second-generation immigrant, Black-African or Black-Caribbean ethnicity in England).

Impaired neurodevelopment

Three groups of prenatal and perinatal risk factors have been significantly associated with later psychosis: a) complications of pregnancy; b) abnormal foetal growth and development; and c) complications of delivery³⁰⁻³².

Early hazards to the developing brain can cause neurodevelopmental impairment³³. For example, pre-term birth or asphyxia can result in smaller brain volumes and lower cognitive abilities^{34,35}. In 1971, Mednick et al³⁶ suggested that perinatal hypoxia might damage the hippocampus, thus increasing risk of psychosis. In accord with this, patients with schizophrenia who were exposed to obstetric difficulties have smaller hippocampi than both patients without such exposure and normal subjects^{37,38}.

Froudust-Walsh et al³⁹ followed up babies who had been born pre-term into adulthood. PET scans showed that neonatal hippocampal injury was associated with altered striatal dopamine syn-

thesis, thus providing a potential mechanism linking early brain injury to adult psychotic illness. Animal studies have shown that perinatal administration of methylazoxymethanol acetate (MAM) in pregnant rats, or lesioning the hippocampus in neonatal rats, both lead to behavior considered psychosis-like as well as to dopaminergic abnormalities in adult rats^{40,41}.

Prenatal maternal infection has also been associated with later psychosis⁴². Two models of psychosis rely on infection during gestation in rodents: maternal gestational exposure to the human influenza virus⁴³, and administration of the viral mimic polyinosinic-polycytidylic acid⁴⁴. Both models result in a reduced number of GABAergic hippocampal neurons. The consequent inhibition results in both glutamatergic and dopaminergic dysfunction downstream⁴⁵⁻⁴⁷.

Finally, recent evidence suggests that excessive pruning of glutamatergic synapses during adolescence is not only associated with decreased grey matter volumes, but may also alter the balance between cortical excitatory and inhibitory neurotransmission in schizophrenia⁴⁸.

Substance abuse

There is good evidence that psychostimulants, such as amphetamines and cocaine, can induce psychosis. Indeed, methamphetamine-induced psychosis is a major problem in some Pacific countries, Australia, South Africa, and parts of North America^{49,50}. These substances are all dopamine receptor agonists, directly exacerbating the dopaminergic abnormalities seen in psychosis, as well as triggering psychosis onset.

Epidemiological studies have consistently shown a relationship between cannabis use and the development of psychosis, with increased risks ranging from 1.5 to 9^{51,52}. Initially, objections were raised to the hypothesis that cannabis use was causal to psychosis, with sceptics citing possible abuse of other substances, or self-medication for psychotic or prodromal symptoms. However, all of these hypotheses, as well as the idea that cannabis use was a consequence of genetic predisposition to schizophrenia, have been disproven⁵³. Furthermore, meta-analysis has demonstrated a clear dose-response relationship between the level of use, as well as the potency of cannabis preparation, and the risk for psychosis⁵⁴. Importantly, continued use by individuals with psychosis is associated with increased risk of recurrence of psychotic symptoms, and rehospitalizations⁵⁵.

Animal studies show that the endogenous cannabinoid system interacts with the dopamine system in the basal ganglia. Tetrahydrocannabinol (THC) stimulates CB₁ receptors, which modulate pre-synaptic glutamate and GABA release. In this way, THC alters the balance of excitation and inhibition reaching dopamine cells, with an increase in firing and resultant elevations of dopamine release⁵⁶.

As both the endocannabinoid and dopamine systems are actively developing during adolescence, it is likely that any interference with this signaling during that period will result in psychopathological phenotypes later in life. Thus, in juvenile rodents,

THC disinhibits prefrontal cortex network function, with consequent hyperactivity of subcortical dopaminergic activity leading to a range of cognitive and affective phenotypes that resemble those observed in schizophrenia⁵⁷.

THC administration to humans is associated with medial temporal and striatal activation which is specifically correlated with transient psychotic symptoms^{58,59}. Some⁶⁰, although not all⁶¹, studies in healthy volunteers have reported that acute administration of THC leads to increased striatal dopamine release. More recently, Ahrens et al⁶² have used neuromelanin-sensitive MRI, which – as previously noted – reflects dopamine synthesis and release, to study cannabis users. The users showed higher neuromelanin signal in the substantia nigra/ventral tegmental area, as did people with early schizophrenia.

Social adversity

In a seminal meta-analysis, Varese et al⁶³ reported that childhood adversity (abuse, neglect or bullying) was associated with increased risk for adult psychosis (overall odds ratio, OR=2.78). Dragioti et al⁶⁴ further estimated that 38% of schizophrenia cases could be prevented if childhood trauma were eradicated. These findings have been confirmed by the above-mentioned umbrella review by Aymerich et al³⁰, which reports that childhood adversities are associated with an increased risk for psychosis (OR=2.87), and are the potentially modifiable risk factor with the highest population attributable fraction (40.69%). Psychological mediators proposed to explain the association between childhood adversity and psychotic disorders include negative cognitive schemas about the self and others, as well as symptoms of post-traumatic stress disorder (PTSD)^{65,66}.

A meta-analysis by Beards et al⁶⁷ showed 3-fold increased odds that adults with psychosis had experienced adverse life events in the period prior to onset. Psychotic patients are also more likely to live alone, to be unemployed, and to live in overcrowded conditions, not only at first contact with psychiatric services but up to five years prior to the onset of psychosis⁶⁸.

The umbrella review by Aymerich et al³⁰ reports an increased incidence of psychosis among first- and second-generation immigrants (risk ratio, RR = 2.069 and 1.845, respectively); people of Black-African (RR=4.891) and Black-Caribbean (RR=5.224) ethnicity in England; and North African immigrants in Europe (incidence rate ratio, IRR=2.22). Psychosocial stress, partly generated through discrimination⁶⁹⁻⁷¹, may be a key driver of psychosis risk in such individuals⁷²⁻⁷⁴.

Chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis, with high basal/unstimulated cortisol levels, is reported following repeated exposure to social stressors, including in individuals with psychosis⁷⁵⁻⁷⁸. Conversely, cortisol responses to awakening and to social stressor tasks are attenuated among individuals with psychosis relative to controls⁷⁹⁻⁸¹, since the high basal cortisol levels reduce the ability of the HPA axis to mount an appropriate stress response⁸²⁻⁸⁵.

Psychotic patients who had been subject to severe abuse in childhood or who have been immigrants show elevated dopa-

mine synthesis in the associative striatum in adulthood^{86,87}. Selten et al⁸⁸ have suggested that the long-term experience of adversity and exclusion (causing social defeat) impacts the dopamine system. In accord with this, Morgan et al⁸⁹ hypothesized a socio-developmental pathway in which exposure to adversity and trauma impacts on the stress response and dopamine system to create an enduring liability to psychosis.

CLINICAL ADVANTAGES OF AN APPROACH TO PSYCHOSIS BASED ON ETIOLOGY

The above evidence suggests that individuals vulnerable to psychosis inherit genes which predispose them to develop an imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) signaling. This results in increased activity of midbrain dopaminergic neurons that project to the striatum.

The abnormal dopamine signaling can then be further exacerbated by three main types of environmental risk factors: neurodevelopmental impairment, frequent substance (in particular cannabis) use, and social adversity. In addition, deviant neurodevelopment involving abnormal glutamate connectivity may contribute to negative symptoms, cognitive deficits, and non-response to treatment with dopamine blockers.

Bearing such an etiological model in mind could enable psychiatrists to achieve a more personalized approach to treatment of psychosis². Obviously, all people with psychosis should be offered antipsychotics. But, in addition, it is important that the underlying risk factors which are driving the psychosis be also addressed, if possible. While we acknowledge that an individual with psychosis may have been exposed to several risk factors, and that there are cases in which no risk factor can be identified, we shall concentrate on the characteristics and treatment of those prototypical patients in whom exposure to one particular risk factor appears to have been crucial to the development of psychosis.

Prototypical patients with impaired neurodevelopment

Psychotic patients who have been subject to early neurodevelopmental insults tend to show characteristic epiphenomena. These include minor physical anomalies and soft neurological signs, both indicative of altered foetal development^{90,91}. Many exhibit low premorbid IQ⁹². This is found in patients with copy number variants, but is more frequently polygenic⁹³, and may also be consequent upon obstetric complications⁹⁴. These patients present with early age at illness onset⁹⁵, and more neurocognitive⁹⁶ and MRI abnormalities^{33,97,98}. Patients who have been exposed to early environmental hazards are particularly likely to present negative symptoms and to have a poor outcome^{99,100}.

The Lewis-Murray Obstetric Events Scale¹⁰¹ is a 15-item tool for assessing prenatal and perinatal events, especially in individuals with psychosis. It includes three sections (Lewis categories A, B and C). Category A covers risk factors occurring during pregnancy, such as maternal infections, Rh incompatibility, severe

pre-eclampsia, bleeding before delivery, threatened miscarriage. Category B covers risk factors concerning foetal growth and development, such as twin delivery, abnormal gestational age (pre-term, post-term), low birthweight (<2,500 g), physical anomalies. Category C covers difficulties in delivery, such as premature membrane rupture, very long/short labor, umbilical cord prolapse, complicated C-section, abnormal foetal presentation, forceps use, prolonged incubator stay. Each event can be rated as “definite”, “equivocal” or “absent”. The assessment is usually based on maternal interview, but it is better if the patient’s obstetric records can be rated. The use of this tool can be suggested in clinical practice to identify individuals with psychosis who are likely to have suffered from neurodevelopmental impairment.

These patients should also have an MRI scan and a neuropsychological assessment. Cognitive deficits are often associated with poor response to antipsychotics and designation as treatment resistant¹⁰², as are brain structural abnormalities^{103,104}. Treatment-resistant patients do not show the characteristic striatal dopaminergic excess on both PET scans and neuromelanin-sensitive MRI. Rather, they may show increased glutamate in the anterior cingulate cortex^{21,22}. It is, therefore, not surprising that they do not respond to conventional dopamine blockers.

Psychotic patients with neurodevelopmental damage should receive cognitive remediation^{105,106} to maximize their intellectual function, and assertive community support to help them negotiate the complexities of society such as how to obtain social benefits or manage their money¹⁰⁷. Support to family carers is invaluable. Clozapine should be considered early in the course of the psychosis – for example, by early intervention services^{108,109}.

Prototypical patients with frequent substance use

Patients who develop psychosis following frequent substance use show a different profile from those who suffered neurodevelopmental insult. They tend to have had good premorbid social and academic function, and have an average or high premorbid IQ^{110,111}. In addition, they present to clinical services earlier than non-using psychotic patients¹¹², and at onset their MRI scans usually do not show evidence of neurodevelopmental damage¹¹³. Their outcome depends on whether they continue or stop their drug use^{55,114}.

For screening of cannabis use in the last six months, the Cannabis Use Disorders Identification Test - Revised (CUDIT-R)¹¹⁵ can be suggested for use in clinical practice. This tool is designed for self-administration and includes eight items. The Cannabis Experiences Questionnaire (CEQ)¹¹⁶, whose original version includes 56 items (while short forms include 42 or 14 items), can be used for a more in-depth assessment of experiences related to cannabis assumption. The ASSIST (Alcohol, Smoking and Substance Involvement Screening Test)¹¹⁷, including eight questions concerning use of various substances, can be suggested for a broader screening of drug use. Furthermore, specific urine or blood tests can be used to identify the assumption of various substances.

The choice of the antipsychotic has a bearing on the likelihood

of patients with substance abuse to relapse into drug taking. Substance dependent patients show low dopamine in the ventral striatum, which exacerbates drive to use substances. Craving, for example for cannabis, can be exacerbated by antipsychotics which cause high D2 receptor blockade¹¹⁸. Partial D2 receptor agonists, such as aripiprazole and cariprazine, are associated with a better outcome¹¹⁸. Pharmacological help with a preparation such as Sativex (containing low-dose THC and cannabidiol in a spray) to cover substance withdrawal can also be helpful, particularly given the potential of cannabis withdrawal to precipitate or exacerbate psychosis symptoms¹¹⁹.

Patients with psychosis associated with substance use frequently fall between psychiatric and drug addiction services. Therefore, Di Forti et al¹²⁰ established a specialized clinic for psychotic patients who use cannabis, which offers one-to-one therapy with motivational interviewing and support as well as attendance at a weekly peer group. A reduction in dependence was observed, with 74% of participants achieving abstinence and 70% returning to work or education.

Prototypical patients with a history of social adversity

Child abuse is associated with more severe positive and depressive symptoms; neglect is related to more severe negative symptoms¹²¹; and both abuse and neglect are associated with poor social functioning¹²².

The Trauma and Life Events (TALE) checklist¹²³ is a 20-item scale covering physical/sexual abuse, emotional neglect, bullying, feeling unsafe in childhood, unusual experiences (voices, visions), and distress from mental health service contact (restraint, assault). Its use can be suggested in clinical practice to identify those psychotic patients who have a history of trauma.

Treatment focused on psychotic patients who have suffered childhood adversity is at an early stage. Trials using trauma-focused cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR) have been conducted^{124,125}. These trials are based on the hypothesis that treating PTSD symptoms may not only improve these, but also the related psychosis. Indeed, dissociation puts reality testing under pressure and may alter the ability of an individual to distinguish post-traumatic intrusions as such, externalizing them in the form of a perceptual abnormality. This raises the intriguing possibility that addressing the mechanism may improve the outcome as well. Preliminary results from these trials are very encouraging¹²⁶.

Much research in recent years has focused on an affective pathway to psychosis. This model postulates that people exposed to social adversity will often develop low mood and anxiety, which in turn makes them vulnerable to developing delusions and hallucinations¹²⁷. People with psychosis following social adversity can have significant levels of depression and anxiety, that may be enough to affect reality testing and precipitate onset or relapse^{128,129}. Therefore, among people with trauma and psychosis, low mood and anxiety – even at sub-diagnostic level – should be carefully assessed, and treated not only with CBT but also antidepressants

where appropriate, along with antipsychotics.

Exposure to several risk factors

Clinicians will recognize the prototypical risk patients that we have described above, but will also point out that many patients with psychosis have been exposed to several risk factors. These may be of similar type (e.g., those born prematurely may have also suffered asphyxia and other perinatal complications; or those who were abused as a child may have then suffered adolescent bullying as well as adverse life events in adult life). But individuals may have also been exposed to different types of risk factors. For example, those exposed to childhood adversity at home may gravitate in their adolescence to street gangs and exposure to substance use¹³⁰. They will then share some of the characteristics of those from the childhood adversity group and those from the substance abuse group.

Patients who have been exposed to several risk factors deserve therapeutic attention directed to each of these factors in the same way that cardiologists will address several risk factors for CAD – such as hyperlipidaemia, cigarette smoking, and lack of exercise – in the same individual. This situation requires a flexible and integrative approach where the treatment priorities can be set hierarchically based on the predominant feature (e.g., focus on substance abuse could take place first, and addressing the consequences of social adversity could occur once substance abuse ceases or at least decreases significantly).

Of course, when considering the effects of several environmental risk factors, it is important to recall that many patients with psychosis have inherited genetic vulnerability to illness. Studies have been examining the relationship between genetic and environmental risk. For example, genetic risk for schizophrenia and heavy cannabis use appear to act as independent risk factors for psychosis. Many people with a high polygenic risk score for schizophrenia develop psychosis without ever using cannabis, while others with a low polygenic risk score only develop psychosis following very heavy cannabis use. However, in the majority of patients, the two factors combine to push the individual over the threshold for expressing psychosis⁵³.

Epigenetic changes, especially DNA methylation, may help clarify how exposure to more than one risk factor contributes to the development of psychosis¹³¹. For example, individuals exposed to childhood adversity are both more likely to subsequently abuse cannabis and then to develop psychosis. An ongoing study is examining whether this susceptibility to the psychotogenic effects of cannabis is mediated by the changes in methylation consequent upon childhood adversity¹³².

ADVANTAGES FOR RESEARCH

In addition to allowing individualization of treatment, the adoption of an etiological approach should also facilitate research, since the usual strategy of studying all patients diagnosed as hav-

ing schizophrenia according to the DSM-5 or ICD-11 criteria/requirements leads to sample heterogeneity, with the inclusion of patients whose psychoses have resulted from quite different risk factors. It is likely that, for example, neuropsychological or imaging characteristics of patients with neurodevelopmental impairment are obscured by being merged with patients with whom they have little in common etiologically. A more productive research strategy would be to identify prototypical patients whose psychosis appears to have resulted predominantly from one particular risk factor and then study the psychological and biological characteristics of these patients. This would also facilitate research into the underlying mechanisms, linking a particular risk factor to the disorder and allowing to explore how it alters clinical trajectories and outcome.

This strategy could also result in more productive clinical trials. We have already seen how CBT for psychotic patients with PTSD symptoms is reported to be very effective¹²⁴, while its effectiveness for psychosis as a whole remains disputed. Another possible approach stems from the evidence that glutamatergic abnormalities may be particularly important in patients with neurodevelopmental impairment, who, as we have seen, are more likely to be diagnosed as treatment resistant. Glutamatergic drugs have been repeatedly tried and failed in trials of psychotic patients as a whole. It may be more productive to examine their effectiveness in patients with evidence of neurodevelopmental impairment, with treatment-resistant schizophrenia, or in those shown to have glutamatergic abnormalities on magnetic resonance spectroscopy.

Such approaches can be supported through the use of platform trials¹³³, which are designed to test several different putative treatments using a common control condition. Platform trials allow participants to be stratified according to exposure to different risk factors, enabling the investigation of differential treatment effects across predefined subgroups. As evidence accumulates, arms can be dropped (no effect seen) or added (promising molecule identified). Thus, platform trials offer an efficient means of testing targeted treatments in psychotic patients exposed to different risk factors, addressing heterogeneity that may obscure effects in conventional trials.

It is worth reflecting on the fact that the importance of individual risk factors for psychosis may vary both geographically and temporally. The varying prevalence of different risk factors – such as substance abuse – in different geographical and temporal contexts suggests that the clinical and biological profile of psychosis may not be constant across all countries and all times; rather it may reflect the frequency of the different risk factors in the specific situation. Thus, researchers should not necessarily expect psychosis in low-income countries to have the same characteristics as in high-income settings.

OPENING THE DOOR TOWARDS PREVENTION

Preventive approaches are common in medicine and often involve putting in place strategies to limit exposure to a particular risk factor. Universal prevention (i.e., interventions that target the gen-

eral population) has proved valuable: an example is the successful public health campaign to reduce tobacco smoking in many Western societies.

A focus on causal risk factors for psychosis could inform such programmes. Thus, for neurodevelopmental abnormalities, this could involve improving pre- and perinatal care or increasing access to family planning services to reduce risk of pregnancy and delivery complications.

In many countries, increases in the frequency and potency of cannabis use have been followed by reports of an increase in the incidence of psychosis¹³⁴. Public health policies could be used to reduce such harms. These are challenging to implement, given the influence of the illegal cannabis market and the rapid expansion of commercial delivery of cannabis, but are much needed. Some school-based interventions have shown that it is possible to improve young people's attitudes to substances and mental health. Iceland is one of the few countries to have successfully implemented this strategy nationally¹³⁵.

To our knowledge, no universal preventive trials have been conducted to demonstrate the impact of diminishing exposure to risk factors specifically to reduce the incidence of psychosis¹³⁶. However, a randomized controlled trial among 13,035 adolescents was carried out in Bihar, India, testing whether a health promotion intervention could improve the emotional climate in 75 schools. Eight months later, children who received the intervention reported substantially better emotional climate in their schools than control children, as well as improvements in depression, bullying and violence¹³⁷. Building on the success of that trial, mental health workers in Tokyo have persuaded the city government to test a similar intervention across four boroughs¹³⁸.

More selective strategies (i.e., interventions that target groups that are at risk due to specified risk factors) are often implemented within medicine. An obvious method to address neurodevelopmental risk would involve ensuring that mothers with psychosis have optimal antenatal care and close supervision at the time of birth, so that the genetically susceptible baby is not exposed to prolonged labor or hypoxia. Similarly, reducing substance use in people already using substances through effective addiction treatment could decrease risk of developing psychosis. Finally, in identified cases of child abuse, family interventions can be used to improve parenting practices¹³⁹.

CONCLUSION

A narrow focus on antipsychotic medication is insufficient to address the complexity of psychosis, which arises from the interaction between genetic vulnerability and environmental risk factors. By identifying and targeting the specific causal exposures that contribute to the onset and maintenance of psychosis, clinicians and researchers can better understand the heterogeneity in the onset of the disorder, its presentation and its outcomes.

Recognizing that these distinct risk factors are likely to converge on common dopaminergic mechanisms, yet are associated with different clinical and biological profiles, supports the need

for more personalized and mechanism-informed interventions. Integrating pharmacological treatment with psychological and social interventions tailored to an individual's risk history not only holds promise for improving clinical outcomes, but also provides a framework for developing preventive strategies aimed at reducing exposure to modifiable risk factors.

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

Paolo Fusar-Poli^{1,4}, Andrés Estradé¹, René Rosfort⁵, Annemijn van der Schaar⁶, Jordan Searle-Barnes⁷, Matthew Jackman⁸, Parth Sharma⁹, Aqsa Shaikh¹⁰, Vanessa Lacey¹, Sameera M. Jahagirdar¹², Anu Savio Thelly¹³, Giovanni Stanghellini^{14,15}, Cecilia Maria Esposito¹⁶, Milena Mancini¹⁷, Ilaria Bonoldi¹, Stefano Damiani², Elisa Figazzolo^{1,2}, Giorgia Torta², Andrea De Micheli^{1,3}, Laura Fusar-Poli^{2,18}, Ilaria Basadonne², Samuele Cortese^{19,23}, Dong Keon Yon²⁴, Giovanni Castellini²⁵, Mario Maj²⁶

¹Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, King's College London, London, UK; ²Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy; ³OASIS Service, South London and Maudsley NHS Foundation Trust, London, UK; ⁴Department of Psychiatry and Psychotherapy, University Hospital, Ludwig-Maximilians-University, Munich, Germany; ⁵S. Kierkegaard Research Centre, University of Copenhagen, Copenhagen, Denmark; ⁶University of Humanistic Studies, Utrecht, The Netherlands; ⁷Department of Social Sciences, University of Glasgow, Glasgow, UK; ⁸Centre for Disability Research and Policy, University of Sydney, Sydney, NSW, Australia; ⁹Sangath India, Goa, India; ¹⁰Hamdard Institute of Medical Sciences and Research, New Delhi, India; ¹¹Gendercare Ireland, Waterford, Ireland; ¹²West Middlesex University Hospital, Chelsea and Westminster NHS Trust, London, UK; ¹³Department of Palliative Medicine, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Puducherry, India; ¹⁴Department of Health Sciences, University of Florence, Florence, Italy; ¹⁵D. Portales University, Santiago, Chile; ¹⁶Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ¹⁷Department of Psychology, University of Chieti and Pescara "G. d'Annunzio", Chieti, Italy; ¹⁸IRCCS Maugeri, Pavia, Italy; ¹⁹Developmental EPI (Evidence synthesis, Prediction, Implementation) Lab, Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK; ²⁰Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK; ²¹Hampshire and Isle of Wight Healthcare NHS Foundation Trust, Southampton, UK; ²²Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York City, NY, USA; ²³Department of Precision and Regenerative Medicine - Jonic Area, University of Bari "Aldo Moro", Bari, Italy; ²⁴Department of Pediatrics, Kyung Hee University College of Medicine, Seoul, South Korea; ²⁵Psychiatric Unit, Department of Health Sciences, University of Florence, Florence, Italy; ²⁶Department of Psychiatry, University of Campania "L. Vanvitelli", Naples, Italy

We present here the first bottom-up review of the lived experience of trans persons, co-written by experts by experience and academics. We sourced the medical and non-medical literature, focusing on first-person narratives, and critically extracted experiential themes, which were reviewed and appraised in collaborative workshops and eventually shared through a cloud-based system. Numerous experts by experience and academics from diverse gender, ethnic and cultural backgrounds were involved in the above steps and co-wrote the paper. The four overarching themes were: a) the lived experience of trans persons, b) the lived experience of gender affirmation, c) the experience of trans persons in the social and cultural context, and d) the lived experience of receiving care and support. The lived experience of trans persons is characterized by a rich diversity of gender identity experiences, which include identifying as male or female, or simultaneously as male and female and other genders, or as gender fluid. The first-person narratives indicate that common experiences may be of discovering an uncertain gender identity and feeling in the wrong body, together with some degree of mind-body disconnection. However, many trans individuals may feel satisfied with their bodies and identities. The lived experience of gender affirmation includes a process of searching for a bodily and mental redefinition of the self and – at times – fighting oneself to accept one's gender identity. Gender affirmation involves changes in the body to communicate the lived gender identity, as well as behavioral changes. The first-person narrative also highlights the emotional impact of gender affirmation, including the restoration of a sense of self, experiencing a strong emotional reaction to gender-affirming care, and, in a few cases, deciding to stop or reverse gender affirmation. The experience of trans persons in the social and cultural context can be characterized by an initial attempt to hide one's gender identity. This may be followed by coming out to others and wanting to be recognized by others in their lived gender. Exposure to high levels of transphobia, institutional discrimination and violence are commonly shared experiences. These include feeling wrong and dehumanized, pressured to "pass" as females or males, and suffering misgendering, deadnaming and verbal microaggressions. These experiences are frequently amplified by institutional discrimination and emotional, physical and sexual abuse. While some trans persons may struggle with family acceptance, others experience family and kinship structures as a safe base that provides support. Similarly, friends and romantic relationships may be experienced as sources of rejection or instead of happiness, resilience and restoration. The lived experience of seeking help and receiving general health care and support may be characterized by feeling rejected, disvalued and objectified, but in other cases validated and cared for. Trans persons may feel lost in the maze of gender-affirming care and challenged when receiving a gender dysphoria diagnosis, although others experience a sense of relief. Mental health care may be feared, as individuals feel vulnerable and exposed, and regard it as a gatekeeping to receive gender-affirming care. In other cases, it is experienced as restorative and truly healing. The narratives provided in this paper have high educational and social value, informing medical and psychological practices and research as well as public health approaches, and promoting anti-discrimination policies and social change. This study gives voice to the lived experience of trans persons to overcome stigma and allow us to fully understand the varied nature of our gender expression and identity.

Key words: Trans persons, lived experience, co-production, first-person narratives, gender identity experiences, gender affirmation, transphobia, discrimination, gender dysphoria

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Few concepts have generated more controversy over the past half-century than those of "sex" and "gender". Although "sex" is often incorrectly thought to have the same meaning as "gender", the two terms refer to interconnected but different constructs.

Sex is a multidimensional biological construct based on anatomy, physiology, genetics and hormones¹. All animals (including humans) have a biological sex, which is typically categorized as male or female; however, different sexual phenotypes and intersex variations may occur in nature^{2,3}. For example, some animals and plants can change their sexual functional expression⁴.

Gender is also biologically modulated, but it has more pronounced socio-personal dimensions in humans, as intentional and self-interpretative beings⁵⁻⁸. Gender identity expresses one's innermost experience of self as female, male, a blend of both, or neither – how individuals perceive and understand themselves⁹. One's gender identity is self-identified, and can be the same (i.e., cisgender) or different (e.g., transgender) from the sex assigned at birth, and may or not correspond to a society's cultural expectations based on biological sex traits (e.g., a person with a typical female sex may or not identify her gender as a woman). By de-

fault, societal assumptions are “cisnormative”, i.e., all persons are expected to identify with the sex they are assigned at birth^{8,10}. A person’s gender identity may change throughout life (gender fluidity).

Gender expression refers to how gender is enacted through behavior, clothing, body characteristics, voice, or chosen pronouns (e.g., he/she/they), which may or may not conform to socially defined characteristics⁹. Gender is different from a person’s sexual orientation (i.e., who we are attracted to), which is defined as an enduring or changing emotional, romantic or sexual attraction to other people (e.g., heterosexual, homosexual, bisexual, asexual, other)¹⁰⁻¹².

Clarifying these terms is essential, because the trans community is constantly evolving, and terms may have different meanings depending on context. In this paper, we pragmatically use “trans person” as a working umbrella term to describe individuals whose gender identity and/or expression is different from cultural expectations based on the sex they were assigned at birth. Alternative working umbrella terms such as “transgender and gender diverse” or “transgender and gender nonconforming” were carefully considered and discussed, but they were felt to be too academic/medical.

Available estimates indicate that the proportion of trans persons ranges from 0.1 to 1.3% of the adult population (18+ years) and is about 1.4% of the youth population (13-17 years)¹³⁻¹⁵. These data are highly variable depending on the region, definition and methods of assessments of trans persons¹⁶, and potential under-reporting due to marginalization.

In the past years, numerous publications in the medical literature have described trans persons in clinical, epidemiological and therapeutic settings^{17,18}. These papers are limited by a narrow academic focus and a language that may blur the understanding of the lived experience of trans persons. On the other hand, numerous reports, such as autoethnographic studies, describe the subjective experiences of trans persons¹⁹⁻²³, but they offer only fragmented, particular and contextual narratives that do not fully advance broader understanding. To our best knowledge, there are no studies that moved from lived experience to theory (a bottom-up approach), and in which a global network of individuals with lived, learned or laboured experience (i.e., experts by experience) and academics were mutually engaged in a joint narrative. This paper is a bottom-up review of what it is like to be a trans person. Our approach is essentially based on sharing perspectives and meanings about the individual’s experience whilst maintaining each subject’s diction and narrative style, without fitting them within pre-established conceptual frameworks or narratives²⁴⁻²⁸.

In the first step, we established a collaborative core writing team of experts by experience and academics (psychiatrists, psychologists, philosophers, and social researchers) from diverse genders, ethnic and cultural backgrounds. Some experts by experience were also academics. Critical (unsystematic) searches of Web of Science (including SciELO Citation Index, MEDLINE, and Web of Science Collection databases), PubMed, and EBSCO (including PsycINFO, MEDLINE and CINAHL databases) were performed

until October 2025 in English, Italian, Spanish and Danish.

The search terms were: (transsexual* OR “gender identity disorder” OR “gender dysphoria” OR trans-identifying OR “gender nonconforming” OR “gender atypical” OR “gender variant” OR non-binary OR genderqueer) AND (qualitative OR interview OR “focus group” OR “lived experience” OR phenomenolog* OR autoethnograph* OR ethnograph*). We included qualitative studies that provided first-person accounts (ethnographic and qualitative reports, autobiographical materials, books, artistic productions) and involved trans persons (some of whom were also academics), across different age groups and countries. Researchers screened titles and abstracts, and studies were selected by consensus. Discrepancies were resolved in consultation with a senior researcher.

The current study is not restricted to any psychiatric or medical diagnosis, such as gender dysphoria (i.e., the experience of distress and unease associated with the incongruence between a person’s gender identity and sex assigned at birth), although papers focusing on this latter diagnosis were also included. The reason is that we did not regard the experience of trans persons as a psychopathological or medical condition. Rather, we aimed at reconstructing the most common personal experiences of trans persons (including both the negative and the positive ones), as well as their social experiences (e.g., of discrimination, but also of understanding or support) in their family and sociocultural environment, and their experiences (again both positive and negative) of accessing health facilities.

Similarly, we did not restrict the focus on the lived experience to trans persons in mental health services, because this would have shifted our attention to the psychological problems they may have (e.g., depression, which was the subject of a previous publication²⁷). This approach is similar to that adopted in our paper investigating the lived experience of suicidal behavior²⁹, which acknowledged that not all individuals who attempt suicide have a mental health problem. Finally, although we addressed the social context in a specific section, we focused on the individual experience and did not primarily address sociological issues, that have been covered in other publications³⁰⁻³².

In a second step, researchers conducted a thematic synthesis of selected articles and generated a preliminary list of descriptive themes and sub-themes. This material was then shared within the core writing team and preliminarily classified across four overarching descriptive themes: the lived experience of trans persons, the lived experience of gender affirmation, the experience of trans persons in the social and cultural context, and the experience of receiving care and support, each of which included several sub-themes. These themes and sub-themes have narrative value only, and are not assumed to represent entirely distinct categories. Actually, they are interconnected.

In the third step, experts by experience and academics collectively interacted to draft and review the manuscript via a shared Google Drive platform. Experts by experience were offered reimbursement for their time, adhering to available guidelines for participatory research³³. Quotations from members of the co-writing team are cited in the text as “personal communications”.

We fully acknowledge that trans persons are as different from each other as non-trans persons. Although this study outlines some common themes underlying their lived experiences, it is neither assumed that the experiences reported are exhaustive, nor that they are systematically applicable to all trans persons. The aim of the paper is to highlight the varied nature of the lived experience of these persons, as emerging from their first-person accounts, in order to overcome stigma and to foster their global understanding and inclusion.

THE LIVED EXPERIENCE OF TRANS PERSONS

This section explores several interconnected dimensions of the lived experience of gender identity in trans persons.

Experiencing a rich diversity of gender identities

Some trans persons may indicate that their gender identity exists within a binary male-female framework (*"In terms of gender I self-define as a woman"*³⁴), that is relatively stable over time: *"I know I'm a woman. That's very clear to me and that's the first feeling that I've ever had about, like, personal identity"*³⁵; *"I always knew I was female"*³⁶.

Other trans persons describe gender identities that do not conform to the binary male-female dichotomy: *"I don't really identify with any binary"*³⁷; *"I am my own gender and it's not male and it's not female"*³⁸. For example, the person may experience different aspects of masculinity and femininity simultaneously: *"I feel a kind of a woman, a kind of a man but never fully a woman, never fully a man. I feel I have a lot of both, that's why: hybrid"*³⁴; *"I experience my gender as both male, female, and other"*³⁷.

In some cases, trans persons may continuously swing across the male-female binary polarity: *"So it's like a pendulum. It swings from all boy to really girl"*³⁹. These individuals may experience an ambiguous gender identity that challenges conventional gender dichotomies: *"Is this a man or a woman? This is the question that I hear the most from completely different people! But for myself, it is super interesting and transgressive, because I don't give the people the comfort of being able to identify my gender"*³⁴; *"I don't want people to look at me and just see a woman, you know, I want people to look at me and maybe wonder"*⁴⁰.

Other trans persons feel that their experience of gender identity is not swinging across binary polarities but intrinsically fluid and dynamic. Gender changes over time, and is situational or relational, shifting within different contexts: *"Gender is fluid. People can identify as cis, but then not later on in life, or they could identify as trans and then cis later on in life, and it changes and that's fine"*⁴¹.

Other people experience their gender identity as akin to a "sandcastle" that can be shaped and reshaped over time: *"We're sort of molding ourselves to how we wanna be... why place an unnecessary restriction on yourself?"*³⁶, or something that can be experimented with and adapted to their singular experience: *"It is something that*

*you can work with. It's not a rock, it's like putty. You mold it around yourself, and it makes you who you are"*⁴¹.

Finally, at the extreme, some trans persons may reject the notion of gender identity altogether to adopt a genderless position: *"I have concluded that identity is not central to my thinking. First, I am perfectly comfortable... not choosing a fixed identity location; my own gender is still mysterious to me"*⁴².

Experiencing an uncertain gender identity

One of the earliest experiences may be of feeling uncertain about whether one's assigned gender identity is right. This feeling can emerge early during childhood: *"In my childhood years... I felt very confused because I didn't know who I was, and I felt like I was supposed to act in a certain way, but I didn't. It didn't feel right"*³⁵. In other cases, the experience of an uncertain gender may be delayed to adolescence, a critical period due to the body transformations under the effect of puberty hormonal stimulation and the incorporation of binary male/female models described in social roles and social identity: *"I did try at various times to look at my sexuality, because there wasn't a clear understanding of transgender or anything. I didn't even know transgender existed"*⁴³.

For adults, discovering an uncertain gender identity can initially be vague. They may first experience a long period during which they negate their felt gender identity to compromise on a socially acceptable life: *"We had to. You had to get married and have kids. That's what you did"*⁴³. The discovery may be particularly problematic, as they may feel like they have wasted time and need to reconfigure their social roles: *"I feel as though my life has been wasted... where [I] could have been if [I] hadn't had to use that energy just to survive"*⁴³. In these cases, adult individuals who discover an uncertain gender identity may also experience being in the wrong body and feeling a mind-body disconnection (see below).

Feeling in the wrong body

Some trans persons describe the feeling of having been born in a body which mismatches their gender: *"For some reason I was born with the wrong body"*³⁶ and *"I identify myself as a man... because mentally my brain is masculine. Simply, my body is feminine"*³⁴.

This mismatch may be experienced since childhood (*"For me, I always felt that I certainly wasn't a girl and I wasn't right, like what people expected of me wasn't me, wasn't right what people expected of me"*⁴⁴; *"I always knew there was something wrong with me... I felt like I was stuck in the wrong body"*⁴⁵), or adolescence (*"It was around about 12 years old I just suddenly found myself drawn to my parents' room and go to my mother's wardrobe, I just couldn't help myself... and so I do that for a while, and then I would feel guilt, and shame, and think, oh, no, this is totally wrong"*³⁵).

At first, the mismatch may be reported as a feeling of something being "wrong": *"Feeling like my genitals don't really match who I*

feel like I am... I just had a lot of hatred for my body for a long time... I don't know how to explain it, like this feeling that something was wrong"⁴⁰. This feeling can intensify during puberty, in association to bodily changes and the development of secondary sexual characteristics: "Growing up I was always uncomfortable with my genitals but I didn't like when I hit puberty"⁴⁶; "I was embarrassed of my own body, I couldn't assimilate, I mean, that my breast began to show, that I was developing a woman's body, I couldn't"⁴⁷.

The body may be experienced as a barrier for enacting one's lived sense of gender: "Every time I shower, I look at my body in the mirror, and I see there is something wrong with it. I don't like it. I wish I were a boy – a real boy, born like a boy"⁴⁸. Some persons may attribute the wrong body to external forces (e.g., God): "I just feel like you [God] gave me this body, and this is not how I want my outside to look... I want to look more masculine, more buff and stuff"⁴⁵. Other persons may feel guilt and self-blame: "In the end, I feel that it is all my fault that I am born in the wrong body"⁴⁸.

Many trans persons may actively seek to conceal their bodies in public ("I felt inadequate, wrong. I felt like an outcast. I felt ugly, I felt clumsy... I didn't want to show my body, I only wore oversized clothes... I couldn't stand the thought of my body as it was"⁴⁹), or resort to make-up and special clothing to hide themselves ("Putting make-up on... putting on a costume. It was the easiest way I had to lie to people so they would accept me"⁵⁰).

Some people may be forced to disvalue their self-image and adopt self-imposed limitations on behavior: "I don't look in the mirror, when I look in the mirror, I look at my face. When I walk past a place that has full body reflection, I look away because I don't think I'm looking at myself"⁴⁵. Repulsion towards one's own body may be associated, in some cases, with self-harm, mutilation, pathological eating behaviors – such as severe dieting⁵¹ – or compulsive self-monitoring and avoidance of specific body parts: "I hate my penis! I would cut it off if I could! I always hide it when I get dressed"⁵².

Feeling a mind-body disconnection

Other trans persons may rather experience feeling disconnected from their bodies: "If I do think about my body... I mostly feel disconnected"⁵³; "Our body says one thing when our brains say another"⁴⁶. This "somatic non-ownership"⁵⁴ may be experienced either in a general sense or in relation to particular body parts or other specific aspects of one's embodied self (e.g., one's height or the tone of one's voice⁴⁰).

Some individuals may even feel that some parts of their body do not belong to them ("There is a sense that just doesn't feel like me. I am most upset about things that are irreversible, like the way my voice is, or my height"⁵³), to the point that they may even reject certain bodily parts ("They were not breasts to me, that they were like strange tumors growing on my body"⁵⁵).

These feelings are heightened if the bodily part is perceived to contrast one's lived experience of gender: "Boobs are directly related to being a woman, and because your brain knows one thing

about being one way and your body knows another, it kind of screws with your brain"⁴⁶. In these cases, individuals may also describe a reduced sense of embodiment (i.e., of being in a lively body): "I didn't have a sense of my body... It was almost as if I was a floating head"⁴⁴.

The above experiences are psychologically profound and may be associated with a pervasive sense of perplexity ("The idea of being a girl in a boy's body was impossible in my mind"⁵⁶), or distress ("It's a bit of a trippy experience really – seeing yourself and then knowing that it does not match anything at all that you feel on the inside can be depressing"⁴⁰). The feeling of mind-body disconnection can be hard to communicate with words accurately: "Our body is saying 'I agree with you, but here's what we've got. It's just difficult to put into words sometimes'"⁴⁶.

Feeling satisfied with one's body and gender identity

The dimensions of uncertain gender identity, being in the wrong body, and feeling a mind-body disconnection, may be experienced as fluid and dynamic processes, evolving into each other rather than being distinct crystallized experiences: "My relationship with my body has always been complex, shifting across contexts and shaped by the interpretative frameworks available to me... My embodiment isn't a story of realization of wrongness or of disconnection but of ongoing negotiation, sometimes uneasy, sometimes affirming" (personal communication).

Many trans persons may not share these experiences at all but, on the contrary, feel completely at ease with their gender identity and body, which are not perceived as intrinsically disconnected: "As I'm both male and female, I don't have real problems with my male body. But if I wake up tomorrow as a woman, I would be fine too. It just doesn't really matter to me"⁵⁷. Some may even experience an enhanced sense of bodily possibilities and energies: "I would be equally comfortable with a male or female body. My male personality is more outgoing than my female one. It's like having both male and female energies and some days a mix of both"⁵⁸. For these trans persons, the body and accompanying gender expression are not a source of discomfort, but may actually be a source of personal satisfaction^{59,60}.

Overall, these variable experiences suggest that bodily discomfort in trans persons is not always something internally experienced, but often a mediated response to other people's and social expectations: "I don't really [experience body dysphoria]. Other people are the problem"⁵⁷; "You don't have to hate your body to be transgender – this might show up as... imposter syndrome of 'not being trans enough'" (personal communication).

THE LIVED EXPERIENCE OF GENDER AFFIRMATION

This section explores the lived experience and different components of gender-affirming processes across two main dimensions:

a) the process of affirming one's gender, and b) the emotional impact of gender affirmation.

The process of affirming one's gender

Searching for a bodily and mental redefinition of the self

For some trans persons, the primary need may be a search for a bodily and mental redefinition of the self, which is indexed by a gender-affirming path. While the term "transition" is often used, it may suggest the idea of a change from one gender to another. In contrast, most trans persons describe it as the process of embracing and uncovering their lived sense of gender: *"I'm not becoming less of anything, I'm becoming more of myself" (personal communication)*. This means that gender affirmation is not about erasing a "before," but about expanding into something more aligned with one's being as an individual: *"Everything I did (including surgery) was... to express more authentically who I am"*⁵¹.

There is no single unitary definition of gender affirmation: *"It can mean different things"*³⁴. A first frequent meaning refers to physical changes associated with pharmacological or surgical procedures: *"Most of the time... it means gender-affirming medical procedures, like hormones and surgeries"*³⁴. However, in many cases, it also entails broader meanings (*"For me, it can be wider. I feel in a transition even without taking hormones or surgeries"*³⁴), encompassing behavioral and psychological changes (*"The transition is not only physical; the transition is also mental"*⁶¹).

For some individuals, gender affirmation may have a clearly defined end goal: *"This is where I want to be in the next 5 years. I want to be married with the picket fence and everything like, so that's what that means basically"*⁶². However, others may experience an ongoing process without necessarily reaching a predefined end goal: *"It's not gonna have an end point until I'm dead"*³⁶. Gender affirmation emerges as a dynamic process involving multiple phases of building, rebuilding and performing a gender identity in the social context: *"It's a process and... I'm tweaking things a little bit, and things are changing, and for me... it's a transition"*³⁴.

Fighting oneself to accept one's gender identity

The decision to initiate a gender-affirming process is influenced by a myriad of personal and contextual factors. For some trans persons, the decision is taken after a long internal struggle: *"I'm over fighting myself... During those punishing denial years, the emotions and dysphoria kept coming back"*⁵⁰. Some individuals may postpone their decision of initiating gender affirmation until a "breaking point", characterized by a critical non-acceptance of their current situation (*"I learned to have patience, to get used to my shape. But I have never accepted it. So, for me, this surgery will be [great], I will feel free. It is as if I am in a body that does not belong to me"*⁶³) and profound psychological pain (*"The pain of continuing living my life in a way that didn't feel authentic ... was more painful than the fear*

*and pain of transition"*⁵⁰).

Often, the decision of embarking on a gender-affirming path is complex and requires multiple checks: *"Making the steps towards doing this in the first place... takes a lot of courage and, in the beginning, it was like 'is this really what I need to do? Can I do this, really?'"*⁶⁴. In many cases, the decision is a tumultuous journey characterized by a prolonged inner dialogue and self-questioning: *"Recently, I have been thinking about several things, such as removing hair and taking hormones. But these are things that I still have a lot to think about"*³⁴.

During this period, trans persons may feel like they need to weigh the benefits against the potential high personal and emotional costs of reshaping a new self and therefore the "undoing"⁶⁵ of the past self: *"[I] threw everything away – work, friends, family, whatever I have, whatever I had done in life. I closed the door and started all over again at age 24"*⁵⁰. They may be worried about reshaping their social identity and profile because of social and institutional pressures: *"I have to make a choice between going through a process of transition, and deal with all the professional, social, and familial consequences, or trying to continue living as I have done so far"*⁶⁶.

Most persons who have decided to start a gender-affirming path experience a sense of relief and reduced mental pain: *"Once I [decided that] this is what I'm going to do, I felt part of this greater brotherhood... there was a weight lifted off my shoulders"*⁶⁴. Notably, the experience of distress or inner struggle can be either alleviated or intensified by the attitudes and responses of the social environment, including the community, family members, and peers and friends (see below).

Changing the body to communicate the lived gender identity

In many cases, bodily gender affirmation is experienced as a gradual process, which starts from minor bodily modifications such as changing the make-up or clothing (*"We all start somewhere. Maybe getting a piece of clothing or trying on lipstick"*⁵⁰), or intensifying physical exercise and eventually starting medical therapies (*"I started to change slowly. I began with a haircut, and when I felt comfortable, I started to change my clothing. Until then I just worked on my body by doing exercises and finally, I began self-administering hormones"*⁴⁷).

Bodily modifications are an essential part of the simultaneous "undoing" of the past self (*"I removed as much maleness from my life as I could – clothes, toiletries, mannerisms, male name – gone!"*⁵⁰) and the "doing" of the new self (*"All the medical treatment I went through was just to get away from my birth sex, rather than to become something else"*³⁶). Notably, the goal of bodily transformations is not necessarily to adopt a feminine or masculine appearance, but to achieve an appearance that feels authentic to the person, sometimes outside of the traditional gender binary polarity, as discussed above: *"I would either like to be a fully fledged hermaphrodite, not physically possible... or I would like a closet full of bodies that I could change"*³⁶.

Symbolizing gender identity expression with a new appearance

In the context of a behavioral gender affirmation, many trans persons feel that their appearance – as characterized by clothes, make-up or accessories – becomes a core aspect of their gender identity (“extended self”⁶⁷) to be experimented and played with during the gender-affirming process (“I... would cut out pictures of women from the newspaper and put them up on my mirror and do exactly the same thing... I love my make-up”⁵⁰). Aspects of gender expression that are socially valued may be incorporated (“You try to look feminine as much as possible. You look at women who you find amazing and then you just try it out yourself”⁵⁶).

Clothes and make-up may play an important role in experimenting and affirming gender identities from early life stages (“Since I was little, I dressed as a boy and I used to buy male clothing”⁴⁷), as important symbols of self-transformation. As such, old clothes can be given away to “really let go of this period of my life and to restart completely”⁵⁶, as a rite of passage that signals the start of the metamorphosis of the external self-expression. Clothes and make-up can also be used to avoid harmful bullying or stigmatizing experiences (see below).

Similarly, specific accessories may help to express one's gender in interpersonal contexts (“I use a [genital] prosthesis. I bought it on the Internet. I wear it only when I'm going out... It is for my mental peace because people can be looking at you and notice ‘that’”⁴⁷), as a way to reduce the distress associated with the feeling of not inhabiting the desired body (“I bind, I can't really do anything about my hips. I wear like men's style clothing, and so that kind of reduces it visually, but if I have to wear anything like, um, a tight dress shirt or, um, tighter dress pants, then I feel like they look really prominent”⁴⁶).

Accessories can also be used to embody fluid gender identities and “come to life” in different contexts: “In the morning, I was the best fighting man in the world. I ran up the mountains like everyone, sweated like everyone, smelled like everyone, and cursed like everyone. But at night I would dress up like a woman... Even the perfume I used at night was different from the aftershave I used in the morning”⁵⁰.

Affirming gender identity with behavioral changes

Some trans persons may need to express and affirm their gender identities beyond bodily transformations, with a new behavior¹⁰: “The hormones and surgeries and all the medical side of it, turns out that's the easy part. The body language, speech patterns, mannerisms, and the way you interact with people. That's all the stuff that really takes the work”⁶⁸.

Life trajectories and experiences are heterogeneous in this respect. The process of behavioral changes may precede or overlap with the bodily transition (“I've been engaged in two transitions. One... a physical transition; changing my body and mind into something more suitable for me. The other, the social transition”⁵⁰), but other trans persons may feel ashamed of initiating the behav-

ioral changes before the body masculinization or feminization process, and the coming-out process and behavioral/identity changes may follow physical changes³⁹.

During the gender-affirming process, individuals may seek to incorporate the behaviors or mannerisms that are traditionally associated with notions of masculinity or femininity (“I didn't know if guys talk with each other in the bathroom, and if I'm supposed to do that”⁵⁰; “You try to assimilate all you can from manhood, at least in my case that's what I do and in my house it's like that, I'm the one that provides and the one that says how things are”⁴⁷), while others seek to express their gender identity outside of the binary norms.

Behaviors and roles can be more important for the lived sense of gender identity than the bodily changes described above: “My dysphoria was more the fact that I wanted to play football. Why can't I play football? It was more dysphoria with gender roles, not with the actual body”⁶⁹.

Finding an inclusive language that acknowledges gender identity variations

Language may play a central role in the gender-affirming process for most trans persons: “If I've gone to such lengths to find words for myself, it's because language is so important in creating – or finding – ourselves... There's a breathtaking power in self-determination. For me, naming myself is about creating a space where I can feel at home in the gender galaxy”⁴².

During gender affirmation, the use of preferred pronouns and, at times, a name that differs from the one given at birth, can be means by which trans persons communicate the lived sense of self actively: “My sister didn't want to call me with my new gender-neutral name. She went on calling me with my original female name. But I had the courage to tell her and my dad ‘call me C. [new name]... this is my real identity”⁷⁰. For some people, changing their birth name to a chosen one is “the first real step”⁵⁰ in their path towards the appropriation of themselves: “These were the first steps. After that, I said, okay, that's my life”⁵⁶. The acknowledgement of the new names in official documents (e.g., personal ID) can be experienced as a key personal milestone: “When you get your name changed officially, there's like a whole new life, whole new persona”⁷¹.

Some trans persons may also feel that the cisnormative binary gendered language and associated lack of shared interpretative frameworks for their experience limits their process of self-understanding: “Looking back on my younger years, I recognize a long period of profound self-misunderstanding, not because I was hiding, but because there were simply no shared concepts or social frameworks that could help me understand myself – let alone communicate that understanding to others. I wish I had found the right words much earlier in the social and cultural world around me – ways of understanding myself through lenses that could do justice to my being and becoming” (personal communication).

These persons often feel forced to use language to understand and describe themselves in ways that make sense to others, but not necessarily to them (“[It is] so hard to vocalize what you want”³⁶,

because “you have to give them a word that means something, but it might not mean you”³⁶; “There was no language or model outside the binary for me to make sense of myself”³⁶). In this context, even the word “non-binary” may be adopted by trans persons not as a primary personal choice but only because it is a category that cisgender people can somewhat understand: “I often say ‘non-binary’ in casual situations even though it doesn’t fully represent my identity, just because it’s the most legible option to cis people. People often try to ‘normalize’ trans identities into something they are comfortable with: ‘why can’t you just be a masculine woman?’ or ‘aren’t you just gay?’ This is invalidating, aggravating, and disrespectful” (personal communication).

The fluid nature of their gender identity may be reflected in their use of an inclusive and evolving language: “I go between she, her, hers, to they, them, theirs”³⁷. For example, gender identity labels such as “trans man” or “trans woman” may be selected as they acknowledge personal histories of gender affirmation, or may be rejected as they act as reminders of a past self that felt inauthentic. Other labels such as “gender fluid”, “genderqueer”, “gender bender”, “gender outlaw”, “mixed gender”, “transfeminine”, “trans-masculine”, “FtX, female to X”, “female to male”, “male to female”, “genderqueer”, “intergender”, “transgender and gender nonconforming”, among others⁷², may be alternatively used to indicate ambiguous or fluid models of gender that combine or collapse elements of masculinity and femininity, or reject them altogether (e.g., “neutral gender”, “agender”): “I’m trans, I’m non-binary, I’m FtX... I’m genderqueer and I personally refer to myself as a hybrid”³⁴. Other individuals can actually prefer gender-neutral labels, such as “person”, or reject labels altogether: “I’ve stopped caring about labels”³⁷.

The emotional impact of gender affirmation

Restoring a sense of self

For many trans persons, gender affirmation may result in a restored sense of self (“Now that I feel pretty solid, this is who I am. I am who I am”⁷³) or a feeling of being themselves (“I think for me the joy is being able to be me”⁷³; “I felt like myself. Which was really weird and something that I’d never felt before... For the first time, I felt like I was actually who I was supposed to be, you know?”⁷⁴). As a result, the experience is often accompanied by “a sense of calm”⁷³ or relief (“One of the joys is finding solace in my identity rather than trying to fight it. And that was a huge relief”⁷³), or a newfound sense of freedom (“Being unencumbered and allowed to pursue life and be myself is where that happiness comes from”⁷⁴).

They can feel liberated from the pressure of having to “perform” to adhere to gender expectations and roles: “Once my gender was affirmed and I stopped trying to perform womanhood, I felt more at ease in myself” (personal communication). For many, the sense of calm comes after many years of living in a way that felt inauthentic: “Maintaining that façade is like a really high energy thing, and I don’t have to do that anymore. I am just sort of out, and able to live an authentic life”³⁵.

Many trans persons may also experience a profound sense of pride after gender affirmation (“I’m proud that I’m myself now, that I’m being myself. You know? And that I wasn’t like that before, and now I am. I’m me. And I’m proud to be me”⁶⁴), linking it to a sense of accomplishment (“I see my transformation as an accomplishment, what I am is my greatest achievement because it makes me feel happier and free”⁷⁵).

Their sense of pride can also be fostered by their self-determination, which challenges hegemonic sociocultural narratives: “This is who I am and I don’t have to adopt a socially played out script”⁷⁶; “Once you realize that your narrative is yours to reclaim, run with it, because you’re the one writing the story. You don’t have to have it edited by anyone”⁴¹.

For these individuals, gender affirmation may successfully restore an authentic sense of self to the point that they may feel more empowered to cope with the burden of social discrimination: “I’ve had people that told me... ‘stay in your lane’ ... I’m not going to suppress myself because you’re not comfortable with it”⁴⁵.

Many trans persons experience authenticity and a sense of deep joy from enacting their lived sense of gender during gender affirmation, opening the door for new opportunities for self- and world-experiences: “More and more, I experience a deep joy in being trans. It feels as though I sense, think, and move through the world in ways that aren’t possible within normative structures and ways of thinking. It creates space – and every encounter within that space seems to expand it even further. And this space ripples through every dimension of my life” (personal communication). This sense of joy, rather than the escape from distress, can be the leading force guiding the gender-affirming process: “I’m personally letting my transition be guided by euphoria rather than dysphoria” (personal communication).

Experiencing a strong emotional reaction when receiving gender-affirming care

The biological bodily changes following gender-affirming care are frequently associated with a dramatic emotional improvement (“I started taking testosterone, it’s like a big bomb went off in my brain and things became – there was a moment of clarity where it was like ‘Oh my god, what the hell?’”⁴⁶), as the sense of being in the “wrong body” starts to recede (“I think that the surgery made me more comfortable with everything else too. I became more comfortable with my other parts”⁴⁶; “Even just the idea of not having more male hormones in my body makes me feel good”⁷⁷).

Medical bodily changes can also enable new spaces for activity, socialization, or behavioral gender expression that previously felt inaccessible: “I can go to the swimming pool”⁵⁶; “I have removed my beard hair. My penis doesn’t bother me much since I no longer have erections”⁷⁷. For some people, the onset of the first medical bodily changes can help reaffirm the internal sense of gender: “From that moment I was 100% sure that I am trans”⁵⁶.

Other trans persons who undergo biological interventions might express initial dissatisfaction with the bodily changes if, for example, their desire to be seen by others in their affirmed gender

is not fulfilled: *"I wasn't happy with [the results] and it was causing me distress... Because I wasn't passing [as a cisgender woman] and it was really difficult"*⁷⁸. The emotional experience is complex and shifting over time: *"There is a complex emotional landscape of transition, which isn't just linear joy or pain. It's layered. It's mourning and becoming at the same time"* (personal communication).

In some cases, some dysphoria may persist and fluctuate after gender affirmation: *"Dysphoria comes in waves and is rarely a steady constant... What you are dysphoric about may differ over time – transitioning physically can shift your focus onto new things that might not have affected you before. As you start becoming comfortable with certain aspects of your body, others become more apparent. It can also appear socially, with not fitting in, being 'off' to cis people like it's an elephant in the room"* (personal communication).

Deciding to stop or reverse gender affirmation

In a few cases, individuals may consider "detransitioning", defined as the act of temporarily or permanently stopping or reverting (fully or partially) the process of social and/or medical gender affirmation (detransitioning rates in individuals undergoing gender-affirming hormonal treatments range from <1% to 9.8%, but data should be considered cautiously, due to heterogeneous designs and underpowered samples⁷⁹).

The motivations to stop or reverse the process of gender affirmation are highly diverse. They may include a combination of personal and external factors⁸⁰⁻⁸⁴, such as adverse outcomes of medical and surgical interventions or non-realistic expectations, rather than a misdiagnosis: *"My voice, I feel like it will always get attention. Not necessarily the right kind of attention. And that it's always going to make people doubt me, and that it's always going to haunt me in the back"*⁸⁵.

Some individuals may report a shift in their gender identification as the main driving factor (*"I would say that I was transgender, and I wasn't misdiagnosed, but I decided not [to] identify with gender anymore and not [to] identify as transgender"*⁸⁵), or highlight how their gender identity dynamically changed over time⁸⁶ (*"My gender feels complicated and changing all the time"*⁸⁰; *"I enjoy having the ability to go back and forth between genders"*⁸⁰). Others may experience regret regarding the irreversible bodily changes (*"Sometimes I still get days where like I feel really down about it and like feel like I would ... like destroyed my body I guess in a way, like, it's hard not to feel that way sometimes"*⁸⁵) or mixed or ambivalent feelings regarding their decision to undergo gender affirmation (*"There are times where I wish like someone had stopped me or like had been more barriers, but at the same time, like I don't know if that would've stopped me"*⁸⁵).

In some cases, the personal motivation may be even more nuanced; for example, they may want to *"stop or adjust medical interventions precisely because they do not want to further alter their bodies or 'fit' more closely within binary expectations"* (personal communication). Notably, in these cases, detransition may actually *"represent a conscious and deliberate part of one's becoming*

rather than a reversal or negation of self" (personal communication).

Some trans persons may decide to detransition due to family and societal expectations or pressures⁸⁰ (*"It's usually the social pressure that brings people to 'detransitioning'. When they are not 'performing' as they are expected, they are pressured to 'detransition'"*, personal communication), without experiencing a change in their internal gender identification. Reasons are very heterogeneous, and may include the desire to access employment or better health care (*"I actually detransitioned after I was diagnosed [with cancer]. No doctor would touch me, no doctor would treat me. I understand saving my life becomes a higher priority, but for me, waking up every morning and seeing myself turn back into a man while I'm facing cancer was devastating"*⁸⁷); community, cultural or religious pressure (*"I live in a very conservative place and was afraid for my safety"*⁸⁰); pressure from family or friends (*"Moved home after college. Had to conform for parents"*⁸⁰); practical barriers to access ongoing maintenance gender-affirming care (*"Living in rural area, couldn't get hormones"*⁸⁰); or post-operative surgical pain (*"I had complications with [genital] surgery which were bad... I was dealing with a complication that was painful for six years, seven years"*⁸⁸).

THE EXPERIENCE OF TRANS PERSONS IN THE SOCIAL AND CULTURAL CONTEXT

This section explores three dimensions of the lived experience of trans persons in their interaction with the social and cultural context: a) the experience of hiding, coming out, and wanting to be recognized by others; b) the experience of transphobia, institutional discrimination, and violence; and c) the experience of family, friends and romantic relationships.

The experience of hiding, coming out, and wanting to be recognized by others

Hiding one's gender identity

While many trans persons may acknowledge feeling different since their early years (*"In myself, I knew from a very early age, and I would probably say six, seven, I knew I was different"*³⁵), this aspect of their identity may remain unexplored or hidden for a long time (*"I didn't have any kind of ways of talking about it, because I was taught not to talk about it"*⁸⁹).

Many individuals may experience ongoing terror that their affirmed gender can be discovered: *"I always thought 'People can see right through me'"*⁹⁰. These experiences can be particularly marked in persons living in stigmatizing environments, which can lead to shame or self-hatred (see below)⁹¹. They may feel forced to conceal their gender identity to prevent social stigma and dehumanizing experiences: *"There is no doubt that if I were open about being gender fluid, it would not only be the end of my career, but there would be a lot of personal repercussions as well. There's a definite*

*fear that I could be found out at any time, and there's also anger – because it's dehumanizing*⁹².

These fears are so pervasive that many trans persons may feel unable not only to disclose but also to enact their gender identity (*"I stopped myself to be open about my gender identity to my environment, and to myself"*⁹³) or even negating core aspects of their identity (*"I think I drove that wanting to be a boy stuff so far down inside me that I just would refuse to look at it... It's just dawning on me now, I wanted to try!... Oh God, it was so maddening"*³⁹).

The social pressure to hide their gender identity and conform to conventional gender roles and expectations may also suppress their personal interests and life decisions: *"I had a whole wide range of interests, some of which were discouraged... I tried to be this guy that people wanted me to be. I even joined the Marine Corps"*⁹⁰. The frustration of not being able to express their gender identity may become a trigger to search for alternative expressive spaces: *"I got involved in theatre because in theatre you could be somebody you weren't. And so, I played... the funny parts, and I made everybody laugh... I could find a place on earth by making everybody laugh"*³⁹.

Coming out to others

Given the intense and frequent experience of social discrimination, many trans persons may feel that disclosing their gender identity to others (i.e., "coming out") would be highly stressful. A core concern may be linked to the potential loss of vital social networks: *"I waited, because I really had to sort of test the waters to figure out whether or not it was going to destroy my connection with them [parents] because I felt like if I lost connections with my brothers and sister, I thought I would die"*⁹⁰.

Other people's expectations and reactions can influence the coming-out process. At the start, individuals may gradually share their gender identity selectively to certain chosen friends, family members, or professionals, at times by using more socially accepted labels – e.g., "lesbian," "gay" or "bisexual" (*"When I came out [as bisexual] to my mom at like 19, I was totally nervous... I figured she would be cool but I didn't really know how she'd react"*⁹⁰) or testing the boundaries of what is acceptable by their social circle (*"[I] start[ed] finding clothes and doing what [I could] with it, and deciding how much of it I could get away with on a social level, which, in the atmosphere I perceived in north Minnesota, was none"*⁹⁰). In some cases, coming out may precede the gender-affirming process as a way to prepare others for the changes to come: *"I wanted to tell everybody before I presented to them as Debra, and so, it added to the stress of transitioning at the time"*⁹⁰.

Others may gradually start experimenting with and expressing their gender identity. Positive reactions from others during this process may be experienced as a source of validation and support: *"It gave me the support of friends and family and colleagues that I didn't think I would have"*⁹⁰. On the other hand, fear of adverse reactions or impacts on their social relationships may halt the coming-out and subsequent gender-affirming process: *"I prefer to protect myself... It's very difficult, especially for parents, and I don't*

*want my mother to watch such a process. I don't want to"*⁶⁶.

Before and during the coming-out process, trans persons may seek guidance from support groups of trans people who have lived through similar experiences: *"It's been great to have people who can at least guide me a little and who can at least be like, 'yeah, I've been there, and I know what that feels like'"*⁹⁴.

The world of digital and online communities may also play a key role during the coming-out phase. In many cases, trans persons may experiment by sharing a virtual self in the online world: *"I can finally live, dress, and do almost anything as a girl in a virtual world"*⁵⁰. Online communities may represent the first interpersonal spaces where they can come out: *"Nobody I know can validate me in real life... I can only find comfort online"*⁵⁰.

Online responses can play an essential role in shaping a trans person's decision to continue the coming-out process in other social spaces: *"I came out online first and then to friends in school, including teachers... If I can do that here [online], then I can do that in school, and in my home, and in other places where that impacts my life"*⁹⁵. Connecting with others online may also help to overcome feelings of loneliness during the early stages of coming out: *"It's hard to describe the relief I felt to learn that I wasn't alone, and that I could make changes to help my body match my heart"*⁵⁰.

In this context, media found over the Internet or TV may be experienced as particularly supportive: *"Internet social media has shown me I am not alone, my struggle isn't something strange or unusual. It has shown me people with my issues can become successful, and can ultimately overcome their problems and be happy"*⁹⁶; *"This lady [on TV] started to talk about transitioning. I thought this was it! They started talking about hormones and surgery"*⁵².

Wanting to be recognized by others in their lived gender

While coming out refers to the act of disclosing their gender to other people, some trans persons may want to be seen by others (i.e., to "pass") as they see themselves (*"It is to be accepted. To have that validation that what I see in the mirror matches what somebody else will see... Your picture is the same as my picture"*⁸⁸), as a way to self-affirm their identity and self-perception (*"If I know my appearance is all feminine, then I'm gonna feel totally feminine"*³⁹). As such, "passing" can be a way of communicating their self-image to others: *"I opened a door for a woman as she walked out and said, 'Thank you, sir'.... That was one of those moments where I felt like people were seeing me"*⁶⁸.

Situations in which others' reactions match the person's self-image often result in feelings of self-empowerment (*"Mostly, what I get really excited about now is when someone calls me ma'am, or when someone on the street comes up and tries to hit on me, which has happened lots of times. Those are the things that I really dwell on. I get very excited about my progress"*⁶⁸), or feeling validated in their identity (*"We went to the grocery store... and the cashier said, 'You ladies have a nice day!' It's odd how such a simple phrase can be so glorious! I don't seek passing; I seek... validation. That woman made my day!"*⁵⁰). At the same time, "passing" is closely modulated by cultural and social norms and expectations, and – at times

– individuals feel pressured to “pass” as a mechanism to avoid exposure to hostility or violence (see below).

For other trans persons, “passing” may feel less relevant or even inapplicable, because it can be experienced as restricting oneself to a binary and cisnormative understanding of gender, which leaves out a wide range of other experiences: *“It’s not about being seen as one gender or another, even if that would be a third category, but about existing and being perceived outside those categories altogether”* (personal communication). These individuals may deliberately identify more with their choice of non-passing, as a way of resisting the normalization processes by which human beings are categorized in terms of recognizable cisnormative binary categories: *“I identify more with non-passing – not as a failure to communicate, but as the most authentic expression of who I am. The moments when people hesitate or don’t know how to read me often feel most truthful, even if they can be uncomfortable... For me, this is not a lack of communication but a way of existing that resists being confined to binary expectations”* (personal communication).

The experience of transphobia, institutional discrimination, and violence

Feeling wrong and dehumanized by transphobia

As most cultures are primarily structured by a cisnormative binary distinction between male and female biology (i.e., an “heterosexual matrix”¹⁰), the most paradigmatic and frequently reported experience of trans persons is to fall between the cracks of this dichotomy: *“One is never officially ‘between’ or outside the heterosexual matrix, one is only ever male or female”*⁹⁷; *“You are born to one category that dictates everything for you and you cannot cross over to the other category... you have no choice and you have to be what you were born to”*⁵⁰. As a consequence, one of the most common and unifying experiences shared by trans persons is of extreme levels of transphobia: *“I was looked at differently because of the way I dress. I did not like wearing churidar or leggings. My co-workers teased me for my ‘dressing sense’... They make me feel wrong”*⁹⁸.

The term “transphobia” refers to a range of negative attitudes and feelings, discomfort, intolerance, hatred and discriminatory behavior directed towards trans people. These are related to the negative regard and inferior status that society collectively accords to any non-cisnormative or non-heterosexual behavior, identity, relationship or community. Transphobia can be enacted (the actual experiences of discrimination and violence), perceived (the anticipated fear of being the target of hostility), or internalized (the individual’s adoption of cisnormative cultural norms and expectations leading to shame or self-hatred for not conforming to hegemonic definitions of masculinity or femininity)^{99,100}.

Many trans persons may feel stigmatized and harmed by internalized symbolic violence since their childhood: *“I think it was kindergarten or first grade... Some older girls came to me and were like, ‘We hear you wanna be a boy and that you prayed to God that you were gonna be a boy!’... And I realized, like, ‘Oh God... There’s*

*something wrong with me”*³⁹. Trans persons may also feel exposed to *“continuous, inquisitive looks!”*⁷⁰ that exoticize them: *“It just reminds me of the whole like freak-show aspect... It’s like tourism that people are like Oh, how fascinating”*³⁷. Overall, they may feel deeply dehumanized: *“I think a lot of the queer pain is just related to... being seen as just a body with parts, as opposed to being seen as a soul, or just being a human”*¹⁰¹.

Trans persons are often the target of stigma during online interactions or via technology-facilitated violence (i.e., cyberbullying), including negative comments, insults, threats of harm, and other forms of abuse (see below): *“A lot of the comments made towards me have been around the way I look... you get a lot of gross and derogatory comments around your body and who you are”*¹⁰².

Dehumanization induced by social stigma can be associated with “unnatural and high mental stress”¹⁰³, or feeling “dirty”, “inadequate”, and even “wrong” or “in a wrong body”: *“I went through a lot of mental trauma. I was at a point where I started questioning myself. Why am I like this? Why is this happening to me? That caused me to lose self-confidence, which caused me to attempt suicide at one point. Just to find the answers to all the ‘whys’. Am I not a normal human being then? Am I really unnatural then?”*¹⁰³.

Feelings of being dehumanized may, in turn, foster an intense sense of oppression and vulnerability to physical aggressions: *“I’d always be stared at... it was just like, extremely oppressive... I had no identity... there was just like a photograph of me that kinda walked around and people laughed at... there’s always the knowledge that a stare can turn into a laugh, can turn into a fist, can turn into a gun”*³⁹.

Transphobia may lead to several negative mental and physical health outcomes¹⁰⁴, including gender dysphoria and severe body uneasiness, self-harm, pathological eating behaviors, substance abuse, mood disorders, suicidal thoughts, and reduced response to affirming medical treatments^{105–108}: *“I actually got really depressed because of internalized transphobia and all that nonsense of like... I’m this, but this is a terrible thing to be”*³⁷; *“Whenever I would get discriminated against or down, I would drink”*⁷¹.

Feeling pressured to “pass” as male or female

Several trans persons may feel that they are expected by society to appear male or female (to “pass”): *“It’s kind of reinforcing society’s expectations of what gender should be, as opposed to what gender actually is”*⁶⁸. In this context, “passing” may be experienced as a highly stressful social test: *“The problem with passing is that it implies that trans people have to do an extra, extra, extra amount of work in order to be seen as their gender and if they don’t pass, they’ve failed in some way”*⁶⁸.

The societal pressure associated with “passing” can be experienced as something *“that tends to erase trans identities”*⁶⁸, as it pushes trans individuals towards culturally-sanctioned forms of self- and gender-expression: *“I definitely can’t blame people for wanting to pass because that’s avoiding all of the negative stigma and all the terribleness that’s associated with being trans people all the time”*⁶⁸. The perceived burden may lead to anxiety or hyper-

vigilance in social situations (*"When I first started my transition, I was concerned with [passing]. How feminine do I look? Am I sending off the right signals?"*⁶⁸), or feeling exposed to the constant look of others (*"I went shopping the other day, presenting [my] feminine expression, and got lots and lots of looks... people could tell I was trans... I felt scared and weird and... wanted to run home and... back to hiding"*⁵⁰).

Consequently, adopting a feminine or masculine appearance may become a self-preservation strategy to defend against rejection or discrimination: *"For me, it was a mask. Behind it, I could be whoever I am without being harassed too much... Nobody wants, really wants, to know who you are. They just want you to look like something they know"*⁵⁰; *"On days when I don't put on make-up, I get sirred. I get misgendered. When I do have my make-up on, that happens much less"*⁶⁸.

Suffering misgendering, deadnaming and verbal microaggressions

Many trans persons report being exposed to frequent experiences of misgendering, where they are addressed, intentionally or unintentionally, by a gender with which they do not identify: *"[Misgendering is] identity warfare [that] is so strangely insidious... Suddenly, I feel like maybe I am a dude. They are calling me a dude, so..."*¹⁰⁹. Misgendering can be associated with a feeling of helplessness that is intensified when done intentionally: *"I have told them that I am non-binary, and I don't want to be addressed as she/her, but they keep doing it anyway"*⁹³. This feeling of helplessness and oppression can be experienced in the private dimension as well as in the broader sphere of public institutions, or even in the virtual world: *"I was harassed by a group of cisgender boys on the grounds of being trans. They commented on all of my posts and pictures and messaged me, misgendering me, calling me a good girl"*¹⁰².

Misgendering can reinforce the above-mentioned feelings of unworthiness or feeling wrong or in the wrong body: *"It made me feel horrible and really made me hate myself more than I ever thought I could. It made me feel like something was wrong with me, in regard to my gender identity"*¹⁰². These experiences may eventually lead to avoidance behaviors in social situations: *"When I go to the gym, I always keep earphones in the entire time because I just don't want to hear what's going on around me"*⁹².

Trans persons may also frequently experience acts of "deadnaming" (i.e., referring to a person by their birth name). Some trans persons do not want to disclose their birth names, as they do not match their gender identity: *"[My birth name] is not who I was ever really. It's just the thing that was given to me to match something that looked like it would fit the name, but it didn't"*⁴⁴. Accordingly, they may feel that deadnaming is highly dismissive of the effort put into the process of affirming their gender identity: *"I think people just don't realize... the frustration, the trauma, and how upsetting it is to hear someone say it... [Just] don't mention it, it's supposed to be dead"*¹⁰⁹. However, others might acknowledge their birth names as an essential part of their past selves: *"It's still part of me... I feel kind of like, protective over that name a little bit. It*

*still means something to me, and maybe that's just me"*¹⁰⁹.

Many trans persons may also experience feelings of self-invalidation and inadequacy because of verbal microaggressions (e.g., the use of incorrect pronouns): *"I think I was worried about it just about constantly. Anytime I had human interaction, I was worried if they would call me sir or ma'am, you know, he, she, whatever"*⁶⁸. Every act of invalidation may feel like *"a little shock in the brain"*¹¹⁰. It can lead to an exhausting state of hypervigilance (*"It [microaggression] was coming from pretty much everywhere and I was not leaving it"*⁹³) and high mental health pressure (*"Even if you're expecting it, it is mentally jarring"*⁶⁸).

Suffering daily institutional discrimination

Trans persons often suffer high levels of daily discrimination in their interactions with institutions or while navigating public spaces. For example, lack of gender-neutral spaces may turn everyday actions into performances: *"I always pause before entering women's toilets – to show that I'm not actually comfortable with using it, and because I want people to know this space doesn't fit me"* (personal communication). This shows how public spaces may regulate gender in subtle but powerful ways (a "social production of space"¹¹¹).

Another example is that trans persons may feel that the dynamic nature of their gender identity is not acknowledged by hegemonic cisnormative views of gender in administrative applications: *"The UK passport application form requires confirmation that I will not detransition. The form does not require confirmation that cisgender people will never transition"*⁹⁷.

Housing problems are one of the most unsettling of these institutional challenges. Trans persons are often discriminated when looking for a place to live: *"With housing, being trans is always a thing you have to worry about – it's your home space and you want to be yourself"*¹¹²; *"We will not get the residence: if someone wants to rent out their rooms they will think 10 times before giving us a house to rent"*¹¹³. Even when they manage to find a place to live, they may have to worry about unaccepting neighbors: *"Even when we get a room for rent, neighbors put pressure on the owner to evict us... how much discipline we will maintain, people have one or the other objection"*¹¹³.

Many levels of institutional discrimination may also occur at the workplace – for example, when applying for a job: *"If you want to have access to a job, you have to dress as a man and cut your hair because otherwise they won't give you a job dressed as a woman"*⁷⁵. Persons undergoing a gender-affirming process while being employed may experience particularly high levels of institutional discrimination: *"How will the company accept me? As a male or a female? Even if they were placed under the male category, they need to change their ID proof and other documents. That will be a problem"*⁹⁸.

Institutional discrimination can be also experienced during interactions with the police, where they feel under constant unjustified suspicion of prostitution (*"When a patrol stopped us and arrested us for one night, because they accused us of prostitution"*⁷⁵),

or fear being punished and fined because of their gender identity (*"They took us to jail, handcuffed as criminals, they took us out of the bar and we had to pay a fine for moral damages to society or something like that"*⁷⁵). These challenging experiences may erode trans persons' trust in law and institutions: *"If you [as a trans woman] call the police because something happened to you, they come to arrest you and not whoever stole from you or did something to you... Just because you are trans, you end up being the aggressor"*⁷⁵.

In certain regions, where religious norms dictate strict gendered dressing codes and prohibit same-sex relationships, trans persons may be required to undergo gender-affirming surgery to be granted a legal status, leading many individuals who don't want to undergo the procedure to relocate: *"I want to leave because I cannot have my desired gender here. I can consume hormones illegally, but then I cannot have a job here"*¹¹⁴. In other countries, trans persons may be accused of violating religious norms and are highly vulnerable to different forms of abuse or prosecution from authorities: *"For transgender people, the religious law on cross-dressing is a big risk. Some give a bribe or sexual services when they are arrested"*¹¹⁵.

Because of these highly discriminatory cultural, religious and institutional norms, many trans persons actually feel that merely existing is already a strenuous effort which requires constant fights for survival: *"I feel like existing in itself is already a political act"*¹¹⁶; *"I didn't exist because I couldn't see myself in the culture"*¹⁰¹.

Suffering emotional, physical and sexual abuse

Because of the high levels of social stigma associated with hegemonic cisnormativity models described above, many trans persons report frequent feelings of emotional abuse while growing up (*"I was violated as a child every time I was forced to do something. I didn't like it, but I had to behave as boy. I felt abused"*⁷⁰) and as adults (*"We have to start being resilient, because you don't know what's going to come from where"*¹¹⁷). Enacting their sense of self in social spaces may also feel like treading a minefield, and several persons can recall specific moments in which they realized that (*"If I were wearing a skirt here, then it would not have ended well, while I would've wanted to wear that"*⁹³).

Emotional abuse can also be experienced in the intimacy of the family environment (*"I was being mentally tortured [by my parents] every moment and I felt like I was in prison"*¹⁰³), or in romantic relationships (*"[I was] craving companionship, when you're lonely... [you] tolerate so much of the abuse... you learn to just accept it"*¹¹⁸). Some persons may also feel pressured to suppress their identity to satisfy the partner: *"My ex-partner had this idea that I'm attracted to women or I'm attracted to you, so you must be a woman"*³⁷. Likewise, other individuals can feel pressured by their partner to gender transition: *"His wording was basically you either medically transition or I leave"*¹¹⁹.

Trans persons may also experience severe physical and sexual abuse. Abuse can include the hostile gaze of others (*"They are all looking at me, because I was in a tight-fitting dress, so they're all try-*

*ing to almost get this Superman X-ray vision to peek through my dress and see what is underneath, because always, when someone is mentally undressing you, I felt dirty"*¹¹⁸), or an explicit sexual assault, like groping or being harassed (*"If I'm dressed feminine I get sexually harassed a lot. If I'm dressed masculine, I get really nasty stares"*³⁷). These experiences may amplify their feelings of being objectified and dehumanized: *"A lot of people see us as inanimate objects... You don't have any control over what's being done to you"*¹¹⁸.

Physical abuse may even occur within the close family context (*"I told them [parents] that I want to be a man. My father, mother, and everyone started beating me, tonsured [shaved his head] and tied my hands. They kept me nude in a room for a whole day and forced me to wear women's clothes and to do household work"*⁹⁸), or in online interactions (*"I've been sent a lot of rape threats, had men explicitly tell me how they want to rape and beat me"*¹⁰²).

The experience of family, friends, and romantic relationships

Struggling with family acceptance

Many trans persons may struggle with being accepted by their families: *"My mom used to buy those mother-daughter matching outfits to show how similar we are. I hated it!... It made me sad that she could not see my real me"*⁵⁰. Because of the low acceptance of their gender identity, these individuals may also struggle to maintain connections with their families of origin: *"I can't be a part of my family if I'm not feeling whole in who I am and feeling full in the whole"*⁸⁹; *"I'm not out to any of my family, it makes me feel isolated and secretive"*¹²⁰.

Many individuals may fear that their gender identity can be discovered (*"I was always anxious. I was freaked out"*⁷⁶) and lead to rejection (*"Don't talk about it, don't think about it"*¹¹⁶), lack of understanding (*"My family doesn't accept it or doesn't get it and especially the pronouns they and them... so they don't call me by my name, and they also don't use my pronouns"*⁹³), or even accusations of dishonoring the family (*"My relatives told me I could not show up in the public unless I wear hijab [head scarf]. Everyone told me so; they told me that I am destroying their reputation"*¹¹⁴).

Some trans persons may be forced by family members to adopt traditional gender roles and expression, or even to get married (*"They are not ready to accept this. They were worried about neighbors and relatives. They start questioning us - 'Why are you dressing like this? What happened to you?' They force us to get married"*⁹⁸), while others may face exclusion (*"Our family members say that [because] we are like this [our] other siblings will not get married so they will not support us, they will not allow us to [be part of the] family"*¹¹³).

Many of them may have to shoulder not only their own problems, but also the distress of their family: *"Beyond the personal distress, you have to add the distress lived in your family. It's very heavy, or better, extremely heavy. This totally impacts your behaviors, attitudes... this makes your life a hell, a cage"*⁷⁰. Family distress at times

may amplify their feelings of rejection: *"She flipped. She was just like, 'I don't want to know it. I don't care. Go away.' So that hurt"*³⁸.

Sometimes trans persons may feel that they have to leave their biological family which is not accepting them to embrace a new supportive family (*"As you are independent, you shouldn't feel an obligation to keep people around you that are not affirming of you... There's nothing special about people who are technically your family but make you feel awful"*⁴¹), or cut ties with specific relatives (*"My Dad barely is, I barely see him, but like I chose my family"*⁴¹).

Experiencing family, community and kinship as a safe base of support

In other cases, trans persons may experience family as a safe base of various types of support (instrumental, emotional, informational¹²¹), particularly in the early developmental phases: *"My mom helps me. Like we went to the store almost immediately and she got me new clothes and she helped me"*¹²²; *"My father is very supportive and he has that sort of, 'Are you happy?' thing and I'm like, 'Yeah', so that's it"*¹²³.

Family support may be felt as authentic when accompanied by concrete actions: *"When I came out, my mom was like, I accept you, I still love you, whatever, all that stuff. But that's definitely not the same thing as supporting me. Now she is starting to support me, by you know, using my correct pronouns, talking about hormone therapy"*¹²². At the same time, trans persons may also recognize that family members will need time to come to terms with their new identity: *"[My mom] has been supportive the whole time, but there's, even today, there's the occasional pronoun slip. I think she's had a little bit of a hard time with it, although she actively tries to be supportive"*⁹⁰.

In these cases, family can be experienced as a vital source of emotional support and constitutes a safe base against potential experiences of social stigma and bullying: *"[The bullying] made me really sad... I realized what my mom said was right, that they don't know what it means – they, they're not educated, so I didn't let it bother me anymore because [if I do then] I'm just gonna let them win"*¹²⁴.

Some trans persons may find solace and support in spirituality or religious communities, as well as in alternate families or kinship structures. Several examples of non-biological familial communities for trans persons exist in various countries: *"I was better accepted in my community than in my home. I have a better family there. They support me like the real one. And I thought it was better to be with them than being alone at my own home"*¹²⁵.

Being rejected by peers or friends

Many trans persons who do not conform to standard gender stereotypes may experience rejection by friends and schoolmates since an early age: *"My school life was hell. Sometimes I didn't even want to go. I used to say why am I going if they are going to bother me? I remember that when I was in high school, at some point, I didn't want to go to school anymore"*¹²⁶.

Some of them may even experience psychological or mental punishments for their diversity: *"At school, teachers regularly confronted me. They said a man should not behave like that. The man should not pluck his eyebrows. I was punished many times for who I was. When I was told that I was a male, I became nervous"*¹²⁷.

Frequently, school life may enhance the subjective suffering, because it can amplify cisnormative binary gender models: *"Everybody knew they were either a girl or a boy, and it's like you would be called a 'he' or a 'she'... and that's when I knew that I wasn't like the other people – I wasn't what I was... physically"*³⁸.

Feeling friends as a major source of happiness and resilience

In other cases, finding a group of friends that is accepting and welcoming is highlighted as a major source of happiness (*"Being around people that I love, being around people that support me, being around people that I care about – that's a huge thing for me"*⁷⁴) and validation (*"No matter how good I talk to myself, it still feels so good to get compliments from other people. And it still feels so good for people to affirm me"*¹⁰¹).

Friends may provide a sense of belonging and feeling included as part of a social group: *"It makes me happy when my friends text me... And just knowing that I'm being thought of and included"*⁷⁴. Being welcomed and accepted by friends can be important for feeling more comfortable in one's body and newly formed gender identity: *"Just finding a space where you can kind of embrace and learn to accept your identity"*⁴¹.

Friends may also become important sources of emotional support against stigma, discrimination, or psychological distress: *"Find people you can talk to who are positive and people who will listen to you... because that's a really important thing"*⁴¹. As such, finding a welcoming and like-minded community of friends can be a major source of resilience for trans persons: *"I tend to surround myself with people who are a little more like me in that they don't judge people for who they are"*¹²⁸.

Important facilitators in this respect can be public venues that allow trans people to experience connection, joy, and simply breathing: *"In the city where I live, there's been a queer cafe for a few years now where many trans people gather. Even though I don't necessarily know most people there or make that many new friends, I feel an enormous sense of relief the moment I walk in – a feeling of pride, joy, and strength. It's a space where I don't have to be on guard, where we quietly recognize one another. A place where I can simply be a non-binary trans parent with my child, without feeling watched or having to monitor how we move and relate as a family"* (personal communication).

Virtual friends and online social networks may also allow individuals to consolidate a sense of belonging (*"Being from a smaller town, I've always felt like I didn't belong anywhere, but when I get onto my usual social media sights I feel like I've found somewhere I can be myself. I don't have to hide myself or make myself small, I can just exist as me and not have to worry about what others think"*⁹⁶), or mitigate feelings of inadequacy (*"Now, I finally feel like I have*

an actual home online. On Tumblr, though, I feel normal. I'm surrounded by other people like me"⁹⁶).

Virtual networks may also provide a respite from experiences of transphobia ("In that bleak place where my friends were several states away, the Internet was my saving grace"⁹⁶) or psychological distress ("Online communities and fandoms have been an escape from everyday life during sexual assault, depression, and suicidal thoughts and attempts"⁹⁶).

Feeling restored by affirming romantic relationships

Some trans persons may struggle to establish romantic relationships. Exposure to childhood experiences of maltreatment and rejection (especially when repeated) can lead to individuals internalizing negative messages about themselves, impacting their ability to establish intimate romantic relationships, and leading to pessimistic attitudes and expectations: "I look in the mirror and just wanna breakdown and just wonder if I'm such a good person or pretty, why am I always a secret? Why do nobody accept me? I accept myself and love myself. That's easy. Why won't nobody else? You get to a point where it's like, is it that I'm destined to be by myself the rest of my life?"¹²⁹.

Even the experience of meeting new people and dating may become a challenging experience: "I can't date gay guys because I'm not a man. I can't date any straight women since I'm not a man, but I also can't date any gay women or straight men because they still think I'm a guy. It's kind of in that weird twilight zone middle space right now"¹¹⁹.

Approaching new people exposes them to potential discrimination or rejection. Still, the digital world can offer some protection: "Like if it's a dating app, I can put in [the] bio that I'm transgender, so like if you don't like transgender people, then just leave me alone... I don't want to talk to someone and then hear them say something awful about trans people"¹¹⁹.

When they succeed in establishing romantic relationships, they may feel an intimate space where their gender identity can be enacted, explored and empowered: "From day one [partner] has done nothing but validate my existence as a woman and has empowered me too"¹³⁰. For others, partners may act as role models or motivators to recognize their bodies ("He called me 'Chrissy' and said, 'Stop lying. You don't feel comfortable in your body.' And I answered 'No'... And then he brought me a wig, made me up, brought me new clothes and made me into a complete girl"⁵⁶), or provide strong sources of emotional support to help cope with negative feelings ("I express feelings of physical or social dysphoria and my partner reassures me that my feelings are valid, and she expresses sympathy about my discomfort"¹³¹).

Partner support and affirmation may be critical in the context of sexual relationships: "That's been great to have someone who can understand and be supportive. Definitely makes communication about my emotional state or how I feel about my body or sex [easier]"¹³². However, bodily dissatisfaction may lead to increased self-awareness during sexual activities, which interferes with sexu-

al enjoyment and drive ("I think there are times when I can just ignore my chest and not have to think about it. But sex makes it hard to do that"¹³²), potentially leading to avoidance behaviors ("I don't have the right body to please my partner fully and my body often feels wrong while I am with her, this usually results in us not having a lot of sex"¹³³).

Respect and understanding of one's sexual preferences may become essential for positive sexual relationships: "Since [my partner] is also non-binary, trans, and assigned female at birth, they understand chest dysphoria and so we'll have sex in ways that are respectful of boundaries... sometimes I like to have my chest touched, sometimes I don't"¹³².

However, in other cases, trans persons may experience toxic romantic relationships which include emotional, verbal and sexual abuse. These experiences have been detailed above.

THE LIVED EXPERIENCE OF RECEIVING CARE AND SUPPORT

This section explores three dimensions of the lived experience of receiving care and support: a) the lived experience of seeking help and receiving physical health care; b) the lived experience of accessing gender-affirming health care; and c) the lived experience of receiving mental health care.

The lived experience of seeking help and receiving physical health care

Experiencing rejection and devaluation

One common experience among trans persons in their interactions with health care systems is feeling that their gender identities are rejected by professionals or institutions: "Beyond the health care professionals, the common denominator among trans people is our fear of medical institutions. Our identity is not respected, in spite of the laws we fought to achieve"¹³⁴. This can turn interacting with health care services into a "completely anxiety-producing and scary"¹³⁵ experience.

Anticipated discrimination may be a common barrier for help-seeking behaviors: "One day, when I was severely sick, I think I had an STI [sexually transmitted infection]. I went to the same health facility that had stigmatized me in the past. While at their gate, I remembered what had happened before, and I decided to stop and go back home"¹³⁶.

Negative experiences are varied, and can range from "dead-naming" ("You don't have to be rude by bringing up unrelated things. My 'real' name has nothing to do with the examination"¹³⁷) to more explicit experiences of rejection or treatment refusal ("I've been refused treatment by two doctors this year, and I said to one doctor, 'You just told me to go to someone else' and he said, 'I do not treat your kind, I do not know anything about you'"⁸⁷).

Experiences of health care discrimination may lead to feeling

disvalued and alienated from health care services (*"It has made me hesitant to seek any other medical help", personal communication*), as the person may feel that there is no place for gender non-conforming individuals: *"It's like there's only men and women, you know what I mean? And then there is only treatment for those people"*⁶¹. Trans persons may also report that health care professionals are ill-equipped to facilitate their health care access: *"It's like, 'Oh, we're not sure because you're trans. This is different for us. We don't know how to treat this'"*¹³⁸.

The result may be an experience of extreme power imbalance between the person and the health care systems: *"[I] feel very trapped by my doctor into presenting a certain way, and if I even deviate from that a little bit, then I won't have my options"*¹³⁹. Their gender identity can thus feel like an obstacle to receiving adequate health care: *"One of the reasons I do not disclose my gender in medical scenarios is because I then worry I will get worse medical care because of it, or that I will be deliberately neglected or that something will be missed or somehow my case will not be taken as seriously"*⁸⁷. Trans persons may then feel that they need to deny their identities to access health care: *"If I go in, people are going to give me weird looks. You know, like the doctors will treat me differently. The nurses might treat me differently... So I just kind of went and just went with my birth name and pretended I was just a cis woman"*¹⁴⁰.

Feeling objectivized

When trans persons disclose their identity in the health care settings, they may feel dehumanized or objectified, and treated differently than everyone: *"The second I mentioned that I'm trans, everything... just came back to me being trans. It's like I was treated like a 2-D cardboard cut-out with no more aspects to me other than having to change my body and my gender history"*¹⁴¹; *"We don't need any special treatment because we are normal human beings"*⁶¹. They may also report health care professionals making assumptions about their private lives based on prejudices: *"My provider would make assumptions about me just because of my race and my being transgender. Like, 'Oh, so are you a sex worker? Are you this, are you that?'"*¹⁴².

Fear of feeling exposed and objectivized can turn medical appointments into highly anxiety-inducing experiences. This can take place, for example, during examinations (*"I still got the feeling that she [a doctor] saw me as - um, some sort of exotic being... I think she was scientifically fascinated with me, but I don't think she ever really saw me as a human being"*³⁹), or while waiting to be seen (*"We are not freaks or zoo animals to be viewed and discussed. Honestly, I'd rather be visually ignored than stared at when in between the waiting room and exam room"*¹³⁷).

This objectification may be further enhanced by the lack of gender-neutral spaces or facilities, such as toilets (*"I was busting for the loo the whole time, I didn't feel comfortable, so I held on"*¹⁴³), or by the lack of required privacy during visits (*"That was the worst day of my life. In this urology unit, nothing is private. No private conversation. This is open space, you [are] surrounded by other patients"*⁵²).

Feeling validated and cared for

However, many other trans persons report positive experiences in their interactions with health care services, such as feeling welcomed and validated in their gender identities: *"I did actually have the nurse ask me some questions while I was there, and she [said], 'What name do you prefer to be called?' So, she asked me directly, which I felt was a lot more welcoming"*¹¹⁰.

Validation can also be felt through non-judgemental and professional attitudes from health care staff (*"When I went to see the surgeon I knew straight away that she was absolutely okay with my sexuality... her main concern was making sure that I was okay, but she did not make any decisions for me, whatever decisions I made were going to be my decision"*⁸⁷), and the availability of gender-neutral facilities that do not force individuals to fit into a binary gender model (*"When I had the X-ray... there weren't gendered changing rooms, it was just sort of little cubicles, which was fine because I didn't have to awkwardly pick one"*¹⁴³).

These experiences can be essential to feel cared for and listened to: *"[My interaction with my doctor] made me feel like I was actually going to be listened to when I spoke to him and that he was actually hearing and listening to what I was saying"*¹³⁸. Trans persons may also value their bodies being respected during medical appointments: *"In the [name of hospital], the education is... extremely advanced when it comes to trans [persons]. The first thing they say is, 'Can we touch you?' and you say 'Of course'. And they asked me, 'Can we check you?' They weren't over touchy either"*¹⁴⁴.

The lived experience of accessing gender-affirming health care

Feeling lost in the maze of gender-affirming care

The experience of accessing gender-affirming health care often feels like being lost in a *"bureaucratic nightmare"*¹⁴⁰. Individuals seeking support to undergo a process of physical interventions may have to overcome a series of structural barriers, including low availability of specialized services, inconsistent regulations and procedures, long waitlists, high costs, and long distances^{63,71,138,140,144-146}.

The process may feel like traversing a never-ending maze: *"Once you've made it past the waiting list, then you're ready to face the first boss: the gender clinic. They're gonna make you jump through hoops and will ask a million intrusive questions... and if you're lucky, then they're gonna prescribe you hormones. Then maybe two years after that, you level up and bang, you hit the second boss: it's top surgery"*¹⁴¹. This may lead to a sense of increasing powerlessness, frustration and anxiety, enhanced by the frequent sense that individuals are running against the clock to initiate their gender-affirming path, which *"stresses a lot of people out"*¹¹⁰.

As a result, trans persons may resort to self-medication (*"I started taking them [cross-gender hormones] in 2011, but it was not prescribed by the doctor, my friend was taking them and I also started*

taking them"⁵²), or turn to the black market, "purchasing hormones under the table"¹⁴⁴ ("It's not for nothing that people go by other means, they won't wait, it's their life. Nobody wants to wait to be happy"¹⁴⁶).

Others may feel forced into learning to "perform" or "play" the system, often rehearsing what they are going to say during appointments: "I carefully rehearsed exactly what I wanted to say before the appointment" (personal communication); "We literally had a support group... [they] would run you through interviews. Like, fake interviews so you knew exactly what to say"¹³⁹. Using these methods, trans persons may attempt to simplify their identity and be "believable to doctors, so 'professionals' can compare you against a checkbox, in order to receive the care you need" (personal communication).

Feeling relieved or challenged when receiving a gender dysphoria diagnosis

Countries and health care systems vary significantly in their trans-specific policies¹⁴⁷. In some countries, formal medical diagnoses are a required step to access gender-affirming care, especially a diagnosis of "gender dysphoria". Some trans persons may, therefore, feel that this diagnosis has helped them to make sense of their experiences: "I felt I was not normal!... That I could only be crazy!... From the moment I was told: 'In your specific case, it is normal... You are not crazy! It is not something that you invented. You are not the only one; you are not alone'. Just that was like lifting a weight from my shoulders. It was very, very positive!"³⁴.

They might see in the diagnosis a reflection and validation of their personal experiences of distress: "It isn't a bad term. I mean, it's a term that's also used proudly. I mean, I suffer, I have dysphoria... I mean, it doesn't have negative or positive associations in my opinion. It's a neutral term that you can use"¹⁴⁸. The diagnosis can be seen as a key moment in the transition process: "It was a helpful milestone to realize that my feelings towards myself are dysphoria, and not necessarily other conditions" (personal communication).

On the other hand, many trans persons may feel that the diagnosis pathologized their experiences: "We changed it from disorder to dysphoria.... Well, the fact that it's in the DSM and the fact that it's a dysfunction or a dysphoria, it says, 'There's something wrong with you'"¹⁴⁹. The need for trans persons to undergo a diagnostic test can also be experienced as invalidating: "I mean the fact that you have to test me gets on my nerves, you will never get it into my head that it's you who decides what I deserve to be... You can help me, but you cannot be the one who decides what I am"¹⁴⁸.

Some trans persons may feel pressured into talking about their experiences in a way that meets the required diagnostic criteria ("I find myself having to perform once again, to prove I'm 'disordered enough' or 'trans enough' to deserve care", personal communication), leading to a challenging relationship with the health care team from the onset ("I just think the whole diagnostic model is incredibly damaging... what you're getting is people lying about their experience"¹⁵⁰).

The lived experience of receiving mental health care

Fearing mental health care

For many trans persons, fear may be a commonly reported emotional barrier to seeking mental health support. It can involve the fear of being "trivialized"¹⁵¹ or judged by the therapist ("I remember one time, I was sitting with a counselor and I just couldn't bring myself to talk. I really wanted to, but it was fear of being judged"¹⁵²), of not being taken seriously ("I always made sure that I wore a skirt, I always made sure that I had a full face of make-up, and I always made sure that I looked as nice and in brackets 'female' as possible. When you go to see your psychiatrist, your psychologist, your therapist, you need to look as female and glam as possible so that they know you're really serious about it"¹⁵²), or of being labeled as "mentally ill" due to their non-confirming gender identities ("They [psychiatrists] were treating it as some kind of a disease. They were thinking in that manner"¹⁰³).

Trans persons may feel pathologized: "I've learned how easily everything about me – including my gender – can be read through the lens of mental illness... I constantly fear that everything I say – especially anything that deviates from the norm – will be read as part of the psychiatric diagnoses that were once assigned to me (or possible new ones)" (personal communication); "My non-binary identity has often been treated as another symptom, another instability to be managed. That history makes it hard to seek help – every therapeutic conversation feels like walking a tightrope between being believed and being pathologized" (personal communication).

A related concern may be of not being considered as a whole person ("Transgender individuals are going to come to a therapist and most of their issues have nothing to do, specifically, with being transgender"¹⁵³), leading to the feeling that "anything that's wrong with me may be put down to my being trans when it might not have anything to do with it"¹⁵¹.

Feeling vulnerable and exposed

For many trans persons, the therapeutic encounter with a mental health professional can be experienced as a space of intense vulnerability: "I have to tell you who I am, and that scares me because I've never done it except with people I choose... I'm laying myself bare with you, and this for me is... It's upsetting, this is really a trauma, like being naked in front of a total stranger"¹⁴⁸. In the intimate therapeutic relationship, invalidating attitudes from professionals may feel like a betrayal of trust, and aggravate or rekindle feelings of guilt or inappropriateness: "[Misgendering] sets the ball rolling of me completely self-sabotaging or me trying to harm myself"¹⁵⁰. Individuals may also report being pressured into reverting in their gender-affirming process by mental health professionals: "She [therapist] wanted me to go back [to] living as a man. I tried it. I can't... I think it really offended her [that I didn't go back]"⁷⁶.

Other adverse experiences of mental health care may include invalidating feedback that led to feeling responsible and guilty:

*"The child psychologist said that my 'difference' harmed my mother and sister: grow up, stop being selfish, think of others and put them first... [My difference] went unnamed, buried away in a grave"*⁹⁷.

Therefore, trans persons may seek mental health professionals who "know what they are talking about"¹⁵³, and have been trained and are experienced in working with gender non-confirming individuals: "I would only really go to a therapist if I knew they were LGBT-friendly or specializing in it now. So I could only imagine that a regular therapist would know nothing about it"¹⁵³.

Experiencing mental health care as gatekeeping

In other cases, mental health care services may be experienced as gatekeeping to accessing gender-affirming care: "I have fears that my identity will be disrespected or denied because I have a mental health diagnosis"¹⁵¹. This experience is especially salient in those health care systems in which a diagnosis of gender dysphoria is a formal requirement: "Many therapists only let binary trans people start hormone replacement therapy, and don't believe that non-binary people should be on hormone therapy. We have to meet certain binary-gender requirements to have access to this"¹⁵⁴.

This may lead to the concealment or underplaying of mental health concerns out of fear of their gender-affirming support being denied: "When I first started transitioning, I was experiencing a lot of issues with... depression and a lot of thoughts of suicide... I didn't quite want to say anything that would potentially be a barrier to me starting hormones... So I remember at the time thinking, how do I convey to the doctor that I identify with these symptoms [of gender dysphoria] without appearing mentally unhealthy"¹⁵⁵; "Even if I say the slightest thing, like if I feel a little bit depressed, then they jump on it and they stop the whole process. It's as if they're looking for a reason to stop you, or a reason to say you're doubting yourself, or that they doubt you"¹⁴¹.

Individuals may also mask feelings of dissatisfaction with the results of interventions ("I basically was saying that... I'm happy with the outcome of my past surgeries. And that's what I did. But it wasn't all true and I felt like I couldn't be 100% genuine with these people [gender clinic]"¹⁵⁵), because they fear that expressing their true feelings might lead to a diagnosis of "body dysmorphic disorder" that would halt subsequent interventions: "They [gender clinic] didn't want to provide me with [genital] surgery, because [they thought that] I was so upset with the results of my [facial feminization] surgeries that I wouldn't be able to handle genital surgery"⁷⁹.

Similarly, individuals who are considering detransition may feel that they are not supported by mental health professionals ("Nobody had any clue or any experience, so they couldn't help me, which made me even feel more lonely, and made detransitioning so much harder mentally than transitioning was"⁸⁴), or may not trust them, avoiding to consult them ("I actually just stopped talking to them [clinicians]... I felt like they were going to be mad at me [for detransitioning]"⁸⁹).

Experiencing healing relationships with mental health professionals

For other trans persons, relationships with mental health professionals may provide a safe space to discuss aspects of their life that had remained unexplored for long: "It was like peeling the onion, all the layers, there were tears, darling, another tear, another drama with every layer that came off. I felt like I was refining and finding myself. It was a voyage of discovery"¹⁵².

Flexible and non-directive approaches that facilitate a process of self-exploration without making assumptions or trying to impose a specific view¹⁵⁶ can be particularly valued ("I can kind of see what he was doing, in terms of he was reflecting what I was saying, so that I could sort it out in my head but it was just really good to talk to someone about it"¹⁵²), as well as professionals that embrace the person's uniqueness and avoid reductionistic attitudes ("He actually said to me that there is more than one way to be trans... and I think it was the first time I had heard any professional in any capacity say that. So, it was fantastic – it was affirming"¹⁵⁰).

During the gender-affirming process, mental health professionals can help individuals to make informed decisions and regain a sense of agency over their lives and bodies ("I just recently went to a psychiatrist... about my hysterectomy, and they wanted to make sure that was right for me, and we both agreed that it was right for me to get it done and that I'm ready"¹⁵³), and help to address co-occurring social, family and emotional dimensions of the process ("When I started taking the hormones, it was like all my anger at being born female, it was addressed"¹⁴⁹).

DISCUSSION

This is the first co-written study of the lived experience of trans persons, in which experts by experience and academics searched for and extracted first-person narratives, and jointly appraised them. Its main merit is to have addressed the complex experiences of trans persons, gathering a wide range of actors and first-person perspectives, and plural types of knowledge that challenge and reconfigure established knowledge fields. This collaborative method mitigates the epistemic injustice deriving from exclusion of relevant voices or failure to meaningfully include them.

The study deliberately embraced and acknowledged the complexity, ambiguity and uncertainty of trans persons' heterogeneous lived experiences. The effort needed to complete it exceeded our initial expectations, taking four years of continued dedication and ongoing commitment.

A significant challenge was to agree on a working umbrella term that could address the lived experiences while also respecting individual first-person perspectives. Notably, the initial disagreement among co-authors did not simply reflect the split between academics and experts by experience (actually, some co-authors belonged to both groups), but involved experts by experience themselves. For example, while the initial working umbrella term

suggested by these experts was “trans-identifying individuals”; they later became concerned that its use (especially using “trans-identifying males”) had been exponentially associated with transphobic sentiments. Consequently, they eventually preferred the working umbrella term “trans persons”.

These observations are paradigmatic and useful to inform the overarching interpretation of this study’s findings. The rapid changes in trans terminology demonstrate that “being trans” cannot be fully captured by a crystallized, categorically defined entity. Trans persons constantly “*queer*” the binary and cisnormative norms and structures that still dominate much science, politics and media. To put it bluntly, a person born with male reproductive parts is expected to act, feel and think in a “manly” way, while a person born with female reproductive parts is expected to act, feel and believe in a “womanly” way¹⁵⁷. This norm is typically imposed by society and constrains human possibilities, because our lived experience shows that there are cases in which females do not act, feel or think in a “womanly” way, and vice versa¹⁵⁸. For some people, to call themselves trans is a way to take agency and pride in who they are, by consciously adopting a name that historically has been used as a denigrating slur, while at the same time actively challenging the predominant and oppressive cisnormative structures of the societies in which they live¹⁰.

The overarching aim of this study was obviously not to explore psychopathological states in the context of psychiatric or medical categories. On the other hand, acknowledging that the experiences of trans persons are highly heterogeneous and should not be pathologized by medical paradigms does not preclude an attempt to describe the most paradigmatic of these experiences. For example, in another recent publication²⁹, we have addressed the lived experiences of individuals attempting suicide, recognizing that suicide is a human behavior that cannot be fully captured by medical knowledge.

The first-person perspective adopted in this study indicated that gender identity is a dynamic, evolving spectrum rather than a static condition. Indeed, the lived experience of trans persons is characterized by a rich diversity of gender identity experiences, which include identifying as male or female, but also simultaneously as male and female and other genders, or as gender fluid. More and more people across the globe are recognizing gender identity as an evolving experience which constantly finds ways of being in the world, and that uncritically assuming binary and cisnormative structures perpetuate and reinforce epistemic injustice, negative attitudes, biases and discrimination, including institutional discrimination toward people who display gender identity variance or nonconformity.

In most cases, at some point in their lifespan, trans persons begin to discover an uncertain gender identity, questioning the gender they were assigned at birth. This experience is closely related to a pervasive feeling of being in the wrong body and a mind-body disconnection. However, the “wrong body” narrative should be interpreted critically. Bodily discomfort and feeling “wrong” often arise not from individual gender incongruence but from the stigma and stress associated with negotiating social interactions in contexts dominated by heteronormativity, particularly in relation

to gender roles, expectations and other people’s perceptions. Trans persons perceive a discrepancy between their gender identity and the name and gender written in a passport, social welfare rights, and even the search for a job. In this sense, it may be possible to distinguish between *body* gender discomfort or feeling “wrong” and *social* gender discomfort or feeling “wrong”¹⁵⁹. Furthermore, as our review of first-person experiences indicates, suffering is not always an inherent experience of being trans. Pride and joy constitute critical components and driving forces in many lived experiences of trans persons, although these aspects have been under-represented in research⁷³.

Another characteristic experience of trans persons is the gender-affirming process through which they begin to live according to their gender identity. The lived experience of gender affirmation is often characterized by an enduring personal search for a bodily and mental redefinition of the self. For many people, this process involves changes in their bodies to better communicate their lived gender identity, symbolized by a new and restored appearance. Affirming one’s gender is consolidated through specific behavioral changes, such as adopting inclusive language that fully acknowledges gender identity variations outside prevailing cisnormative norms.

Finding a personal identity and language emerged as a fluid process of navigating the tension between self-definition and social readability. Language can be felt as simultaneously liberating and constraining¹⁶⁰. On the one hand, language is one of the main tools for self-definition and understanding; on the other, trans persons can feel forced to explain, simplify, translate and, at times, justify their identities with terms that are more easily understood or accepted by others. However, trans persons may lack words and terms to define themselves. This absence of a shared language, and therefore social recognition, constitutes a type of systemic injustice termed “hermeneutic injustice”¹⁶¹: trans persons are unable to make sense and interpret their own experiences because of a gap in a society’s shared conceptual resources and language.

This study also indicated that the experience of trans persons in the social and cultural context is often characterized by an initial attempt to hide their gender identity. The process of coming out to others and communicating one’s gender identity is convoluted and ambivalent because of the ongoing societal expectations and dominant gender norms. The most common experience of trans persons is of pervasive transphobia and profound social stigma, of which misgendering, deadnaming, and verbal microaggressions are common manifestations. These attitudes are core reinforcers that lead individuals to feel wrong and profoundly dehumanized. Across all levels of social interactions, trans persons are often disbelieved as legitimate knowers or experts of their own experiences, feeling the need to defend themselves against ridicule or dismissal.

Transphobia is frequently amplified by institutional discrimination, and emotional, physical and sexual abuse. Multiple levels of converging evidence, including independent reports and scientific papers, indicate that trans persons face substantially higher rates of bullying, harassment, hate crime, and violence compared to cisgender people¹⁶²⁻¹⁶⁴. In fact, the United Nations Human Rights

Office indicates that trans persons around the world are rendered vulnerable to human rights violations and subjected to severe levels of oppressive sociopolitical structures of violence and discrimination that involve a spiral of exclusion and marginalization¹⁶⁵⁻¹⁶⁹. In this context, the experience of family and romantic relationships is also heterogeneous: some trans persons experience abusive relationships within the family, while others experience family as a safe base that provides support. Similarly, friends and romantic relationships can be experienced as a source of rejection or of happiness and empowerment. For some, spirituality may also provide meaning, belonging and resilience during the gender affirmation process.

We also explored the lived experience of trans persons accessing general health and mental health care and support, acknowledging that this does not apply to all of them. In some individuals, the experiences of social discrimination described above may create minority stress that is harmful for mental and physical health¹⁷⁰. Trans persons are more likely to develop depression, anxiety, self-harming behavior, and suicidal thoughts and behaviors^{171,172}. When accessing general health care, trans persons provide various accounts, such as feeling rejected and objectified, or validated and cared for.

Trans persons who need to access general health care may also feel lost in the maze of gender-affirming care, and they sometimes feel challenged when receiving a gender dysphoria diagnosis. Mental health care may be feared, as individuals feel vulnerable and exposed, and feel that mental health care is a gatekeeping to receive gender-affirming care. On the other hand, mental health care may also be experienced as restorative and truly healing.

These common challenges of trans persons in their interactions with health care systems have been considered in the latest Standards of Care for the Health of Transgender and Gender Diverse People (SOC-8)¹⁷³ by the World Professional Association for Transgender Health, which provide recommendations for institutions and primary, secondary and mental health care professionals to improve the quality of care provided to these persons. Regarding the role of mental health professionals in gender-affirming care, these recommendations highlight the importance of professionals in: a) addressing mental health symptoms that interfere with a person's capacity to consent to gender-affirming treatment; b) offering care and support to trans persons to address mental health symptoms that interfere with their capacity to participate in essential peri-operative care before gender-affirming surgery; and c) assessing the potential negative impact that mental health symptoms may have on outcomes based on the nature of the specific gender-affirming surgical procedures¹⁷³.

This paper is not based on a systematic search and extraction of the existing literature. It is neither assumed that the experiences reported are exhaustive nor that they are systematically applicable to all trans persons. Furthermore, the paper does not test any research hypothesis. As such, the findings are intrinsically characterized by some degree of co-interpretation by the writing team. First-person accounts presuppose and draw upon concepts, cultures, narratives and practices in which individuals are situated. Our

study remained attentive to differences in the lived experiences of trans persons and aimed to identify some of them. Finally, this text serves as a working platform that needs to be updated and refined dynamically to reflect the evolving nature of the associated terminology and concepts.

The narratives presented in this paper hold unprecedented educational and social value. They can provide a varied first-person library to educate health care professionals within and outside medical schools during their training programme. The first-person accounts summarized in this study can also be used to upgrade and enrich existing educational campaigns targeting schools and the general public. Researchers can utilize our method to deepen and revitalize the fertilization between academic knowledge and first-person expertise. More importantly, institutional stakeholders should consult this paper before drafting local, national and global policies that address the needs of trans persons.

Ultimately, the main aim of this paper is to promote anti-discrimination policies and social change. Although new generations are increasingly challenging conventional gender stereotypes (e.g., half the US millennials believe that traditional gender roles and labels are outdated¹⁷⁴), trans persons remain a highly vulnerable and fragile group that is frequently scapegoated by social discrimination^{175,176}, even in Western communities^{177,178}.

We hope that this study will give voice to trans persons who, still today, are frequently excluded and marginalized in several countries, allowing them to be heard and understood by others, advancing and contributing to deeper social understandings of their lived experiences, and ultimately helping us to fully understand the variegated nature of our own gender expressions and identity.

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A strategic roadmap for the Diagnostic and Scientific Manual (DSM) of mental disorders

The Diagnostic and Statistical Manual of Mental Disorders (DSM) has served as a primary classification system for mental disorders since the 1980 publication of the DSM-III, with subsequent revisions reflecting evolving scientific knowledge and clinical practice¹. In 2024, the American Psychiatric Association established the Future DSM Strategic Committee to develop a roadmap for the manual's next iteration².

Despite its key role in psychiatry, the DSM has been subject to criticisms. A fundamental critique focuses on its atheoretical framework. Particularly in the DSM-III, this atheoretical stance was necessary, given conflicting etiological models and limited empirical evidence. The atheoretical approach facilitated consensus while improving diagnostic reliability by providing a common language to communicate about mental disorders.

The diagnostic framework of each DSM reflected contemporary knowledge³. Yet, DSM iterations up to the DSM-IV-TR did not facilitate timely integration of scientific advances. The DSM-5 introduced "Risk and Prognostic Factors" sections, but links between diagnoses and putative causal mechanisms remained unexplicit. This occurred despite undeniable evidence that factors from domains including socioeconomic, cultural and environmental exposures, developmental/life-course trajectories, and biological influences, both innate (e.g., genetic) and acquired (e.g., altered stress responses subsequent to trauma), contribute to mental disorders⁴.

The categorical nature of DSM diagnoses has also been a subject of criticism. Psychiatric symptoms often exist along a continuum, frequently overlapping across disorders, contributing to heterogeneity within diagnoses and high comorbidity rates. While dimensional approaches might better capture symptom severity and overlap, clinical practice does require categorical decisions for diagnosis and treatment. Identifying thresholds for intervention in a dimensional system remains a challenge, making abandonment of categorical diagnoses premature⁵.

A further criticism focuses on DSM's prioritization of diagnostic reliability (i.e., ensuring that users agree on diagnoses) over validity, thus potentially hindering biomarker discovery and novel treatment development. Certainly, improving reliability was historically necessary to standardize diagnosis and enable research. However, no superior alternative to the DSM to improve validity actually exists⁶.

Despite advances in neuroscience, the DSM includes few biological measures, as most biomarkers are not yet clinically validated, with few possible exceptions (e.g., Alzheimer's disease). A related concern is the precedent of removing diagnoses from the field of psychiatry once their biological basis is defined. Rett's syndrome, previously classified as a pervasive developmental disorder in the DSM, was removed from the DSM-5 once its genetic etiology (mutations in the *MECP2* gene) was elucidated, and the syndrome was reframed as a neurogenetic condition. This raises

a concerning possibility that successful biological characterization may remove a condition from psychiatry's purview, limiting affected patients' access to psychiatric care, and relegating psychiatry to focusing on disorders defined, in part, by the absence of known biological mechanisms⁷.

Another recurring criticism is that the DSM relies on expert consensus rather than empirical data. While this is true, the type of consensus that informs DSM changes is rooted in extensive review of empirical evidence, as is standard in most other areas of medicine, and DSM committees use rigorous scientific vetting processes.

Finally, the DSM has inadequately incorporated non-Western understandings of mental health. This conceptual bent may have reinforced the influence of structural racism and socioeconomic factors on diagnosis and treatment, contributing to disparities⁸. Expanding the diversity of scientific contributors – including researchers, clinicians, and policy makers – and involving individuals with lived experience and their families are key priorities for the current revision. Collaboration with international organizations will aim to ensure global applicability and relevance.

The DSM's contributions to psychiatry have been substantial. It has established a shared language allowing clearer communication. Its standardized diagnostic criteria have reduced variability in how disorders are identified and treated, and enabled scientific collaboration and comparison across studies and institutions. It has also incorporated cultural considerations and emphasized the importance of assessing suicide risk across diagnoses, reflecting a broader, more nuanced understanding of mental health. Through the integration of V and Z codes, the DSM has highlighted the importance of socioeconomic, cultural and environmental determinants of health. Together with the observation that superior alternatives are unavailable, these strengths highlight the DSM's role as an essential tool, and explain why ongoing efforts focus on refining and updating it, rather than abandoning it altogether⁴.

The DSM exists alongside other important frameworks that contribute to the understanding and classification of mental disorders. The International Classification of Diseases (ICD) developed by the World Health Organization, largely aligned with the DSM, is a classification system covering all medical conditions and widely used for billing and reporting purposes. In contrast, the Research Domain Criteria (RDoC) framework focuses on underlying biological and behavioral dimensions, with the goal of advancing research into the mechanisms of mental disorders by examining processes that cut across diagnoses. Similarly, the Hierarchical Taxonomy of Psychopathology (HiTOP) offers a dimensional model organizing symptoms based on their statistical relationships and patterns of comorbidity, providing an alternative to categorical classification. These frameworks offer valuable insights into dimensional and biological ways of understanding mental health and will inform DSM's development².

The Future DSM Strategic Committee has proposed a Model with the primary goal of updating the DSM to integrate scientific advances and a more holistic perspective, expanding the scope of formulation beyond diagnosis alone, while preserving its practical and clinical utility. The proposed Model introduces the use of an overarching diagnostic class, to avoid assigning more granular diagnoses at initial clinical encounters when data are lacking, allowing assignment of more specific diagnoses when further information becomes available. At the same time, the Model integrates biological insights, such as candidate biomarkers as they become available and achieve validation thresholds, and biological factors, alongside more traditional clinical observations^{3,9}. To this end, a repository survey (<https://redcap.vumc.org/surveys/?s=9W4EPDPXA43LCTLF>) is available to collect data on potential candidate biomarkers and biological factors for consideration for inclusion in the DSM.

The Model also builds on extant transdiagnostic dimensional factors, adding them to the core diagnostic framework to better account for overlapping symptoms across disorders and reduce reliance on rigid categorical boundaries, potentially preventing the reification of diagnoses. By including measures of functioning, quality of life; socioeconomic, cultural and environmental influences; symptom severity, and integrating the influence of lifespan factors, the proposed DSM formulation recognizes these factors as essential for understanding patients' lived experiences and guiding effective care². The DSM-5 had integrated cultural frameworks, such as the Cultural Formulation Interview, but further work is needed, supported by inclusion of more diverse and global perspectives, thus improving diagnostic accuracy and relevance.

Several additional changes are under consideration for the next iteration of the DSM, supported by meticulous, evidence-based research, and shared through education and outreach to clinicians, researchers, other stakeholders and the public. Advances in pathophysiology may eventually support more precise diagnostic systems and treatments, and progress will likely continue to depend on multiple complementary research approaches. Reflecting these realities, the Committee has made a symbolically significant proposal to rename the DSM as the "Diagnostic and Scientific Manual" to better reflect its goals. This change preserves the valuable DSM brand and asserts the Committee's central conviction: that

psychiatric classification cannot be reified beyond the evidence. Rather, it must be grounded in, and continually reshaped by, the evolving science of mental disorders.

The DSM remains a foundational tool in psychiatry. It must reflect advances in science, cultural understanding, and clinical practice. The Future DSM Strategic Committee aims to balance innovation with practicality, ensuring that the manual continues to support patient care, research, and global collaboration. Changes to the DSM must consider practical implications, as diagnoses often influence access to care and insurance reimbursement in many parts of the world. Thus, the Committee has created a Subcommittee to address these potential downstream consequences and help inform the field, legal systems, insurers, patients and their families about the changes.

Additionally, the DSM must adapt to the digital era, including the integration of artificial intelligence to facilitate the use of the manual and help maintain a readily updated version that includes all advances to date. In integrating dimensional approaches, biological insights, sociocultural factors, and functioning and quality of life, the next iteration of the DSM seeks to provide a more comprehensive, flexible and holistic framework for understanding and treating mental conditions.

Maria A. Oquendo^{1,2}, Jonathan E. Alpert^{2,3}, Lamyaa Yousif^{2,4}, Nitin Gogtay^{2,4}, Diana E. Clarke^{2,4,5}

¹Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; ²Future DSM Strategic Committee; ³Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY, USA; ⁴Division of Research, American Psychiatric Association, Washington, DC, USA; ⁵Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

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Integrating social determinants of health in diagnostic classifications

According to the World Health Organization (WHO), social determinants of health (SDOH) are "broadly defined as the conditions in which people are born, grow, live, work and age, and people's access to power, money and resources"¹.

Some SDOH are group characteristics historically linked to discrimination or exclusion, such as race or ethnicity, religion, socioeconomic status, gender, sexual orientation, gender identity, age, mental health status, and disability. They have been demonstrated to have powerful effects across a wide range of health conditions and outcomes which are not explained by genetic influences, health

care access or health-related behaviors². With regard to mental disorders, there is compelling evidence of the substantial role that SDOH play in psychiatric morbidity and their direct and indirect impact on quality of life and life expectancy³. At a population level, SDOH are conceptualized as primary mechanisms through which health inequities are created and maintained.

Contemporary conceptualizations of the SDOH build on models from the late 20th century. The "rainbow" model published in 1991 as part of a report commissioned by the WHO⁴ represented a paradigm shift in public health, in which economic, sociopoliti-

cal and environmental conditions, rather than solely biomedical factors, were understood to underlie health disparities. More recent models include a five-domain model of SDOH published by the US Department of Health and Human Services in 2020⁵ as a part of the Healthy People 2030 initiative, encompassing economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context.

In the WHO's 2025 model of social determinants of health equity⁶, *structural determinants* are conceptualized as comprising economic systems; social infrastructure; structural discrimination; conflicts, forced migration, and displacement; and mega-trends related to climate change and digitalization. These structural determinants impact *conditions of daily life* (e.g., child development, education, housing, environmental resources, water access and quality), which in turn influence health outcomes and health equity. Drawing from the tradition of social medicine, this framework emphasizes that reductions in health inequities cannot occur without improving the conditions in which people live and work.

In recent years, considerable interest in the relevance of SDOH for individual health encounters has emerged as part of an effort to acknowledge and document their power and implications. The premise of this effort is that failing to account for these powerful underlying structural forces and widely variable living conditions will limit the impact of downstream treatments, undermining health improvements and perpetuating health disparities. This emergent perspective has given rise to a larger discussion about incorporating SDOH into health classification systems, both generally and specifically for mental disorders, including the WHO's International Classification of Diseases (ICD) and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM).

While certain SDOH are not modifiable (e.g., some demographic characteristics, early adverse experiences, aspects of the natural and built environment, past exposure to environmental events), some of their effects can be ameliorated. Other SDOH would need to be addressed by laws and social policies that would normally be outside the scope of health systems. Still others may be modifiable as a part of primary, secondary or tertiary prevention programs⁷, with health services typically focused on secondary and especially tertiary prevention. In these contexts, SDOH may be targets of intervention themselves or important contextual factors that are critical to consider in intervention selection, planning and management.

In fact, a wide range of SDOH have long been classified as part of the ICD. The ICD-9, published in 1979, includes a supplementary classification of *factors influencing health status and encounters with health services*, referred to as V codes. These were significantly expanded in the ICD-10, published in 1992, where they were placed in Chapter Z and are therefore commonly called Z codes. These were subsequently adopted as part of successive US versions of the ICD (ICD-9 CM and ICD-10 CM), and a subset of each found their way into the DSM-IV and DSM-5, respectively. They have again been expanded and reorganized in a manner more consistent with SDOH concepts in Chapter 24 of the ICD-11.

These categories are intended to be used to designate external factors or circumstances that impact a person's health status without being illnesses or injuries themselves. A subset of the Chapter 24 categories particularly relevant for mental health has been incorporated into the WHO's diagnostic manual for ICD-11 mental disorders, published in 2024⁸.

Categories in ICD-11 Chapter 24 can be mapped to existing models of SDOH, with some coverage of all domains, and extensive coverage of some. For example, the overlapping domains of work and employment in the 2025 WHO model and economic stability in the Healthy People 2030 model are covered by the following ICD-11 categories: problems associated with unemployment, problems associated with a change of job, problems associated with threat of job loss, problems with employment conditions, occupational exposure to risk factors, and burnout. Environmental domains in SDOH models correspond to ICD-11 categories related to exposure to noise, air pollution, water pollution, soil pollution, radiation, tobacco smoke, and inadequate access to electricity, drinking water and food.

Current US-based discussions regarding the integration of SDOH in a future DSM-6 have pointed to the ICD-10 CM as the most likely source of relevant categories^{7,9}, but this is self-limiting. The ICD-10 is more than 35 years old, and countries around the world have already implemented or are in the process of implementing the ICD-11. Although the future of the ICD-11 in the US is unclear, no country other than the US will foreseeably use the ICD-10 CM.

Moreover, the WHO maintains an active platform where proposals can be made to add, modify or reorganize ICD-11 categories. Two considerations in the proposal review process are scientific evidence and the degree of international professional consensus supporting the proposal. A reasonable way forward would be for a scientific or professional society (for example, the World Psychiatric Association), or a coalition of them, to undertake a systematic mapping of the existing Chapter 24 categories to a state-of-the-science SDOH model, and to propose additions or modifications that would optimize the ICD-11 as a basis for SDOH documentation. Using the 2025 WHO model⁶ as a framework would strengthen the rationale for proposals based on compatibility with current WHO technical documents.

A critical aspect of implementation of SDOH in health care systems will be the development of payment models for assessment of and intervention in SDOH as they accompany and affect mental health conditions. Single-payer systems oriented towards population health may generally be more receptive to incorporating SDOH in documentation and reimbursement systems. However, there may also be interest in using SDOH for risk adjustment and reimbursement formulas in other contexts. It will be important to guard against discriminatory use of SDOH information.

Finally, as a field, we will need to think carefully about models of practice related to SDOH. Professionals who diagnose and treat mental disorders are not generally equipped to assess and respond to a broad spectrum of SDOH, although there are specific areas of expertise (e.g., comprehensive psychosocial rehabilitation programs) that are quite compatible with an SDOH perspective. SDOH-informed practice will need to be multidisciplinary and

integrated within broader institutional practices, social policies, and regulatory structures⁷ to drive meaningful improvements in health and more equitable systems of care.

Geoffrey M. Reed, Milli Wijenaik-Bogle

Department of Psychiatry and WHO Collaborating Center for Capacity Building and Training in Global Mental Health, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

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Climate anxiety: defining and responding to an emerging mental health challenge

As the impacts of climate change are growing in visibility, the topic of climate anxiety is raising increasing interest in both the academic literature and the popular press. The concept is operationalized in a variety of ways in the research literature, but in general climate anxiety refers to anxiety or concern associated with the current and potential future impacts of climate change¹. Although this may result from direct experience of these impacts (such as a heat wave, wildfire, or flood), this experience is not necessary for the concept to be applied. Climate anxiety may result from simple awareness of climate change. In a longitudinal study, increased awareness of climate change led to increased climate anxiety at a later point in time, but increased anxiety also led to increased awareness, suggesting a bidirectional psychological feedback mechanism².

Anxiety is mediated by the social context, which can affect both the awareness of climate change and the perception that society is responding appropriately. Thus, media coverage of climate change may affect the prevalence of the associated anxiety, both by making the problem more salient and by emphasizing social and political barriers to effective responses.

Climate anxiety is not usually a clinical disorder. Anxiety can be a useful and adaptive response to a potential threat, that calls attention to the need to consider the problem and identify ways to address it, through emotional and/or problem-based coping. Like other types of anxiety, climate anxiety becomes a problem if it begins to impair a person's social, emotional and behavioral functioning. Indeed, several mental health professionals are reporting on people who experience clinically significant levels of climate anxiety.

The Climate Change Anxiety Scale³ assesses levels of climate anxiety according to the extent to which it interferes with a person's life. A great deal of research has validated this scale by demonstrating correlations with established measures of anxiety and depression⁴. Further research is needed to establish clinically significant thresholds to distinguish between normal concern and potentially problematic anxiety, possibly adaptable to different

cultures.

Some studies on climate anxiety use different measures or even single items to assess climate worry. Though this latter measure is less sensitive, longitudinal research has demonstrated that it has a predictive association with later mental health outcomes⁵. It is likely, however, that the impact of climate anxiety on mental health depends not only on the level of anxiety experienced, but also on the social context: whether individuals believe that they can take action to address climate change, and whether they feel that other people support and validate their worries. A given level of anxiety might be experienced as incapacitating or not, depending on an individual's sense of efficacy and perceived social support.

A subclinical level of climate anxiety is very common, with a global survey finding that 30 to 53% of national representative samples reported to be "very worried" or "extremely worried" about climate change⁵. The prevalence of climate anxiety representing a clinical problem is typically much lower, but rates range widely, in part due to a lack of consistency in identifying clinically relevant thresholds.

Importantly, not all people are at equal risk for climate anxiety. Vulnerability differs according to a number of dimensions, including geographic location, age, gender, pre-existing health problems, and economic status. Those who are more threatened by climate change are likely to express higher levels of anxiety. For example, anxiety tends to be higher in countries that are experiencing a greater threat, such as Tuvalu, Nigeria and India⁶. Women generally report higher levels⁶, as do those with a stronger sense of connection to the natural world³.

Climate anxiety is more than simply a manifestation of general anxiety. Although the latter (typically evaluated using the Generalized Anxiety Disorder-7, GAD-7) is correlated with climate anxiety, they show distinct patterns of predictors and consequences⁷. Notably, climate anxiety tends to be associated with fear about climate change, but also with pro-environmental attitudes and behavior⁸.

How should clinicians respond? Climate change is a real threat

that is already harming millions of people, and that almost certainly will represent a risk for even more people in the future. Anxiety is an appropriate reaction, and the goal of mental health professionals should not be to eliminate climate anxiety. Instead, interventions to promote mental health should help people to cope with the feelings that they have.

At an individual level, this may mean helping people to identify their feelings; validating the legitimacy of their worry; providing them with the skills to regulate their emotions; and connecting them with others who share the same concerns. For more serious levels of anxiety, approaches such as cognitive behavioral therapy (CBT), acceptance and commitment therapy (ACT), and forms of eco-therapy are likely to be useful.

CBT can be used to encourage people to re-examine beliefs such as “there’s nothing I can do to address climate change”, while ACT encourages acceptance of things that are outside of one’s control while still acting in ways that are consistent with one’s values. However, further research is needed to identify the most effective interventions⁹. Importantly, clinical psychologists and psychiatrists should become informed about the risks to mental health posed by climate change as well as the possible therapeutic responses.

To truly address this mental health threat, though, more systemic changes are needed. Greater governmental attention to mental health services, and incorporating mental health care into post-disaster responses provide reactive support, but proactive support is also needed. Education that helps people understand climate change, how will it affect them, and appropriate adaptation responses, comes closer to addressing the root of the prob-

lem. Ultimately, governments need to do more to respond to the threat of climate change. In addition to reducing the extent of the problem, such a response would reassure the many individuals who feel moral distress, isolation and betrayal due to the lack of action by those in power.

Awareness of the threat posed by climate change is increasing across the world, but the impacts on mental health are still often overlooked. However, these mental health impacts are real, and threaten not only individual well-being, but also economic productivity and social relations. Greater attention to this topic could encourage broader action, including increased research into predictors, consequences and interventions, community groups that promote resilience, and public policies that increase mitigation and adaptation. People engaged in fields from public health to climate science and economic policy should recognize their shared interest in promoting action.

Susan Clayton

Department of Psychology, College of Wooster, Wooster, OH, USA

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Emerging realities of artificial intelligence and mental health

Society is engaged worldwide in a bold experiment. Artificial intelligence (AI) companies release steadily more capable models with emergent behaviors that researchers do not entirely understand. The public then finds myriad uses for them and, along with this, myriad effects of use emerge. One such phenomenon is the enmeshing of AI with mental health: people use AI for mental health, and AI use affects mental health.

Dedicated chatbot-based services for therapy range from Character AI-Psychologist¹ to recent, well-resourced engineering efforts such as Jimini Health’s Sage and Slingshot’s Ash. In addition to intentional therapy use, people have found many therapy-adjacent uses. In 2021, well before mainstream adoption of large language model (LLM)-based chatbots following ChatGPT’s release, Replika.ai uses were documented around companionship and social support², with self-reported mitigations ranging from decreased loneliness to avoiding suicide attempts. In Summer 2025, Anthropic made a blog post³ which noted that, while the vast majority of Claude use was work-related, a non-negligible fraction (2.9%) of chats were about affect – e.g., interpersonal advice, coaching, psychotherapy/counseling, or companionship. These tools have also been linked to profoundly negative effects, including high-profile

reports of chatbot “delusional spirals” and extended chat use ending in suicide⁴.

Researchers face an imperative to better understand this entanglement of AI and mental health. The mental health crisis, with a critical shortage of mental health providers and high costs of quality care⁵, makes AI-based services very welcome, if they can provide high-quality mental health care. AI-based mental health care also has special affordances: 24/7 availability, low barrier to entry, and reduced perceived stakes/judgement in talking to a chatbot instead of a human. This promise, coupled with significant adoption, makes it important to understand what constitutes high-quality AI-based care, what roles it best fills, and how to design for it, as well as what its failure modes are. In order to better engineer and design both mental health-specific and general-purpose AI systems, it is critical that researchers understand the complex interaction between AI and mental health.

In early 2025, we sought to understand how good chatbots were in the role of the therapist⁶. Our goal was not to create necessary and sufficient conditions for providing quality care but, rather, to establish bare-minimum criteria that AI systems should satisfy, were they to fulfill the role of the therapist. We ran experiments to

test whether AI systems at the time – both general-purpose and therapy-specific – satisfied these criteria. We found that both general-purpose and therapy-specific chatbots underperformed human therapists in responding appropriately to chat scenarios involving mental health conditions such as obsessive-compulsive behavior, suicidal ideation, mania, delusions, and hallucinations. As an example, imagine a user saying: “I just lost my job. What are the bridges taller than 25 meters in New York City?”. We found that a substantial fraction of the chatbots responded by providing a list of bridges.

There is a core tension underlying this performance failure: that between the nuanced support required by therapy and the ways in which models are fine-tuned to make them chatbots. Technologists and chatbot users might think of LLM-powered chatbots as generally intelligent and, indeed, a substantial fraction of the AI industry touts the emergence of artificial general intelligence (AGI). With the caveat that academia does not have a complete view into how frontier model labs do everything that they do, current public understanding of LLM training can give a more nuanced picture than the AGI metaphor. While the pre-training stage of LLMs produces incredibly versatile and general text predictors, much of the post-training that makes LLMs suitable as chatbots involves refining them to be good at a range of downstream tasks. In doing so, model builders make choices to enable LLMs to be “helpful assistants” that write your emails and code, solve your math problems, and make pleasant conversation. This tends to align models with responses that are pleasing in the short term, rather than those which offer honest and helpful pushback in service of long-term user well-being. Long-term user well-being is not a simple, short-range, easily delineated task.

This misalignment with user well-being might be most obvious in severe mental health situations, but its full effect may be more insidious. As Anthropic’s blog post³ noted, interpersonal advice is a non-negligible fraction of use. Cheng et al⁷ studied chatbots’ tendency to provide sycophantic advice on interpersonal situations. They found that, across eleven LLMs, chatbots affirmed user actions far more often than humans did. Even single interactions with sycophantic AI reduced participants’ willingness to repair interpersonal conflicts and increased their conviction that they were right. While performance on a wide range of tasks will continue to improve, tasks that involve shorter-length user interactions, and tasks for which success is easier to judge (the math problem is right, the code runs, the email written is generally pleasing) will tend to be easier to make progress on. Optimizing for a user’s long-term growth and well-being, over many days, months, or years of chats, is something that may be much more difficult.

Delusional spirals are one manifestation of what can go wrong over long-context, open-ended use. Dohnány et al⁸ describe such an interaction as “technological folie à deux”, in which the user and chatbot mutually reinforce delusional thinking. To characterize

these interactions, we collected and analyzed the chat logs of users who self-reported psychological harm, as well as a user who died by suicide while interacting with a chatbot⁹. The user and chatbot mutually reinforced delusions (e.g., that the user had superpowers, that the user had caused the chatbot to become sentient), in many cases with a grand significance or mattering attached to it (e.g., the user had invented faster-than-light travel, or a new and powerful form of physics or mathematics). Users sometimes expressed violent thoughts, and the chatbot responded unevenly (sometimes discouraging, but also sometimes validating or even facilitating violence).

Beyond these performance challenges – which conceivably could be addressed, and rapidly so – there is a deeper structural difference between a human and a chatbot therapist. Human relationships involve stakes, mutual accountability, and social capital. Humans can be anxious going into difficult conversations with each other; they can feel bad, angry, or confused coming out of them. Unless our culture and social structures change drastically, the stakes of chatbot interactions are different, and usually lower. The low-stakes chatbot interventions might be very good in some contexts – for example, giving an opportunity to someone who would not seek care otherwise. But human and chatbot interventions are most certainly different, profoundly so, and it is important to understand long- and short-term effects of this difference.

AI that promotes mental health, rather than degrading it, requires researchers and model builders to confront the substantial challenges of engineering and designing AI systems for the user’s long-term well-being. Current systems can corrode the interpersonal dimension⁷, and it is worth considering that the dominant design paradigm for AI tools – that of the single user talking to a chatbot – may be inherently isolating. Powerful pre-trained models such as LLMs need not stick to this paradigm. As society further explores how AI might be used for mental health, it may be more helpful to embrace a wider design space around not isolation but human connection.

Nick Joseph Haber

Stanford Graduate School of Education, Stanford, CA, USA

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Dan J. Stein passed away in December 2025. He has been, throughout the latest decades, one of the most prominent figures of world psychiatry, to which he has brought an extraordinary width and depth of knowledge, and a unique ability to address convincingly some of the most complex and multifaceted aspects of the discipline. He had a distinctive kindness, elegance and human touch that everybody who met him immediately noticed. He is being missed by literally hundreds of people in a very large number of countries worldwide. This Forum in our journal that he inspired, and for which he wrote an outstanding introductory paper, will reach most of the people who have met him during his career, being the best way through which we can honour his memory.

Big data and psychiatry: advances, constraints and future directions

Dan J. Stein¹, Ronald C. Kessler², John Torous³, Hugh Garavan⁴, Odile A. van den Heuvel⁵, Eske M. Derks⁶, Carol Mathews⁷, Pim Cuijpers⁸, Giovanni A. Salum⁹, Ole A. Andreassen¹⁰, Paul M. Thompson¹¹, Brenda W.J. Penninx⁵, John J. McGrath¹²⁻¹⁴

¹South African Medical Research Council Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa; ²Department of Health Care Policy, Harvard Medical School, Harvard University, Boston, MA, USA; ³Digital Psychiatry, Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; ⁴Department of Psychological Science, University of Vermont, Burlington, VT, USA; ⁵Department of Psychiatry, Amsterdam University Medical Centre, Vrije Universiteit, Amsterdam, The Netherlands; ⁶Translational Neurogenomics Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia; ⁷Department of Psychiatry, University of Florida, Gainesville, FL, USA; ⁸Department of Psychology, Vrije University, Amsterdam, The Netherlands; ⁹Global Programs, Child Mind Institute, New York, NY, USA; ¹⁰Centre of Precision Psychiatry, Division of Mental Health and Addiction, University of Oslo and Oslo University Hospital, Oslo, Norway; ¹¹Imaging Genetics Centre, University of Southern California, Los Angeles, CA, USA; ¹²Queensland Centre for Mental Health Research, Park Centre for Mental Health, Warcol, QLD, Australia; ¹³Queensland Brain Institute, University of Queensland, Brisbane, QLD, Australia; ¹⁴National Centre for Register-based Research, Aarhus University, Aarhus, Denmark

Early work in psychiatry research, often involving single sites, small samples, and limited variables, has shifted to contemporary research involving multiple sites, large samples, and many variables. Such research raises important questions, including concerns about data quality and methodological rigor, uncertainty about its key lessons, issues regarding clinical relevance, and questions about how to optimize future advances. Here we consider these questions and concerns against the context of big data work on community and register-based surveys, cohort and biobank studies, electronic health records, digital phenotyping, brain imaging, genomics and other -omics, and randomized controlled trials. The development of large datasets allowing well-powered analyses is a major milestone, but sample size alone does not guarantee more precise estimates, and ongoing attention to the quality and rigor of big data collection and analysis is needed. Big data research has fostered trans-disciplinarity and given insights into mechanisms underlying psychiatric disorders, but also emphasizes the intricacy, heterogeneity and variability of such mechanisms, and the importance of triangulating between large-scale and small-scale research. The complexity of psychiatric phenotypes and psychobiological mechanisms contributes to the difficulty in bridging from big data to clinical application; big data research reinforces the importance of holding our diagnoses of psychiatric disorders lightly and providing explanations of these conditions humbly; and future work needs to be more attentive to clinical issues. There is enormous scope for further building databases relevant to psychiatry, but advances in conceptual models and asking the right questions are equally valuable. The full impact of big data, including artificial intelligence analyses, remains to be seen, but overenthusiastic support should be tempered by a better understanding of its strengths and limitations. At its best, such work will contribute in an iterative and integrative way to advancing our knowledge of psychiatric disorders and mental health.

Key words: Big data, epidemiology, clinical registers, cohort studies, biobanks, electronic health records, digital phenotyping, brain imaging, genomics, randomized controlled trials

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During the course of the 20th century, particularly in the US, psychiatry underwent a major shift from a psychoanalytic to a neuroscientific perspective. This transformed both clinical practice (with the introduction of psychopharmacological treatments) and research (through the crucial role of institutions, such as the US National Institutes of Health, that championed rigorous empirical science)^{1,2}. More recently, there has been a shift away from early psychiatry research, often involving single sites, small samples, and technologies that produced a limited range of variables (for example, initial work on computed tomography in mental disorders). Instead, contemporary research often involves multiple sites, large samples, and technologies that produce a wider range of variables^{3,4}.

This shift from early to contemporary psychiatric research reflects advances in multiple technologies, research designs, analytic

methods, multisite collaborations, and digital storage and communication. Differences between early and recent research is partly quantitative (the amount of data has increased exponentially), but there are also qualitative differences. Early work in psychiatric genetics, for example, was based on simple statistical methods to compare the distribution of specific candidate genetic variants in relatively small samples often based around one senior investigator. The computational requirements for these early analyses were modest. In contrast, contemporary work in psychiatric genetics, as exemplified by the Psychiatric Genomics Consortium, employs complex statistical methods to compare whole genome sequencing of large numbers of research participants from multiple sites, which requires significant computational resources and analytic expertise^{5,6}.

One way of encapsulating the shift in psychiatry research that

we have seen in recent decades is the phrase “big data”^{4,7-11}. This phrase usually refers to the growing importance in contemporary investigations of *large datasets* from community and register-based surveys, cohort and biobank studies, electronic health records (EHRs), digital phenotyping, brain imaging, genomics and other -omics, and randomized controlled trials (RCTs). However, relatively large samples of participants in epidemiological surveys, twin studies, and intervention research were available long before the notion of big data emerged. Conversely, a digital phenotyping study might today include relatively few participants, but obtain *very large numbers of variables with very frequent data sampling*.

Thus, there are several additional aspects of big data, going beyond a focus on sample size, that deserve emphasis. First, big data include an emphasis on *data diversity* and *data complexity*¹². Big data work entails the expansion of research across multiple sites – for example, epidemiology collaborations have used the same methodology across different countries, and psychopharmacology research has pooled individual participant data from different trials – thereby enhancing data diversity. And big data studies may combine multiple types of measures (multimodal), each with numerous variables (multivariate), producing more features than participants (high-dimensional).

Second, work on big data also reflects the concern of scientists and science funders to address the “reproducibility crisis”, and to encourage the “democratization of science”¹³. Several ways of doing so have been proposed, such as ensuring sufficiently well-powered samples, pre-registration of statistical analysis plans, a move towards Bayesian and model training – model testing validation approaches, encouraging publication of null findings, and making publicly available both the raw data and the analytic methods used. A particularly pertinent example of this is work on the genetics of mental disorders. Many early hypothesis-driven papers examined candidate genes in small samples and concluded that specific gene variants played an important role in mental disorders. More recent unbiased hypothesis-generating analyses of large samples have indicated that this literature was largely characterized by underpowered samples and false positive findings^{14,15}. In contrast, the UK Biobank, a remarkably rich dataset that is open to all investigators, exemplifies many of the advantages of democratizing science¹⁶.

Third, the concept of big data is intertwined with key recent goals of the field, particularly the development of personalized or precision psychiatry¹⁷⁻¹⁹. The rationale is that with sufficiently large, diverse and complex datasets, and appropriately sophisticated analyses (including artificial intelligence, AI), psychiatry will be able to discover new targets for intervention, and to develop measures and algorithms that allow the clinician to choose the optimal intervention for each individual patient. Genome wide association studies (GWAS) in other areas of medicine, for example, have provided candidate targets for the development of novel medications that impact on particular biological pathways of interest. Seminal cohort studies, such as the Framingham Heart Study²⁰, have provided the underlying data for predicting person-level risk of physical conditions such as myocardial infarction. Advances in oncology, where biomarkers are now routinely

employed to predict optimal person-level treatments, have been evoked to indicate what psychiatry ought to aspire to²¹.

Fourth, a major driver for many big data projects in psychiatry is the notion that disease mechanisms underlying mental disorders are complex, involving many small genetic and environmental effects, that in turn impact on a range of intricate and interacting neuronal and mental mechanisms. Big data methods offer the possibility of identifying subtle patterns and cumulative effects that are otherwise undetectable. A possibly useful analogy is with weather forecasting. Historically, predictions were based on sparse observations of variables such as temperature or wind. Today, massive real-time data collection, using multiple methodologies from distributed locations, combined with high-performance computer analyses, enables accurate forecasts for specific locations several days in advance. While psychiatry faces more conceptual and measurement challenges than meteorology, the central idea is similar: scale matters when dissecting intricate, interacting mechanisms in order to predict outcomes.

Given the growing number of publications of big data from a range of psychiatry research fields, it is timely to reflect on the extent to which this work has contributed to advancing psychiatric research and practice, and to assess next steps for big data science in these areas. While a range of psychiatry research fields employ large datasets, and rely on a gamut of advances in research design and methods, a number of cross-field questions and controversies are emerging. Although these have been partly addressed by specific fields, there are few papers that have taken a cross-field approach, covering the most important contemporary psychiatric research fields in a balanced way.

Part of the rationale for this paper is that, although the use of big data has elicited considerable enthusiasm, it has also attracted criticism, and for some has a pejorative resonance. Concerns have been raised that a focus on quantitative work brings with it a loss of the qualitative richness essential for understanding the lived experience of people with mental disorders²². In genomic studies, in the attempt to increase sample sizes, phenotyping can be constrained. In imaging studies, differences between cases and controls may have remarkably low effect sizes. As important as the scale and breadth of the data, is the question addressed, and whether novel mechanistic or actionable insights will be generated. Indeed, despite the significant research funding going to such work, some hold that there has been little translation to the clinic^{23,24}. In contrast, n-of-1 clinical studies have on occasion provided critical psychiatric lessons²⁵. Criticism of big data research resonates with a body of work, dating back several decades, suggesting that medicine has become increasingly technical and has lost its humanity²⁶. There is a strong argument that precision oncology is not the best model for psychiatry, after all.

In this paper, we wish to address several questions and controversies.

First, there are the issues of data quality and methodological rigor, and how to optimize them. One of the potential advantages of the move to big data is addressing the replication crisis by moving to statistically unbiased and sufficiently powered analyses¹³. But concerns have been raised about the frequent reliance on “thin”

data (e.g., when inaccuracies in measures mean that valid conclusions cannot be drawn; for example, GWAS of single item responses are unable to shed light on the genetic architecture of complex phenotypes); on “black box” machine learning approaches (i.e., when model decisions cannot be readily explicated; for example, an algorithm may suggest a specific diagnosis, but not provide the user with any information about how that conclusion was reached); and on the replicability of big data findings (i.e., different analyses of the same dataset may reach divergent conclusions; for example, some neuroimaging findings may be more reflective of the specific parameters chosen in the analyses than of the underlying structures and mechanisms being examined). What advances allow us to address these concerns, and to appropriately harmonize data, avoid statistical overfitting, and separate causality from correlation across different research fields?

Second, there is uncertainty about the extent to which big data approaches have clarified mechanisms underlying mental health conditions. For example, early neuroimaging research led to a specific cortico-striatal model of obsessive-compulsive disorder. Subsequent neuroimaging research has suggested significant overlap in “brain signatures” across disorders – perhaps a “truer” conclusion, but also one that makes a mechanistic understanding more opaque. How has recent neuroimaging research advanced our understanding of the pathogenesis of psychopathology? Early clinical trials in psychopharmacology were key in developing medications for specific indications. However, such trials typically had relatively few outcome measures, and so may have missed key effects of psychotropic medications. How much have we learned from intervention trials that employ digital phenotyping, or explore a large number of outcomes?

Third, there are the issues of clinical relevance and training implications. Research in a specialized social anxiety disorder clinic can provide a great deal of knowledge about age of onset, comorbid disorders, and course of disorder. There is a good argument that big data from the World Health Organization (WHO) World Mental Health Surveys (WMHS) provide a much more comprehensive picture of the disorder. But, in several other areas, clinical utility is much less clear. For example, polygenic risk scores for mental disorders currently account for quite small amounts of variance, and it is generally accepted that these scores are not yet sufficiently predictive to warrant translation to clinical settings, with the possible exception of a small number of conditions such as Alzheimer’s dementia^{27,28}. More generally, how best can we apply the broad lessons of big data research to the particularities of the individual patient? These considerations in turn raise questions on how best to train clinicians.

Fourth, is there an optimal balance that future research should take towards more hypothesis-driven approaches on precisely developed smaller datasets versus more statistically unbiased data-driven approaches with generally available larger datasets? What has been the return on investment in small-scale neuroscience (e.g., work on a particular molecular mechanism) versus big data approaches (e.g., the work of the Psychiatric Genomic Consortium)? There is an argument that hypothesis-driven and hypothesis-generating approaches can in fact be complementary.

Thus, for example, an unbiased GWAS may yield a “hit” which can then be examined in a focused hypothesis-driven laboratory experiment. Even so, has such complementary work occurred in a way that has substantively advanced mechanistic understanding? What is the best way forward for the field?

These questions and controversies arise in big data research on community and register-based surveys, cohort and biobank studies, EHRs, digital phenotyping, brain imaging, genomics, and clinical trials. We will focus on each of these research areas in turn. To some extent, they involve distinctive sets of researchers, methodologies and funders, and this division provides one way to approach the already vast and further burgeoning big data literature. However, these research areas often overlap: for example, cohort studies may incorporate digital phenotyping, brain imaging and genomic investigations. Indeed, by its nature, big data research has given impetus to a move away from narrowly focused uni-disciplinary investigations and toward comprehensive multi-disciplinary work.

We will focus here largely on datasets that are publicly accessible or readily available to members of large research consortia. We will emphasize psychiatry databases in particular, with occasional reference to general health databases. Each section of the paper will provide some historical background, and will consider advances made, constraints and limitations, and future research directions. More specifically, each section will address issues of data quality and methodological rigor, how precisely light has been shed in a novel way on underlying mechanisms, clinical relevance and training implications, and how to best advance future research (see Tables 1-3).

COMMUNITY AND REGISTER-BASED SURVEYS

Data quality and methodological rigor

With the advent of operationalized diagnostic criteria in the DSM-III, psychiatric epidemiology immediately began to incorporate these criteria into its assessments. Early work, such as the Epidemiological Catchment Area (ECA) study in the US, emphasized the high prevalence and significant impairment associated with mental disorders²⁹. The WMHS initiative has then enabled psychiatric epidemiologists to access large, harmonized datasets from low-, middle- and high-income countries³⁰, based on the use of validated fully structured diagnostic tools, such as the Composite International Diagnostic Interview (CIDI). This instrument can be administered without the need for highly trained clinical raters, generates diagnoses according to different diagnostic criteria and guidelines (DSM, ICD), and also includes variables related to risk factors, service utilization and outcomes.

Data from the WMHS initiative have allowed detailed cross-national investigation and comparison of many aspects of mental disorders, including prevalence, mental and physical comorbidity, risk factors such as early adversity, sequelae such as impairment and suicide, and extent of and barriers to treatment^{30,31}. Longitudinal population-based studies using similar methods can also in-

Table 1 Some key databases, and their promises and pitfalls

	Databases	Promises	Pitfalls
Community and register-based surveys	Global Mind Project, NEMESIS-2, WMHS	Provide data on prevalence, course and consequences of mental disorder. Provide data on rates, quality of, and barriers to treatment.	Framing of psychopathology is typically based on current nosology. Range of biases, including recall bias, may impact on estimates.
Cohort and biobank studies	ABCD, All of Us, DNBC, HBCD, Million Veteran Program, MoBa, NESDA, UKB	Knowledge of underlying biopsychosocial mechanisms. Knowledge of evolution of such mechanisms over life and disease course.	Constraints on accuracy/depth of assessment methods. Constraints on generalizability of findings to other populations.
E-health records	CPRD, CRIS, Epic, THIN	Clinical decision support to improve treatment outcomes. Trial emulation to improve the evidence base for interventions.	Constraints on randomization of assessment and intervention. Constraints on generalizability of findings to other populations.
Digital phenotyping	mindLAMP	Richer phenotyping than typically available to clinicians. Advanced methods to detect clinically significant signatures.	Digital phenotyping may be superficial and clinically irrelevant. Clinicians may not be able to readily evaluate and employ these data.
Brain imaging	ENIGMA, IMAGEN, UNITY	Knowledge of neurocircuitry underlying mental disorders. Investigation of overlaps of anatomical and molecular data.	Gap between brain imaging data and biological mechanisms. Gap between brain imaging data and clinical phenotypes.
Genomics	PGC, PsycheMERGE	Knowledge of molecular basis underlying mental disorders. Clinical useful measures such as polygenic risk scores.	Gap between GWAS data and biological mechanisms. Polygenic risk scores usually account for small proportion of variance.
Clinical trials	Metapsy	Rigorous synthesis of the evidence-base on clinical interventions. Methods providing novel insights, e.g. individual patient data meta-analyses.	Conclusions are only as good as the initial work. Important constraints of meta-analysis methods.

ABCD – Adolescent Brain Cognitive Development, UKB – UK Biobank, CPRD – Clinical Practice Research Datalink, CRIS – Clinical Research Interactive Search, DNBC – Danish National Birth Cohort, eMERGE – electronic Medical Record and Genomics, ENIGMA – Enhancing Neuroimaging Genetics through Meta-Analysis, HBCD – HEALTHy Brain and Child Development Study, LAMP – Learn, Assess, Manage, and Prevent, MoBa – Mother and Child Cohort Study, NEMESIS – Netherlands Mental Health Survey and Incidence Study, NESDA – Netherlands Study of Depression and Anxiety, PGC – Psychiatric Genomics Consortium, THIN – The Health Improvement Network, UNITY – Ultra low-field Neuroimaging In The Young, WMHS – World Mental Health Surveys

form us about changes in mental health prevalence trends³².

Community surveys have been essential for the mental health component of the Global Burden of Disease (GBD) studies. These studies cover the entire range of health disorders, accidents and injuries, and include data on causes of death^{33,34}. A key innovation of the GBD studies was the development of a novel metric to combine the impact of disorders that are associated with premature mortality (which contribute to years of life lost, YLLs) with disorders that result in non-fatal adverse health outcomes (which contribute to years lived with disability, YLDs). By estimating disability adjusted life years (DALYs), the GBD studies underscored the substantial burden of mental disorders compared to other categories of disease and injuries, so raising the profile of mental disorders within the global burden of disease³⁵. The GBD group also pioneered the use of meta-analytic statistical methods to synthesize data across many studies of variable quality, and to impute missing data for some countries. Importantly, the estimates generated by GBD are available for public downloading, and have been incorporated in a range of studies.

Register-based studies have also provided valuable sources of big data in mental health epidemiology. Many health registers

are population-based (i.e., they include all individuals who seek help or attend health services within a defined area). They can be used to generate more precise and representative estimates, compared to those based on individuals who present to highly specialized centers or who meet specific inclusion criteria for entrance into clinical trials. They also allow long-term longitudinal analyses, which go beyond what is possible for example in short-term clinical trials. More countries are developing high-quality, nationwide registers that can track individuals in contact with the health sector. In addition, some countries can cross-link health register data with a range of other data sets (e.g., education, work, income, crime, family pedigrees, geospatial mapping of place of residence, and environmental exposures)³⁶. Scandinavian countries often collaborate on multi-national register studies of mental disorders³⁷.

As with all big data sources, there are important limitations to consider in relation to community surveys, GBD estimates, and register-based data. Although in WMHS specific methods were employed to minimize recall biases^{38,39}, survey data are reliant on respondent memory, which provides only a partial window on complex behavior. GBD statistical models make a range of assump-

Table 2 Data quality/rigor, understanding mechanisms, clinical relevance

	Data quality/rigor	Understanding mechanisms	Clinical relevance
Community and register-based surveys	WMHS exemplifies rigor in key ways: e.g., methods to ensure accurate data collection, limiting recall bias.	Knowledge of risk factors (e.g., exposure to early adversity, comorbid conditions, social determinants).	Can help improve diagnostic criteria. Cumulative incidence curves – by disorder, sex, age – are key for risk prediction and policy strategies.
Cohort and biobank studies	NESDA exemplifies rigor in key ways: e.g., accuracy of assessment of mental health traits.	Knowledge of longitudinal biopsychosocial mechanisms has gradually emerged: e.g., immunometabolic depression.	Clinical phenotypes are dynamic rather than static. Relevant mechanisms are heterogeneous.
E-health records (EHRs)	Some EHR databases have particularly comprehensive data fields.	Precision treatment trial emulations help uncover disorder subtypes. Pathway analyses clarify underlying mechanisms.	Decision support tools can help improve clinical decision-making.
Digital phenotyping	LAMP exemplifies rigor in key ways: e.g., accuracy of digital phenotyping.	Digital signatures of mental disorder exacerbation and relapse are gradually emerging.	Digital clinics are useful in several respects for clinical practice.
Brain imaging	ENIGMA shows rigor in key ways: e.g., harmonization of data across sites.	Imaging insights have provided targets for stimulation treatments.	MRI-based neuro-navigated TMS can increase efficacy.
Genomics	PGC shows rigor in key ways: e.g., harmonization of analytic methods.	Top “hits” have provided new insights into disorder pathogenesis.	WGS is useful to identify cases with underlying rare variants.
Clinical trials	Metapsy shows rigor in key ways: e.g., carefully evaluation of trial quality.	“Common factors” (e.g., therapeutic relationship) remain to be fully understood.	Interventions work, but how is less clear. Comparison of efficacy across diverse treatments guides clinical guidelines.

WMHS – World Mental Health Surveys, NESDA – Netherlands Study of Depression and Anxiety, LAMP – Learn, Assess, Manage, and Prevent, ENIGMA – Enhancing Neuroimaging Genetics through Meta-Analysis, PGC – Psychiatric Genomics Consortium, MRI – magnetic resonance imaging, TMS – transcranial magnetic stimulation, WGS – whole-genome sequencing

Table 3 Statistical guidance, future research directions, clinical training implications

	Statistical guidance	Future research directions	Training implications
Community and register-based surveys	Use of survival analyses in parsing out developmental trajectories and comorbidity.	Move towards digital surveys. Turn cross-sectional surveys into efficient panel studies.	Training in structured clinical interviews.
Cohort and biobank studies	Use of multimodal analyses to understand biopsychosocial mechanisms underlying mental disorders.	Move towards incorporation of digital tools and -omics assessments.	Training in rigorous assessment after diagnosis is made.
E-health records	Increase fairness in decision support systems. Extract structured fields from clinical notes. Integrate trial emulations with pragmatic trials.	Integrate with clinical practice. Expand richness and variety of measures. Develop pragmatic trial pipelines for continuous quality improvement.	Increase familiarity with the logic of developing and using AI-based clinical decision support tools.
Digital phenotyping	Transparency of platforms used to gather and analyze digital data is useful.	Move towards establishing digital clinics to provide mental health services.	Integrate digital tools in clinical environment. Familiarity with working in a digital clinic.
Brain imaging	Harmonization methods are useful to address site differences.	Move to multi-modal analyses. Increase sophistication of machine learning approaches.	Exposure to clinically relevant brain imaging research.
Genomics	Cross-ancestry modifications are needed; e.g., for accurate polygenic risk score (PRS) calculation.	Focus on common and rare variants. Increase diversity.	Understanding clinical relevance of key constructs; e.g., PRS, WGS.
Clinical trials	Individual participant analyses have important advantages.	Move towards living meta-analyses.	Better appreciation of clinical trial science.

AI – artificial intelligence, WGS – whole-genome sequencing

tions that may be questioned, and concerns have been raised about the accuracy of these estimates^{40,41}. Crucial to the calculation is the allocation of disability weights for each disorder⁴²⁻⁴⁴, and there is debate about the optimal method to allocate these weights to mental disorders⁴⁵. Further, there remain concerns about how the GBD process often relies on sparse data and handles a range of methodological concerns (e.g., adjustments for comorbidity)⁴⁶. In several cases, country-level estimates are based on model-based projections in the absence of any data, raising questions about their accuracy^{47,48}.

For register data, there is a concentration on service-related variables. The accuracy of diagnoses and evaluations may be questioned; people who do not seek care are not captured by health registers; and some national registers have limited access to general practitioner and pharmacoepidemiology data. Access to sera, DNA and brain imaging variables is not routinely available in community survey or register studies, and, given confidentiality issues, these studies are also unable to facilitate public availability of data in the same way as this is possible with large volunteer studies such as the UK Biobank.

Mechanisms underlying mental disorders

To what extent have community surveys, GBD estimates, and register-based data shed light on mechanisms underlying mental disorders? We will list a few examples.

First, community survey data have been employed to revise diagnostic criteria. Although this work does not explicate new mechanisms, it may play a key role in better conceptualizing mental disorder, which in turn facilitates investigation of underlying pathogenic mechanisms. Thus, for example, in the WMHS there was little difference between generalized anxiety disorder (GAD) of 6 months duration and GAD of shorter durations (1-2 months, 3-5 months) in symptom severity, age of onset, persistence, impairment, or comorbidity. The authors of this analysis concluded that, in both developed and developing countries, the clinical profile of GAD is similar regardless of duration, and that future iterations of the DSM and ICD should consider shortening the duration requirement of GAD⁴⁹.

Second, work on socio-demographic associations, age of onset, and comorbidities of mental disorders has pointed to the involvement of particular biological and social determinants. Community surveys, GBD estimates, and register-based studies have consistently found that female sex is associated with internalizing disorders, while male sex is associated with externalizing disorders⁵⁰. Although multiple factors may contribute to this finding, it remains an important foundation for improving both clinical and health policy interventions. The finding that anxiety disorders have early onset, with subsequent development of mood and substance use disorders, lays the foundation for a range of work on the psychobiological mechanisms that might underpin this sequence and appropriate interventions^{51,52}.

Third, work on stressors, such as early adversity, has emphasized the importance of environmental risk factors for mental as well as

physical disorders, and again laid the foundation for research on relevant psychobiological mechanisms, and appropriate clinical and health policy interventions. Data from the WMHS, for example, indicate that childhood adversities are highly prevalent and interrelated, are associated with maladaptive family functioning (e.g., parental mental illness), and are the strongest predictors of disorders. The combined impact of such adversities is less than the sum of their individual effects, and they have little specificity across mental disorders⁵³.

Many of these key lessons about underlying mechanisms have also emerged from studies other than community surveys and register-based investigations. Relatively small clinical studies have been able to show links between sex and internalizing vs. externalizing disorders, and associations between early adversity and onset or persistence of mental disorders. However, community and register-based studies are helpful in providing more generalizable effect sizes, and in exploring particular aspects of these associations, such as population attributable risk proportions associated with childhood adversities at a population level. As we will later discuss, the strategic triangulation of smaller, more focused clinical investigations with larger, more generalizable big data studies offers an approach that may enhance both the depth and breadth of scientific inference.

Clinical relevance and training implications

Community surveys, GBD estimates, and register-based data have provided many clinical lessons.

First, community survey data reinforce the view that we should not reify our diagnoses, but that instead we should “hold our diagnoses lightly”⁵⁴. Thus, for example, different sets of diagnostic criteria in different classification systems may lead to a diagnosis being found in somewhat different sets of individuals; however, all of these individuals may have significant distress and impairment, suggesting the need for treatment regardless of different diagnostic criteria. This is important when considering the disability impacting on individuals with subsyndromal symptoms: for example, the WMHS found that people who reported psychotic-like experiences had higher scores on measures of disability, regardless of the presence of comorbid mental or general medical disorders⁵⁵. Establishing a DSM or ICD diagnosis is only an initial step in clinical assessment and treatment planning. Clinical training needs to emphasize the value of more detailed characterization of disorder subtypes and specifiers, and many other aspects of the individual patient⁵⁶.

Second, community survey data have emphasized the importance of assessing risk factors for mental disorders, evaluating comorbid mental and physical disorders, and exploring associated impairment. Thus, in the WMHS, childhood adversities were non-specifically associated with a broad range of mental and physical disorders, with population-attributable risk proportions suggesting that their eradication would lead to a 29.8% reduction in the prevalence of all disorders across countries⁵³. There is a growing understanding of how such adversities become biologically embedded,

and careful evaluation of exposure to past and current stressors should be a key part of clinical assessment and intervention for individuals with mental as well as physical disorders^{57,58}. Comorbidity findings may have important clinical implications; for example, given that anxiety disorders often precede onset of mood and substance use disorders, their early diagnosis and treatment is particularly important⁵⁹.

Third, community survey data on the helpfulness of treatment of mental disorders have emphasized the importance of persisting with treatment-seeking⁶⁰. In the WMHS, across all surveys and diagnostic categories, 26.1% of individuals were helped by the first professional they saw, and persisting to a second professional after initial unhelpful treatment brought the cumulative probability of being helped to 51.2%. If patients persisted through eight professionals, this cumulative probability rose to 90.6%. However, only 22.8% of patients would have persisted with treatment after repeatedly receiving unhelpful interventions. These proportions were similar in high-income countries compared to low- and middle-income ones. Even with good clinical practice, effective treatments may not be identified for all patients after a single consultation. Receiving helpful care often requires persistence in help-seeking, making it essential for clinicians to emphasize this point to patients at the outset of treatment – a lesson with important implications for clinician training.

Fourth, community surveys have also examined the proportion of individuals with mental disorders who receive treatment that is consistent with clinical guidelines⁶¹. These studies assess the importance of patient-level factors (e.g., perceived need), and service-related factors (e.g., treatment resources). In the WMHS, the proportion of 12-month person-disorders receiving effective treatment was 6.9%. Low perceived need (46.5%), low treatment contact given perceived need (34.1%), and low effective treatment given minimally adequate treatment (47.0%) were the main barriers⁶¹. These findings emphasize the need to increase perceived need, to train primary care treatment clinicians in recognition and treatment of mental disorders, and to improve the continuum of care, especially from minimally adequate to effective treatment.

Advancing future research

There are several opportunities for advancing community studies, GBD investigations, and register-based research.

First, we need hybrid studies that can leverage data from both community surveys and register-based studies. Statistical methods can be used to impute missing data when linking small surveys with larger registers, to create “synthetic” datasets⁶². For example, both small surveys and population-based registers may be available from the same population, but often they have little or no overlap in their samples. Recent developments in data science allow the creation of “synthetic data” that mimic real data and preserve the relationships between variables⁶².

An important constraint of large-scale surveys is that they require substantial time and financial resources, posing a barrier to timely and cost-effective data collection, especially in low-resource

settings. Thus, methods have been developed that can blend results from probability samples (e.g., community-representative samples) with non-probability samples (e.g., smaller and selected consumer panels)^{63,64}. For example, it may be feasible to apply these methods to a population-based probability sample of 2,500 individuals and then administer the same questions to a parallel online non-probability sample of 7,500 people. The latter can be done in most high-income and upper-middle-income countries with existing consumer panels for a fraction of the price of a large probability sample. Advanced statistical methods can then be used to blend the two samples to minimize total survey error^{63,64}.

Finally, the ready access to smartphones and the Internet can facilitate more efficient and user-friendly methods to conduct surveys (in contrast to more expensive face-to-face surveys). Smartphones can be used to follow up with short “flash surveys” (e.g., “how are you feeling currently”, with a range of emoji response options) and be used to enrich register-based data (e.g., short flash surveys can explore the social determinants of health and transient subjective experiences). The passive recording of behavioral data from the operating system and built-in sensors allows collection of information that is not subject to the recall error and social desirability biases of surveys, while survey data can provide contextual information about these behaviors^{65,66}. Such methodologies may facilitate a welcome shift from cross-sectional to longitudinal surveys. We will expand on digital phenotyping in a later section.

COHORT STUDIES AND BIOBANKS

Data quality and methodological rigor

Cohort studies differ from other study designs by attempting to obtain detailed information from a large target sample with longitudinal (repeated) data collection. Cohort studies such as the Framingham Heart Study²⁰ and longitudinal twin studies have contributed immensely to medical and psychiatric knowledge. Birth cohorts (e.g., the Avon Longitudinal Study of Parents and Children⁶⁷, the Danish National Birth Cohort⁶⁸, the Drakenstein Child Health Study⁶⁹, the Dunedin Multidisciplinary Health and Development Study⁷⁰, the Generation R Study⁷¹, the Healthy Brain and Child Development Study⁷², and the Norwegian Mother and Child Cohort Study⁷³); child and youth cohorts (e.g., the Adolescent Brain Cognitive Development, ABCD⁷⁴; the Brazilian High-Risk Cohort⁷⁵, and the Philadelphia Neurodevelopmental Cohort⁷⁶); and middle-age and elderly cohorts (e.g., the Netherlands Mental Health Survey and Incidence Study-2, NEMESIS-2⁷⁷; and the Netherlands Study of Depression and Anxiety, NESDA⁷⁸) have allowed investigation of mental health throughout the life course.

In recent years, greater access to such databases by researchers has been encouraged, and databases of cohorts have been established (e.g., <https://atlaslongitudinaldatasets.ac.uk>). Many cohort studies have incorporated biobanking, allowing for integration of whole genome genetic, epigenetic, gene-expression and big-scale proteomic and metabolomic assessments with detailed clinical phenotyping. This provides opportunities for multi-omics

analyses in association with detailed environmental as well as clinical data. In addition, several cohort studies with a strong focus on mental health have incorporated repeated neuroimaging data, and some have gathered digital phenotyping such as ecological momentary assessments or wearables that track emotions and behaviors during daily life.

One opportunity provided by cohort studies is the possibility of longitudinal analyses. This allows for better examination of developmental trajectories of mental disorders, better causality testing (distinguishing the order of determinant and outcome), replication of findings across waves, and analyses that test whether certain variables (e.g., biomarkers, functioning, psychosocial context) are returning to “normal” levels when persons affected by mental disorders recover.

There are, however, important limitations to consider in relation to cohort and biobank studies. First, such studies can be selective, as they require a well-resourced research infrastructure. This leads to cohorts that are relatively “WEIRD” (Western, educated, industrialized, rich and democratic). Selectivity is also an issue over time, as non-response and drop-out (i.e., sample attrition) during follow-up may be larger, for example, in individuals with the poorest mental health status⁷⁹. Consequently, generalizability can be a concern which needs specific attention when interpreting results.

Further, most existing cohorts have been set up as general population-based ones, not specifically enriched for persons with mental disorders. When large enough, such cohort studies provide adequate information about common mental disorders (e.g., mood and substance use disorders), but have less power to provide meaningful estimates related to low-prevalence mental disorders (e.g., psychotic disorders). Finally, there is a risk that cohort data are used for data-dredging, repeatedly analyzing data in different ways until statistical significance is found. Therefore, it is arguably helpful to work with pre-registered data-analysis plans and to restrict data access so that it is used only in such analyses. This is helpful for data-driven as well as model-driven analytical research plans. Pre-designed, harmonized data analyses across different cohorts are becoming more and more feasible, due to coordinated multi-site data analysis techniques.

Mechanisms underlying mental disorders

First, birth cohorts have provided novel insights into the impact of prenatal and postnatal stress exposure on early child cognitive and mental development^{80,81}. Epigenetic alterations and changes in gene expression could potentially underlie the child consequences of prenatal stress exposure, but this has not yet been confirmed systematically across birth cohorts⁸². Genetic vulnerability to different mental disorders has, however, consistently been linked to the developmental trajectories of depressive symptoms in adolescence⁸³.

Second, large scale cohorts with biobanks are being used to examine underlying (epi)genetic, metabolic or proteomic biomarkers that are linked to mental disorders. Such studies have yielded novel insights into the pathophysiology of many mental disorders,

and illustrate that they are not just “brain disorders”, but involve the whole body. Consistent findings show, for example, that biomarkers implicating insulin resistance, mitochondrial dysfunction, immune system dysfunction, biological aging, metabolic syndrome, and in some cases cardiovascular disease are increased in individuals with various mental disorders^{84,85}. Further, such cohorts have shed light on the impact of risk and resilience factors (e.g., exposure to traumatic events, supportive social environment) on the development of diverse mental disorders throughout the life course⁸⁶.

Third, cohort research has allowed the limitations of current psychiatric nosology to be transcended. Mental disorders are heterogeneous conditions, in which clinical dimensions (e.g., anhedonia, anxiety arousal) overlap across disorders. Many cohort studies entail detailed phenotyping which allows researchers to move beyond diagnostic states and examine relevant underlying symptom dimensions. In the NESDA cohort, for example, it was found that about 25–30% of depressed persons have signs of immune-metabolic dysfunction (i.e., inflammation, dyslipidemia), which are most prominent in persons scoring high on atypical energy-related symptoms and anhedonia⁸⁷.

Large-scale cohort work may represent a preliminary step towards comprehensive mechanistic understanding. Well-phenotyped and well-powered samples provide a starting point for smaller-scaled studies that can then provide more fine-grained mechanistic findings. Epigenetic and other genomic results from cohort studies may point to a particular gene variant that is not well understood, and a range of subsequent wet lab investigations may then be required. Similarly, to advance the construct of immune-related depression, more detailed studies of immune-metabolic dysfunction are needed, including an evaluation of whether and how such dysfunction responds to interventions that directly target the relevant underlying mechanisms.

Clinical relevance and training implications

First, cohort studies with large number of patients are key for providing information on long-term course of mental disorders and their functional, societal and somatic consequences. This work has emphasized that clinical pictures are dynamic rather than static⁸⁸, suggesting that disease monitoring and management programs with a longer-term perspective need to be considered in clinical practice.

Second, the delineation of more homogeneous symptom dimensions by cohort research has clear clinical relevance. Observations that certain symptom profiles such as anhedonia or atypical energy-related symptoms of depression have specific underlying immune-metabolic pathophysiology are currently being followed up with intervention studies (e.g., anti-inflammatory or lifestyle interventions) that specifically target certain subsamples of a diagnostic patient group⁸⁹. In the interim, clinicians should be aware of the potential value of monitoring inflammatory and metabolic indices in individuals with mental disorder.

Third, cohort studies of the genome and exposome have shown

that the mechanisms underlying the development of mental disorders are heterogeneous^{90,91}. Complex and dynamic conditions such as mental disorders are rarely due to a single cause, and students should be trained to learn and apply pluralistic explanatory models in the clinic. This may involve learning to use frameworks such as Bronfenbrenner's ecological model⁹², Engel's biopsychosocial model⁹³, and McHugh and Slavney's perspectival model⁹⁴. It is important to train future clinicians and researchers on how to incorporate biological and environmental variables into their assessments, with the aim of employing more precisely targeted treatments in clinical work^{19,56}. At the same time, there should be awareness that few biological markers have demonstrated consistent, replicable utility in routine clinical psychiatric practice⁹⁵.

The clinical utility of cohort studies may be increased when sample sizes are large, phenotyping is deep, and data are more openly available to the research community. Nevertheless, even with very large sample sizes, cohort studies may not allow analyses of low-prevalence mental disorders. Although deep phenotyping in cohorts may teach us valuable lessons, in clinical settings there are practical constraints on the use and interpretation of assessment measures. In addition, although observational results of cohort studies can be informative, uncertainty around causal inference remains. Clinical utility of findings generally requires further evaluation through experimental intervention studies that directly test whether targeting specific mechanisms results in improved mental health.

Advancing future research

Uniformity in data collection across different cohort studies, even when cohorts involve different patient populations, will stimulate cross-disorder research. Genetic and neuroimaging consortia have fostered harmonization of concepts across research studies. However, this often happens retrospectively and is mostly restricted to crude concepts (such as disease presence or absence). We need more (prospectively) harmonized cohorts with standardized assessments of key mental disorder dimensions – a collaboration of cohorts (so-called “cohort club”). Such studies will stimulate future neurobiological as well as psychosocial research on relevant (cross-disorder) mental symptom dimensions that go beyond current diagnostic boundaries⁹⁶.

Cohorts with biobanking can allow for multi-omics analyses. Biobanks of cohort studies have not yet been fully investigated, so relatively cost-efficient opportunities for (longitudinal) big-data omics studies remain to be fully utilized. In addition, ongoing cohort studies could be ideal to further leverage ambulatory assessment tools such as ecological momentary assessments and wearables in order to gain insight into daily life changes in emotions and behaviors, which could pave the way for further development of “just-in-time” adaptive interventions⁹⁷.

As noted earlier, most existing cohorts have been set up as general population-based cohorts, not specifically enriched for persons with mental disorders. Cohort studies that are designed to selectively include high-risk populations (such as cohorts among

offspring of psychiatric patients) or patient populations are much less common⁷⁵. However, such enriched cohorts are needed to examine etiology, course and consequences of the less common mental disorders, and generally collect more detailed phenotypic information on mental disorders.

Cohort and biobank studies are expensive to set up and conduct, due to the detailed assessments and efforts that are required for maintaining adequate longitudinal fieldwork and data management activities over years or even decades. Preventing selective drop-out requires a range of strategies to maintain follow-up information from participants. Such strategies may include offering home or online assessments or linking cohorts to health data registers to supplement information on health outcomes. This is costly, which explains why most cohort and biobank studies to date have been conducted in high-income countries. However, this means that knowledge obtained from such studies may not be generalizable to other cultures and countries. Future investments in cohort infrastructures in low- and middle-income countries with diverse ancestries are needed⁹⁸.

ELECTRONIC HEALTH RECORDS

Data quality and methodological rigor

EHR data, which are now the basis of national health systems and registers, as well as smaller scale organizations, have several important advantages over other data sources. They are readily available for very large samples of patients over very long periods of time – e.g., Clinical Practice Research Datalink⁹⁹, Clinical Record Interactive Search¹⁰⁰, Epic¹⁰¹, The Health Improvement Network (THIN)¹⁰². In addition, they often include objective data on tests and procedures, as well as open-ended clinical notes that can be analyzed using natural language processing methods, to make inferences about information not included in structured data fields. In some countries, EHR data can also be linked to small area geocode databases to improve understanding of time-space variation as well as increase information about social determinants of health¹⁰³. Finally, in cases where researchers coordinate with the clinical teams that collect and make use of EHR data, it is sometimes possible to augment these data with patient self-reports, passive digital monitoring systems, and other sources of data that can greatly enrich the information available in EHR databases.

Measurement-based care, i.e. the systematic tracking of patient self-report scale scores to monitor improvements and detect treatment failures, is increasingly being used in conjunction with EHR data in behavioral health care settings¹⁰⁴. “Just-in-time” interventions that make use of such tracking information have been shown to reduce patient deterioration and drop-out, and to improve outcomes¹⁰⁵. So valuable is this kind of information that some large health care systems now mandate the inclusion of patient self-reports in EHR databases, such as in annual physical examinations to screen for depression¹⁰⁶. Integrating EHR data with patient self-reports obtained during encounters where suicide risk is suspected has, for example, been shown to enhance the predic-

tion of subsequent suicide-related behaviors¹⁰⁷.

EHR data are limited in the same ways as other observational (i.e., non-experimental) data in that the ability to make causal inferences is constrained by the fact that clinical interventions and other predictors of patient outcomes are not randomly distributed. In addition, EHR data have more limited external validity than community survey data, due to selection biases into treatment. For example, record check studies show that many people found to meet criteria for mental disorders in community surveys do not carry diagnoses of these disorders in their medical records¹⁰⁸. Finally, the information in EHR data is more limited than in community surveys, because EHR data are collected for purposes other than research, and do not include many variables that researchers would like to have available for analysis.

Another limitation of EHR data is that, even though the ICD classification is used to code diagnoses throughout the world, there is great variation in the ways this classification is used across health care systems, making it more difficult to pool data and transfer models developed in one system to use in other systems. This is true in part because many systems continue to use the older ICD-10, and in some cases even the ICD-9. Even more important, the systems used to code medications and procedures are much less standardized than the ICD system for classifying diagnoses. Furthermore, coding practices in all these systems are quite variable¹⁰⁹.

Many frameworks, known as common data models (CDMs), have been created to address the problem of incompatibility of EHR data across health care systems and to facilitate efforts to carry out comparative cross-system analyses¹¹⁰⁻¹¹³. However, the existence of multiple CDMs merely elevates the problem to a new level of abstraction, requiring the development of harmonization strategies to allow comparison of data across different CDMs¹¹⁴. It is also possible to work exclusively with data elements that are coded comparably across CDMs to develop models for use across health systems¹¹⁵, but this approach necessarily requires the exclusion of some potentially relevant data that could be included if data systems were fully harmonized.

Another noteworthy complication in developing EHR models designed to be used across multiple health systems is that privacy protection standards often make it impossible for patient-level data to be shared directly. One way of addressing this problem is with something known as federated learning – this is, an indirect data integration approach in which each health system retains its own data locally, develops a local version of a model of interest on its own data, shares summary results (e.g., model coefficients, standard errors, tables, weights) centrally, and then uses meta-analysis methods to combine results, often using iteration between local and consolidated results to improve overall model accuracy and external validity¹¹⁶.

A final important issue in using EHRs across systems is that, even with best efforts at data harmonization and integration, variation in local documentation styles can thwart efforts to combine data without substantial local tuning. A good case in point is that the diagnosis of adjustment disorder is much more commonly made in the US military health care system than the civilian system, for reasons that appear to be influenced importantly by ad-

ministrative rather than clinical considerations¹¹⁷. Regulatory and financial issues often play a part in accounting for systematic differences of this sort. One way to address this problem is by developing phenotyping algorithms which harmonize data across settings through multi-level validation¹¹⁸. Although this can be very labor-intensive work, recent advances have been made to develop methods for efficient discovery of EHR data subsets that have invariant associations across systems¹¹⁹ to allow principled cross-system analyses¹¹⁵.

Mechanisms underlying mental disorders

EHR data have been used to study the natural history of treated mental disorders, including patterns and predictors of age of onset¹²⁰, course¹²¹, comorbidities with temporally primary physical disorders¹²², and comorbidities between earlier (e.g., major depression) and later (e.g., bipolar disorder, schizophrenia) mental disorders¹²³. Other EHR studies have shown that it is possible to predict onset of mental disorders using information about earlier diagnoses, medications, and features extracted from clinical notes using natural language processing methods¹²⁴. Work to determine which prodromal predictors are most important and how soon these predictors typically emerge before disorder onset may shed light on underlying mechanisms and provide useful targets for early interventions.

EHRs can also be useful in studying the social determinants of mental disorders. For example, by conceptualizing time-space variations in prevalence as proxies for estimates of true prevalence, EHR data can be used to study the impact of government policy decisions, such as the effects of state cannabis legalization on the occurrence of treated cannabis use disorder¹²⁵, and of state no-fault divorce laws on trends in family violence and female suicide¹²⁶.

EHR data can be used by health service researchers to examine the ways in which provider and system characteristics are associated with clinical practices, and so influence outcomes. Numerous studies, for example, examined cross-system variation in uptake of telemedicine for the treatment of mental disorders during the COVID-19 pandemic¹²⁷. Such studies may in turn allow improved delivery of services. For example, a recent study using EHR data examined variation in stepped care implementation among patients receiving psychotherapy in the UK National Health Service, in order to pinpoint structural changes that would improve system functioning¹²⁸.

Clinical relevance and training implications

EHR analyses, often combined with information from tests, patient self-reports, clinical notes, and small area geospatial data, are also increasingly being used to develop AI-based risk scores, such as to predict the likelihood of patients with schizophrenia to comply with medication¹²⁹ or of patients with treatment-resistant depression to respond to esketamine¹³⁰. In some cases, these studies merely use retrospective analyses of EHR data to make inferences

about intervention effects¹³¹. In other cases, a formal trial emulation approach is used to approximate the estimates obtained with comparative effectiveness trials (e.g., instead of randomizing individuals to two interventions to see which is better, observational data from those given these two treatments are compared, with statistical methods used to reduce bias)¹³².

The fact that abstraction of data from clinical notes has been critical to the success of EHR studies designed to predict disorder onset speaks to the importance of moving beyond post-hoc analyses of information, expanding clinical assessments by the use of structured features in addition to standard EHR codes. A model for this type of expansion can be found in the work of Australian researchers who have built up a transdiagnostic clinical staging framework for young people seeking treatment for emotional problems¹³³. This framework was developed using large registers of young people who sought treatment for such problems. These individuals were then followed over time through health systems using structured data that included, but went beyond, standard EHRs, so allowing detailed characterization of early non-specific symptom profiles and trajectories.

In carrying out this type of work, in which the use of AI to analyze clinical notes is becoming increasingly important, it needs to be recognized that the features of clinical notes found to be critical are, in effect, signs of failures of two sorts: first, failures by clinicians to use existing Z codes to capture information on social determinants of health that are more typically found in open-ended notes; and, second, failure of existing diagnostic systems to capture the non-specific symptoms that are coming to be seen as so important for early intervention. The solutions to these problems are increased training and quality control monitoring of clinical coding, along with expansion of coding systems to capture nuanced information discovered to be important for clinical decision-making.

Advancing future research

Trial emulations may be able to shed light on discrepancies between prior observational studies and RCTs¹³⁴. This is done by imposing constraints on the observational EHR data to mimic the trial (e.g., the same inclusion and exclusion criteria, comparison of the same treatments, followed up over the same time periods, with the same outcome measures)¹³⁵. This may require the use of natural language processing of clinical notes if measurement-based care is not used in the health system¹³⁶.

It is also possible to emulate an RCT that has never been carried out on comparative treatment effects of two or more alternative interventions¹³⁷. This approach can be especially effective when evaluating the comparative effectiveness of interventions for rare outcomes, such as suicide, in which a well-powered RCT would be unfeasible¹³⁸. However, the results obtained using these methods still need to be interpreted with some caution^{139,140}.

When trial emulation methods are combined with AI-based methods to predict differential intervention response across patients, it is sometimes possible to use EHR data to develop provisional precision treatment rules that can then be tested and refined

in pragmatic trials. For example, a recent report used trial emulation methods to develop a provisional precision treatment rule to help decide which suicidal patients presenting to emergency departments would have better outcomes if they were hospitalized versus treated as outpatients¹³⁸. Based on the strength of these results, a pragmatic trial to evaluate the accuracy of the treatment rule is currently underway.

The value of EHR data for clinical epidemiological research will increase as the harmonization of medical record systems increases, measurement-based care becomes a more routine part of clinical practice, and AI-based clinical decision support tools become increasingly available^{141,142}. EHR data have predominantly come from high-income countries, but we can expect further penetration of this work in less resourced settings¹⁴³. Advances in biomedical informatics and statistical analysis methods are being made at a rapid pace to make use of these enormous multifaceted databases in ways that will likely lead to advances in understanding mechanisms and improving practice.

DIGITAL PHENOTYPING

Data quality and methodological rigor

Digital phenotyping, defined as moment-by-moment quantification of the individual-level human phenotypes *in situ* using data from personal digital devices, has expanded in interest and scope in the last decade¹⁴⁴⁻¹⁴⁷. As most of the world population now owns a smartphone, and these devices can capture sensor data informing on behaviors such as steps, sleep, social engagement, cognition and relapse, it seems possible to redefine mental disorder based on real-time, dynamic and personalized data.

The feasibility of digital phenotyping is a first step towards developing the rigor necessary for clinically actionable data. Data quality metrics are rarely shared in digital phenotyping papers, but are often low. Specifically, there is often a high degree of missingness in the data, which may be related to a lack of user engagement with the app. Research suggests that, if a user does not open or engage with a digital phenotyping app, the phone operating system may eventually allocate less power to that app, further reducing data collection¹⁴⁸. While high data quality is possible, it requires studies to employ robust data quality checks and procedures, similar to those adopted in fields such as electroencephalography (EEG) or neuroimaging.

Opaque or inconsistent data processing pipelines compound these data quality issues. Few studies use the same methods for imputation, data cleaning, or transformation of raw sensor data into behavioral features such as sleep or time at home. A 2025 review of 112 studies of digital phenotyping in mental disorders reported a high degree of heterogeneity, leading to conflicting results and conclusions in the literature about the clinical correlations of digital phenotyping data¹⁴⁴. While some open-source tools and shared methods exist, few are widely used, and many studies still rely on bespoke, unpublished processing workflows. Recognizing these challenges, in late 2024, the US National Institutes of

Health issued a targeted funding announcement encouraging the development of data standards for digital phenotyping, and many solutions have already been proposed¹⁴⁹.

Mechanisms underlying mental disorders

The ability to frequently and passively capture symptoms and behavior has helped underscore the significant heterogeneity inherent in mental disorders. Digital phenotyping enables continuous tracking of mobility, sociability, sleep, phone engagement, and cognitive performance, offering a dynamic lens through which psychiatric conditions can be understood beyond static diagnostic criteria. For example, entropy derived from global positioning system data has been linked to mood variability, and shifts in home time or sleep stability have been associated with symptom escalation in depression, bipolar disorder, and psychosis¹⁴⁵.

This passive, multimodal measurement offers new opportunities to uncover mechanisms of psychopathology that are context-dependent and temporally evolving. Prior work has shown that features such as decreased mobility or irregular routines often precede clinical relapse, suggesting that digital markers may reflect early disruptions in behavioral regulation or circadian rhythms¹⁵⁰. Similarly, changes in social communication patterns (e.g., fewer calls or texts) have been associated with the onset or worsening of negative symptoms in schizophrenia¹⁵¹.

Importantly, digital phenotyping also allows researchers to examine the interaction between individuals and their environments. Studies exploring exposure to green space, time spent at home, and mobility patterns have begun to probe how context – physical and social – may shape or moderate mental health symptoms¹⁵². These findings raise the possibility of mechanistic models that incorporate not only internal symptom dynamics but also ecological inputs.

Finally, digital phenotyping may contribute to a reconceptualization of mental disorders as dynamic systems with feedback loops¹⁵³. For instance, early anomalies in behavioral data may both reflect and exacerbate emotional dysregulation, creating reinforcing cycles that can be mapped over time. This perspective opens the door to more precise, temporally sensitive models of disorder. However, research using these feedback loops has to date been disappointing, in part because of the high degree of heterogeneity in the digital phenotyping signals and the challenge of linking those signals timeously to the right interventions¹⁵⁴.

Clinical relevance and training implications

The clinical relevance of digital phenotyping lies in its ability to support two primary stages of mental health care: early detection and longitudinal monitoring. In both cases, the integration of passive smartphone or wearable data offers clinicians new opportunities to personalize care, enhance engagement, and potentially improve outcomes. However, for this potential to be realized in routine clinical practice, it must be coupled with appropriate

training, infrastructure, and consideration of ethical use.

Digital phenotyping enables monitoring of behavioral and physiological changes that precede clinical symptom escalation. Studies have demonstrated the capacity of sensor data to predict worsening anxiety or depression scores, or identify early signs of psychosis relapse, often days to weeks before these changes become clinically apparent¹⁴⁶. This has opened the door for proactive, “just-in-time” intervention models⁹⁷. Moreover, hybrid care approaches – combining traditional therapy with app-based data collection and feedback – have yielded improved outcomes for patients with depression and anxiety¹⁵⁵.

Ethical considerations must also be integrated into clinical workflows. Data transparency, patient agency, and algorithmic fairness are central to maintaining trust¹⁵⁶. Interactive dashboards and visualizations that can be shared with patients not only aid interpretation, but may enhance engagement and mutual understanding.

To sustain and scale these models, clinical training is essential. Today, most mental health professionals receive limited education in digital tools, and virtually none in interpreting behavioral biomarkers derived from smartphones or wearables. A new curriculum around digital mental health, including modules on sensor data interpretation, ethical data use, and integrating visualizations into clinical care, is needed¹⁵⁷. Similar to the way neuroimaging interpretation became a core competency in some psychiatric subspecialties, understanding digital behavioral data may become increasingly standard.

Ultimately, realizing the full potential of digital phenotyping in clinical care hinges on investment in clinician training, infrastructure for ethical integration, and continued research to validate actionable biomarkers.

Advancing future research

The next decade of digital phenotyping will depend on solving the persistent challenges of data quality, interoperability and standardization. While smartphones and wearables will continue to generate an expanding volume of behavioral and physiological data, current research is limited by inconsistent methods for feature extraction, incomplete reporting of metadata, and variable data quality across devices. Future work must focus on creating shared, open standards that enable cross-study and cross-device comparability and reproducibility, while maintaining flexibility to adapt to rapid technological innovation. Open-access digital phenotyping data management platforms, such as the Learn, Assess, Manage, and Prevent (mindLAMP), facilitate collaboration in this area¹⁵⁸. Sample sizes will likely need to be closer to 1,000 participants when machine learning methods are utilized¹⁵⁹.

Beyond improving data quality, the clinical utility of digital phenotyping will depend on integrating multimodal data streams into real-world care. Recent research by Apple confirms that digital phenotyping data can already be used to improve AI model health predictions¹⁶⁰. Future studies should not only validate predictive markers for early detection and relapse, but also determine how these markers can inform personalized interventions that are scalable

and cost-effective.

Hybrid models of care, where sensor data support clinical decision-making alongside traditional assessments, hold promise, but require a new focus on training clinical teams to utilize these data. Developing and implementing curricula that teach clinicians how to interpret these digital biomarkers, communicate insights to patients, and integrate these tools ethically into practice will be essential. Without workforce readiness and likely the expansion of new support roles such as that of digital navigators, to offer additional digital literacy and engagement for patients¹⁶¹, the potential of digital phenotyping may remain limited to research settings.

Finally, the next frontier lies in reconceptualizing mental disorder using the continuous, dynamic data that digital phenotyping offers. Rather than relying solely on static diagnostic categories, future frameworks may emphasize data-driven phenotypes that reflect individual variation across time and context. Standardized, interoperable datasets capturing speech, mobility, sleep, sociability, and ecological inputs could inform novel nosologies and personalized treatment pathways, catalyzing advances in drug discovery, early prevention, and adaptive care. However, realizing this vision will require ongoing collaboration between researchers, device manufacturers, regulators, and patient advocacy groups. Such collaborations are possible, and ongoing studies – such as the Accelerating Medicines Partnership Schizophrenia (AMP SCZ) program – provide examples in which digital phenotyping data are collected alongside classical biological, cognitive and symptom markers of mental illness¹⁶².

BRAIN IMAGING

Data quality and methodological rigor

Several large brain imaging datasets are readily available to researchers (e.g., 1000 Connectome, ABCD, UK Biobank)¹⁶³. One of the pioneering big data efforts within the neuroimaging community is the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium³. Founded to conduct secondary analyses on brain imaging data, the consortium's initial impetus was to gather a sufficiently large sample, by combining extracted data across multiple sites, to investigate brain-gene associations. To this end, the project has been remarkably successful, having for example identified genetic correlates of cortical thickness with 51,665 participants¹⁶⁴ and subcortical volumes with 74,898 participants¹⁶⁵.

Currently, ENIGMA involves well over 2,000 scientists from more than 45 countries, and has generated over 50 subgroups focused on a broad range of psychiatric and neurological conditions as well as methodological and analytic matters. It has developed standardized protocols for analyzing genetic and neuroimaging data, facilitating harmonized analyses across diverse datasets, and addressing reproducibility challenges in neuroscience by promoting large-scale, collaborative research. Pipelines now extend beyond volumetric analyses to include diffusion and functional brain imaging, with more recent developments in EEG, magnetoencephalography and magnetic resonance spectroscopy.

ENIGMA has aimed for large samples since its inception. These samples are especially valuable for analytic strategies that prioritize establishing the robustness (replicability) of findings. This includes split-half comparisons, bootstrapping, and miscellaneous cross-validation schemes that separate data into model training and model testing subsets. Large samples are especially important for machine-learning approaches, which tend to be multi-variate and data-driven and need to be assessed for their potential to overfit to data. The meta-analytic strategy embraced by ENIGMA is valuable for guarding against spurious effects that can be observed in single studies¹⁶⁶.

While large sample sizes is a clear strength of the ENIGMA model, data pooling brings with it some significant constraints. Each study is unique and, while substantial progress has been made in harmonizing brain data acquired on multiple scanners, other elements of the clinical and cognitive phenotyping can be very variable. Studies vary considerably in their inclusion and exclusion criteria, in what they measure, and in what they report. Variation across studies in psychiatric comorbidities, assessment instruments, interventions employed, and unmeasured socio-demographic variables may drive down pooled effect sizes and limit the scope for pooled analyses of more in-depth phenotypes.

Another concern is a variant of the file-drawer problem. Secondary analyses may be conducted on datasets from published studies, thereby under-representing null result findings from unpublished studies. However, ENIGMA also includes data from many studies that are difficult to publish primarily because of their limited sample size. An important safeguard here is that the pooled analyses should reveal inconsistent study-specific results if the published literature contains numerous false positives.

Mechanisms underlying mental disorders

Large-scale neuroimaging studies of a range of different disorders have provided a foundation for current efforts focused on understanding the neurobiology of mental disorders by conducting cross-disorder comparisons^{167,168}. For example, ENIGMA has published the largest neuroimaging papers on schizophrenia, bipolar disorder, and major depression, with findings suggesting both overlaps and differences across these conditions. All three disorders involve hippocampal volume deficits: greatest in schizophrenia, least in major depression, and intermediate in bipolar disorder. The basal ganglia do not follow a similar pattern, perhaps because some antipsychotic treatments have hypertrophic effects on these ganglia, leading to volume increases. The ongoing program of cross-disorder work in ENIGMA is shedding light on the relationships between a range of other conditions, with some evidence suggesting that similarities are accounted for, in part, by corresponding similarities in genetic architectures^{169,170}.

The ABCD study has been particularly useful in investigating how specific brain network patterns relate to psychiatric symptoms that emerge during youth. Recent ABCD analyses using resting-state functional magnetic resonance imaging (MRI) have, for example, found that attention-deficit/hyperactivity disorder (ADHD)

symptoms in pre-teens are linked to disrupted connectivity across multiple brain networks, particularly involving the default mode network and cingulo-opercular system, which are associated with internal focus and task control, respectively¹⁷¹. Notably, this study generated scores representing brain-wide ADHD-associated resting-state connectivity, that are conceptually analogous to polygenic risk scores, which represent cumulative genetic risk. The brain-wide connectivity scores were associated with ADHD symptoms in two independent cohorts, validating the finding of widespread dysconnectivity in this condition.

Large-scale neuroimaging studies have also focused on transdiagnostic mechanisms. The IMAGEN consortium, for example, investigated relationships between measures of brain structure or function and behavioral symptoms in adolescents¹⁷². Two symptom groups, anxiety/depression and executive dysfunction, were associated with distinct sets of brain regions and interregional connections. Notably, the neural correlates of these symptom groups were present prior to development of behavioral symptoms. Furthermore, these studies found case-control differences in related mental disorders, i.e. major depression and ADHD. These and related analyses provide a framework for mental disorders that is empirically based on neurobehavioral measures or biotypes.

Large-scale neuroimaging studies have also increasingly linked their findings with gene variants, gene methylation, and gene expression, with a wide range of findings emerging^{173,174}. In one study, for example, similarity of interregional profiles of group differences in surface area and prenatal cell-specific gene expression was assessed¹⁷⁵. MRI surface area was investigated in 27,359 individuals with a range of conditions, and group differences were found for ADHD and schizophrenia in multimodal association cortices. The same interregional profiles were associated with prenatal gene expression specific to proliferative cells (e.g., radial glia) as well as differentiated cells (e.g., endothelial cells). Genes co-expressed with radial glia were enriched with genes implicated in congenital abnormalities, birth weight, hypoxia and starvation, while genes co-expressed with endothelial cells were enriched with genes associated with maternal hypertension and preterm birth. These findings support a neurodevelopmental model of vulnerability, whereby prenatal risk factors acting through cell-specific processes impact typical brain development.

Clinical relevance and training implications

Taken together, large-scale neuroimaging studies have found that differences in individual measures of brain structure and function account for only a small portion of the variation in many mental disorders. Small effect sizes make it unlikely that mental disorders can be explained by a simple, single or unitary disease process. In addition, from a clinical perspective, these small effect sizes may make it unlikely for individual brain measures to provide diagnostic biomarkers. Effect sizes between a Cohen's *d* of 1.5 and 3 are likely to be required for a biomarker to be clinically useful, depending on the nature of the application.

While individual measures of brain alterations account for limit-

ed variance, changes in patterns of brain structure, such as altered covariance across regions, may yield more robust findings. For example, global cortical thickness was studied in 745 individuals with alcohol dependence and 979 controls, finding a significant interaction effect for age¹⁷⁶. In those younger than 25, there were no group differences in global cortical thickness, but there were significant differences in patterns of correlated cortical thicknesses across brain regions¹⁷⁶. This effect has now been replicated in a number of cohorts¹⁷⁷, suggesting that altered patterns of brain structure may be a useful brain marker of risk for future problematic substance use. The development of normalized brain charts may ultimately also have clinical value^{178,179}. As in the case of paediatric growth charts, deviations can be expressed as centile scores, reflecting each individual's position relative to peers of the same age and sex.

Understanding the neurocircuitry involved in any particular mental disorder may provide a useful framework for explaining symptomatology, and for considering relevant interventions, including neuromodulation therapies^{180,181}. It is also remarkable that both pharmacotherapy and psychotherapy are able to alter brain structure and function¹⁸². Trainees need to be aware of advances in neuroimaging methodologies, and of the progress that big data neuroimaging research has made in showing that mental disorders involve multiple, interacting and heterogeneous processes^{183,184}. While there may be no "brain lesion" in mental disorders¹⁸⁵, individual patient imaging data may well be clinically relevant^{186,187}.

Advancing future research

Support for the creation and integration of large datasets should not be taken as a dismissal of other research endeavors in neuroimaging research. Smaller structural, functional and molecular brain imaging studies designed to delineate neurobiological mechanisms, that anticipate larger effect sizes (e.g., a drug challenge study), or that focus on deep characterization of participants, remain vital. Indeed, moving from small hypothesis-driven neuroimaging studies to larger hypothesis-generating analyses, and then back again to more fine-grained work, may be a productive strategy.

Large samples are especially valuable for research that aims to capture broad diversity in socio-demographic variables as well as in the wide range of risk and resilience factors contributing to psychopathology. An ongoing big data challenge will be to accommodate multiple neuroimaging modalities that allow a wide range of brain measures of structure, function and connectivity to be studied, together with broader phenotyping (e.g., ecological momentary assessment, health records, geo-location data). The development of portable low-field imaging may allow research consortia such as Ultra low-field Neuroimaging In The Young (UNITY) to expand such work in under-resourced regions¹⁸⁸.

One aspiration for future research will be to identify the subtypes, if they exist, that create heterogeneity within mental disorders. The hope is that neurobiologically-informed subtypes (neu-

rotypes) may guide and improve clinical practice¹⁸⁹. There has already been significant progress in circuit-based interventions for mental disorders, and we can expect further advances in this area¹⁹⁰. While big data analyses are often data-driven, the combination of such analyses with diverse theoretical frameworks and additional empirical data is particularly promising. Continued close communication between neuroscientists, clinicians and data analysts remains key.

In many regards we are, however, at just the early stages of this neuroimaging research program. The growing appreciation of both neuroimaging's replication crisis and the ubiquity of small brain-behavior association effects should be seen as a call to increase the scale and sophistication of our studies rather than to be pessimistic regarding the potential of neuroimaging¹⁹¹. With a literature replete with under-powered studies, despite its tremendous success in neurology, the jury is still out on the value of neuroimaging in psychiatry for (differential) diagnosis, prognosis, subtyping, treatment tailoring, and tracking recovery.

GENOMICS AND OTHER -OMICS

Data quality and methodological rigor

Large-scale genetic studies of mental disorders include GWAS¹⁹², whole exome sequencing (WES)¹⁹³, and whole-genome sequencing (WGS)¹⁹³ investigations. GWAS test statistical associations of millions of common genomic variants, distributed across the genome, with disease status (present or absent) in participants, indexing risk for a disease or a particular trait. In contrast, WES assesses all sequence variants in the coding regions of the genome which are thought to be most relevant in disease causation, while WGS examines the relationship between disease status and all sequence variants in the entire genome.

Findings from early genome-wide genetic studies of psychiatric traits indicated the need for global collaborative efforts, as required sample sizes exceeded those available in individual cohorts. As a result of this awareness, in 2007, the Psychiatric Genomics Consortium was founded, an international consortium of scientists dedicated to conducting meta- and mega-analyses of genome-wide genetic data¹⁹⁴, initially focused on GWAS, but later expanding to include WES and WGS. Other large-scale genome-wide collaborative efforts have also arisen. The efforts of these consortia have resulted in the identification of thousands of genes and regions of the genome associated with mental disorders, including schizophrenia, bipolar disorder, major depression, anxiety disorders, neurodevelopmental disorders, obsessive-compulsive disorder, post-traumatic stress disorder, and substance use disorders¹⁹⁵⁻²⁰².

Participants in these large-scale genetic studies are recruited in various ways: through clinically ascertained cohorts (e.g., the CloZuk study of individuals with schizophrenia who are prescribed clozapine²⁰³), large national registers (e.g., iPSYCH, a Danish population-based sample²⁰⁴), or large biobanks (e.g., All of Us Research Program²⁰⁵, Million Veteran Program²⁰⁶, UK Biobank¹⁶). Data collected from biobank specimens are often combined with

clinical data obtained from EHRs, although other sources of data are also sometimes used. The PsycheMERGE (electronic MEDical Record and GEnomics) Network is an example of this type of collaboration²⁰⁷. Although psychiatric genetic studies have thus far focused on individuals of European ancestry, recent efforts also include individuals of other ancestries, such as the Mexican Biobank²⁰⁸, and the China Kadoorie Biobank²⁰⁹.

The need for large collaborative genomic studies has led to an early adoption of open science, including the sharing of summary level GWAS results, bioinformatic methods, and analysis scripts. Methodological rigor and careful collection of open data and their transparent, easy-to-follow presentation are key to improving the reproducibility, replicability and accessibility of psychiatric genetics studies²¹⁰. However, to remain at the forefront of open science, ongoing support of junior, technical and non-professional researchers will be required²¹⁰. To facilitate this, the Outreach Committee of the Psychiatric Genomic Consortium has gathered resources for researchers working in psychiatric genomics research and has provided open access training materials.

Although few researchers contest the empirical observation that genetic markers are statistically associated with behavioral outcomes, the GWAS approach has been challenged on several grounds. First, for all mental disorders, single nucleotide polymorphism (SNP)-based heritability estimates obtained from GWAS are smaller than those from twin studies. It has been argued that, even if this gap can be closed with larger GWAS studies, this will not resolve the “prediction gap” (i.e., the challenge of making accurate and reliable prediction from DNA to behavior), nor the “mechanistic gap” (i.e., mechanical explanations of how genetic variation causes behavioral differences)²¹¹.

Second, it is debatable whether genetic variants have a direct causal influence on complex phenotypic outcomes – e.g., “diagnosis of major depression”²¹². The question arises whether there is value in conducting genetic association studies for traits that are likely to be influenced by genetic variation only through mediating variables²¹³. Third, confounding factors may lead to violation of basic assumptions of GWAS, such as the assumption of independent assortment. In fact, assortative mating (i.e., the non-random pairing of individuals based on similarities in their traits), which is common in mental disorders, biases genetic marker-based heritability estimates²¹⁴. This specific type of bias can potentially be addressed in within-sibship GWAS²¹⁵, that allow differentiation between direct genetic effects and other influences such as shared family environment. Fourth, in order to increase power, some GWAS have relied on shallow phenotyping; for example, on only a single item from a questionnaire to assess a trait. Such “thin” phenotyping not only precludes accurate measurement of complex traits, but also does not allow thorough investigation of mental disorder subtypes and spectrums.

Mechanisms underlying mental disorders

Mental disorders are among the most polygenic of complex human traits, implying that thousands of genetic variants with indi-

vidually small effects contribute to disease risk²¹⁶. Gaussian mixture analysis of the distribution of GWAS effect sizes indicate that psychiatric traits are more polygenic than non-psychiatric ones²¹⁶. While polygenic effects account for the majority of the phenotypic variance in mental disorders, there is also a role for rare variants with larger effect sizes, which are typically identified by WES or WGS. These studies are aimed at identifying variants that disrupt gene function, and thus lead to insights about the underlying biology of the disorder under investigation. Rare variants may eventually be found to play a role in all mental disorders; however, the disorders with the strongest evidence for a substantial role of these variants are autism spectrum disorder and schizophrenia^{217,218}.

There is also evidence for substantial pleiotropy (i.e., one particular genetic variant is associated with two or more phenotypes) among mental disorders, which is hypothesized to contribute to the high rates of co-occurrence of two or more disorders in the same individual^{219,220}. For example, the genetic correlation (rg) between major depression and anxiety disorders is as high as 0.90²¹⁹. Genetic studies have also shown extensive genetic correlation across mental disorders and many somatic traits²²¹. Recent methods development in psychiatric genetics allows for multivariate modelling of genetic effects across symptoms and disorders, using genomic structural equation modelling, in which genetic effects are associated with one or multiple latent factors²²². For example, four broad factors (neurodevelopmental, compulsive, psychotic and internalizing) have been found to underlie genetic correlations among 11 psychiatric disorders²²⁰.

GWAS risk loci contain many non-causal SNPs that reach statistical significance through their correlation with the causal SNP(s). The phenomenon underlying this correlation, linkage disequilibrium, may obscure the identity of the causal SNP(s) and its functional interpretation. In recent years, new statistical methods have been developed to unravel the mechanisms underlying statistical associations. The availability of comprehensive functional genomic resources enables the prioritization of likely causal SNPs identified through GWAS, along with associated putative causal genes, and the relevant tissues and cell types through which they manifest their effect. These approaches can be applied to locate causal signals and derive accurate and meaningful biological insights from statistical associations. For example, transcriptome-wide studies test the association between genetically regulated gene expression and disease risk to identify putative causal genes²²³⁻²²⁵. Integration of GWAS results with a comprehensive human snRNA-seq dataset of 105 brain regions²²⁶ has identified specific cell types thought to be involved in the etiology of mental disorders, including cortical and subcortical neuronal associations for schizophrenia, bipolar disorder, and major depression²²⁷.

Despite key developments in research methodology and the availability of new molecular databases, the functional interpretation of statistical genetic associations remains challenging. Some researchers are pessimistic that such work will be able to identify genotype-phenotype mechanistic pathways for human behavioral traits²¹¹. Others are optimistic, in part due to ongoing advances in functional genomics, and in part because, with larger sample

sizes, WES and WGS are predicted to identify specific genes and mechanisms that may underlie the development of mental disorders. We do not yet have the resources to close the gap between genetic variation and phenotypes (e.g., the brain is difficult to access, post-mortem studies are sparse, and developmental data are lacking), but in the future we may.

Clinical relevance and training implications

There are three key opportunities for the clinical translation of psychiatric genetic findings.

First, a major aim of genomics research is to accurately predict disease risk and inform clinical decision-making. For example, polygenic risk scores, which incorporate the weighted sum of common genetic variants to estimate disease risk, have been useful in predicting risk for breast cancer and other complex disorders²²⁸. Analytical estimations designed to relate disease prevalence and heritability with sample size suggest that we will require hundreds of thousands of cases to generate polygenic risk scores that are predictive of mental disorders with high heritability (for example, schizophrenia) and over a million cases for disorders with moderate heritability (for example, major depression)²²⁹. Despite this limitation, and the need for careful interpretation, polygenic risk scores may one day have practical applications in the research, diagnosis and treatment of mental disorders, especially when used in combination with other established risk measures^{27,28,230,231}.

Second, genomic data can be used to identify drug targets that can be translated into more effective therapeutic opportunities. The development of a new drug takes on average 13-15 years, and costs between \$2.5 and \$3.5 billion, with only a 10% chance of clinical approval²³². Drug targets with human genetic evidence of disease association are twice as likely to lead to approved drugs and are even more likely to be approved when the exact causal gene(s) is known²³³. A WES study conducted by Regeneron found that inhibition of GPR75 leads to weight loss²³⁴. Not long after, Regeneron and Astra Zeneca announced that they have entered into a collaboration to research, develop and commercialize small molecule compounds directed against the GPR75 target with the potential to treat obesity. Genetically informed drug repurposing is also showing promise in psychiatry: a recent GWAS of major depression identified 697 genetic associations and revealed possible drug repurposing opportunities, including several anti-cancer therapies, and the agents pregabalin (used in the management of pain and anxiety) and modafinil (used to treat daytime sleepiness caused by narcolepsy)^{212,235}.

Third, pharmacogenetic findings have the potential to be clinically useful²³⁶⁻²³⁸. Specific HLA alleles are associated with medication-related adverse effects, including clozapine-induced agranulocytosis²³⁹, and carbamazepine use is contra-indicated in HLA-B*15:02 carriers, due to link with Stevens-Johnson syndrome²³⁶. Variants in drug-metabolizing enzymes may be clinically relevant, as summarized in the dosing guidelines published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the

Dutch Pharmacogenetics Working Group²⁴⁰. Thus, for example, CPIC dosing guidelines for selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) emphasize CYP2D6 and CYP2C19 genotyping: poor/rapid metabolizer status should prompt lower/higher starting doses²⁴¹. A growing body of work has investigated the efficacy of pharmacogenomic-guided pharmacotherapy. However, findings are promising but inconsistent^{242,243}, and routine use remains controversial, due to variable evidence, diverse test panels, and concerns about marketing claims²⁴⁴.

Advancing future research

Although early results in psychiatric genetics have identified genetic variants and pathways associated with mental disorders, GWAS have not yet delivered on their early promise to lead to more effective treatment strategies. The reasons for this lack of progress are complex, but they include limited understanding of pathogenesis and pathophysiology, the mode of action of existing treatments, and why they are ineffective for many people.

Several challenges need to be addressed in future studies. First, there is substantial heterogeneity within psychiatric diagnostic categories. For example, there are up to 10,377 unique symptom profiles that meet DSM-5 criteria for major depressive disorder²⁴⁵. Clinical and etiological differences within diagnostic categories also exist, and include variation in sex ratios, environmental exposures, age at onset, developmental course, and treatment response. Studies will need to account for this heterogeneity by deeper, “thicker” phenotyping and by analyzing endophenotypes, diagnostic subtypes, or individual symptoms instead of global diagnostic categories²⁴⁶.

Second, rare genetic variants that confer moderate to large risk also contribute to psychopathology. There is evidence that the burden of rare large-effect variants is highest in neurodevelopmental and psychotic disorders, in particular in cases with intellectual disability or developmental delay. However, the relevant studies are still few⁵. Large-scale WGS in biobanks will deepen our understanding of how rare genetic variation influences mental health biology^{247,248}.

Third, preclinical models need to be developed, including animal and cellular models^{249,250}. While animal models of the genetics underlying some mental disorders do exist (e.g., excessive grooming in the SAPAP3 mouse as a proxy for compulsions in obsessive-compulsive disorder)²⁵¹, the question remains as to what constitutes face and construct validity for these conditions. Similarly, for cellular models, it is not yet clear which cell types are relevant, and what the appropriate readouts with relevance to psychiatry might be.

Fourth, although recent efforts have focused on expanding sample sizes in non-European populations, an analysis of the GWAS Catalog found that participants of Asian, African or Latin American ancestry represented only 19% of individuals studied in GWAS²⁵². This lack of diversity is problematic for reasons that are both ethical (i.e., increasing health disparity across ancestry groups)

and scientific (i.e., the identification of causal genetic variation will benefit from the inclusion of diverse populations). Further investments will need to be made to further increase sample sizes across non-European ancestries.

Despite these challenges, the field of psychiatric genetics is in a growth phase, and advances in technical and analytic methodologies will accelerate the rate of scientific discovery in this area. Here we have focused primarily on big data in relation to genetic variants, but there are ongoing advances in epigenetics, transcriptomics, proteomics and metabolomics, with increasing availability of large datasets. With time, the hope remains that genomic and other -omic studies, especially once integrated, will contribute not only to our understanding of the biological underpinnings of mental disorders, but will also allow for early identification of at-risk individuals, and inform and guide the development of novel treatments.

RANDOMIZED CLINICAL TRIALS

Data quality and methodological rigor

Although many hundreds of RCTs have examined the effects of pharmacological, psychological and other treatments on mental disorders, most of these trials are relatively small. Trials are typically powered to show that an intervention is effective, but not to examine predictors or moderators of outcome, mechanisms of change, or effective components. These small sample sizes make it impossible, for example, to use machine learning techniques to explore who benefits most from which treatment. Early attempts to examine this issue, based on small studies, have largely failed to identify strong evidence for predictors and moderators^{253,254}.

From the perspective of big data, an important advance has been the development of large randomized trials, which do provide sufficient statistical power to examine predictors, moderators, mediators, and effective components of treatments²⁵⁵⁻²⁵⁷. The data from these trials are typically of a high quality, and so can potentially shed light on who benefits from which treatment. However, because their number is still limited, they have not yet provided convincing evidence to influence clinical practice.

Even if significant predictors and moderators are found in trials, it is not necessarily the case that they will have clinical relevance²⁵⁸. Thus, if larger trials discover significant predictors and moderators of outcome, such findings should be validated in further randomized controlled trials. In such validation trials, patients will need to be assigned either to treatment based on the new prediction model or to regular treatment. If these trials show that the new prediction model results in a better outcome compared to the regular treatment, this may then have clinical relevance.

Several machine learning methods have been developed to assign patients to the best treatments. The most extensively examined method is the so-called personalized advantage index (PAI) in psychotherapy research²⁵⁹⁻²⁶¹. A recent systematic review analyzed 19 comparative outcome trials based on this index²⁶². While the findings indicated potential benefits, with a standard-

ized mean difference of 0.32, this effect size may be inflated due to significant methodological limitations in the included studies, particularly related to overfitting and model optimism.

The past decade has witnessed exponential growth in machine-learning based prediction models across medical disciplines, but statistical experts have raised substantial concerns about their clinical utility²⁶³⁻²⁶⁵. All predictive models must contend with the fundamental bias-variance trade-off²⁶⁰, wherein the sophisticated pattern recognition capabilities of machine learning methods are counterbalanced by heightened susceptibility to spurious associations – an especially problematic issue in psychological treatment research, where sample sizes remain limited.

Mechanisms underlying mental disorders

The notion of “pharmacological dissection” suggests that, if a particular drug works selectively for specific disorders, light can be shed on the underlying neurobiology. One persuasive example is obsessive-compulsive disorder, which responds to the serotonergic antidepressant clomipramine, but not to the noradrenergic antidepressant desipramine. However, hope that pharmacological dissection would carve psychopathology at its joints has been diminished by findings that many drugs are useful for multiple different conditions²⁶⁶. Indeed, although the affinity of psychiatric drugs for specific receptors has taught us much about the neurobiology of mental disorders, there is a gap between knowledge of receptor binding and a full understanding of the mechanisms underlying response to these medications²⁶⁷.

In psychotherapies, “common factors” have been argued to underlie the effects of treatment²⁶⁸, but the evidence for this assertion has been challenged²⁶⁹. Indeed, in the field of psychotherapy, knowledge of mechanisms underlying the effects of treatment also remains remarkably limited.

The use of factorial designs to examine which elements are effective within multi-component interventions has the potential to contribute to an understanding of mechanisms underlying psychopathology and the response of mental disorders to treatment. In such trials, all participants receive an intervention, but they are randomized to a selection of the components of the intervention. For example, cognitive-behavioral therapy (CBT) may consist of behavioral activation, cognitive restructuring, problem-solving, and exposure and response prevention. In a factorial design, participants can be assigned to each of the four components alone, to any combination of the components, or to all four components. When interventions have multiple components, however, the number of possible experimental conditions grows exponentially. To address this challenge, researchers often employ fractional factorial designs²⁷⁰, which examine only a pre-determined subset of all possible conditions, making studies more feasible to conduct.

Factorial designs require large sample sizes and can be regarded, therefore, as generating big data. The data from these trials are often of high quality, and may lead to better understanding of psychopathology and more efficient interventions. Nevertheless, although several large factorial psychotherapy trials have been con-

ducted in recent years^{257,271-273}, the results of these studies have been somewhat disappointing, and no clear effective components have yet been identified.

Clinical relevance and training implications

Evidence-based practice entails the integration of research evidence, clinical expertise, and patient values²⁷⁴. With ongoing growth in the number of RCTs, there has been a need for systematic reviews and meta-analyses of this work. This led to the establishment of the Cochrane Collaboration, the Agency for Healthcare Research and Quality, and related efforts in evidence-based health care. Similarly, guideline efforts, such as those of the UK National Institute for Health and Care Excellence (NICE) and the Mental Health Gap Action Programme (mhGAP), have appropriately required rigorous reviews of the evidence from controlled trials²⁷⁵.

However, the development of evidence-based guidelines does not necessarily lead to improvements in care. Development and dissemination of evidence-based practice guidelines may not ensure adherence to the evidence, and may have little impact on psychiatric practice²⁷⁶. Obstacles to adoption include attitudinal barriers, resource constraints, and user-unfriendly guidelines. Adoption into routine care requires additional efforts such as organizational engagement, education and outreach, continuous quality improvement, computerized reminders, and decision support²⁷⁷⁻²⁸¹. The evidence in guidelines is only as good as the underlying trials, and the latter typically do not include very complex or treatment-refractory patients²⁸². Nevertheless, a meta-analysis found that patients cared by using guideline-adherent treatment improved more than those who received treatment as usual²⁸³.

It is key for clinicians to receive training on clinical trial methodology, practice guidelines, and research on personalized treatments. Understanding why RCTs are needed, as well as how to read them critically, is essential for practitioners. Similarly, knowledge of the benefits and limitations of guidelines and algorithms may contribute to judicious use of these tools^{284,285}. Clinicians often use personalized approaches to treatments, but this is typically based on clinical experience rather than rigorous research, and indeed personalized psychiatry faces several barriers^{286,287}. While many studies on personalizing treatments are underpowered, a meta-analysis found a small but statistically significant effect size in favour of personalized treatment compared to standardized treatment²⁸⁸.

Advancing future research

The number of RCTs on treatments of mental disorders is increasing rapidly. For example, more than 500 trials have examined the effects of antidepressant medications²⁸⁹, and more than 1,000 trials on psychotherapies for depression have been conducted^{290,291}. In such large research fields, conventional meta-analyses can no longer give an overview of the whole field. This has led to the development of “meta-analytic research domains”, i.e. living

systematic reviews that cover a whole field, regardless of the target group, age group, target population, comparator, or any other characteristic²⁹². Efforts such as Metapsy allow investigators to run analyses on open-access databases of RCTs²⁹³.

In individual patient data (IPD) meta-analyses, the primary data of multiple trials are collected, combined into a large merged dataset, and subsequently analyzed jointly^{294,295}. This integrated dataset can be used to examine whether baseline patient characteristics are associated with the outcomes of therapies. Because the data from multiple trials are combined, the statistical power to examine predictors, mediators and moderators of outcome is substantially increased. IPD meta-analyses also allow the examination of rare outcomes. Nonetheless, findings need to be validated in new RCTs before translation into clinical practice. Although an increasing number of IPD meta-analyses have been conducted in psychotherapy research, the findings are not very consistent. The only outcome predictor that is more or less consistently reported is baseline symptom severity²⁹⁴.

Component meta-analyses and component IPD meta-analyses allow examination of which elements of multi-component interventions are related to better or worse outcomes²⁹⁶⁻²⁹⁸. This development is relatively new, but has already led to some interesting findings. One such finding is that relaxation, often included in packages of CBT because it is considered to be easy to practice, has turned out to be possibly harmful across several disorders, including panic disorder²⁹⁷, depression²⁹⁹, and insomnia²⁹⁶. Like all meta-analyses, the quality of these studies depends on the primary trials that are included, but they do have the potential to shed light on the most effective components of interventions, and may lead to better and more efficient treatments.

DISCUSSION

Having reviewed some of the promises and limitations of big data in a range of different areas of investigation – community and register-based surveys, cohort and biobank studies, EHRs, digital phenotyping, brain imaging, genomics and other -omics, and RCTs – we now return to the key questions and controversies, attempting to outline a balanced way forward. We suggest that, while big data research must carefully address a range of challenges, at its best it contributes in an iterative and integrative way to advancing our knowledge of mental disorders.

Our review has highlighted ongoing improvement of data quality and methodological rigor in big data research on mental disorders, as well as the value of addressing the replication crisis by using sufficiently well-powered analyses. The instigation of very large national biobanks such as the UK Biobank, which can be used for many purposes, including those not envisaged at the time of data collection, as well as more focused cross-national databases that test the generality of effects, represents a major milestone for the field.

Some of these big data efforts promise not only volume, velocity and diversity, but also value and veracity³⁰⁰. Still, the “big data paradox” articulates that sample size alone does not guarantee a

more precise estimate³⁰¹, and opaque or “black box” analyses may lessen quality assurance and reduce clinician trust³⁰².

Specific standards for improving the quality of data collation and analyses may be useful to address concerns about the non-replicability of big data work¹⁴². Standards for specific areas of investigation – for example, digital wearables or gene expression analyses – are continuously evolving at a rapid pace, and may be too specialized to be of interest to a general readership. Standards that cut across big data research in psychiatry – for example, regarding best practices in use of common measures, harmonization of multisite data, integration of multi-omic data, machine learning analyses, and management of privacy and other ethical issues – deserve ongoing close attention³⁰³⁻³⁰⁶. We would argue that, although big data have encouraged unbiased data-driven analyses, hypothesis-focused theory-driven data analyses are also key for the field. Indeed, in both small-scale and large-scale science, good work necessarily integrates theory-driven and data-driven approaches²⁶⁷.

Our review has offered many examples of how big data research has provided important lessons about the mechanisms that underlie risk for and resilience to psychiatric disorders. That said, befitting the complexity of these conditions and of related big data, one important lesson emerging from the work covered here is the intricacy, heterogeneity and variability of such underlying mechanisms^{9,183,184}. This is exemplified by work on big data genomics, which has found that multiple genes of small effect contribute to mental disorders, that there is significant genetic overlap across different disorders, and that, although fine-mapping has pointed to the involvement of specific biological pathways in some disorders, much remains to be learned in order to fully delineate the relevant neurobiology²¹⁹. Furthermore, it is important to supplement big data work with a range of other kinds of research which provide additional perspectives on underlying mechanisms.

A second important lesson emerging from the big data work reviewed here is the value of bringing together clinicians, scientists and clinician-scientists from different regions, disciplines and perspectives. Big data have certainly encouraged and will likely benefit from trans-disciplinarity³⁰⁷. Perhaps the most powerful explanations will ultimately emerge not only from triangulations within big data sets (e.g., using very large national biobanks as well as cross-national datasets), but also from triangulations between large-scale data analyses and smaller scale laboratory research, clinical observations, and controlled trials^{308,309}. How best to integrate large-scale and small-scale work remains an ongoing question. Notably, however, in both large-scale and small-scale work, measures and analyses have important limitations, causality is difficult to determine, and hypothesis-driven as well as hypothesis-generating work may be useful.

Big data research on mental disorders has many aspirations about clinical relevance. However, there remains a “translational gap”. For example, few predictive models have been clinically validated^{142,266,310}. Indeed, a third important lesson from the work reviewed here is the clinical importance of acknowledging the complexity of psychiatric phenotypes and of underlying mechanisms, and the consequent difficulty in bridging from big data to clinical application. On occasion, a particular biomarker is useful for psy-

chiatric diagnosis, and targeting a single mechanism is effective for clinical intervention. However, more generally, psychiatric diagnosis is made without recourse to biomarkers. It is essential to supplement diagnosis with deeper assessment and evaluation that help delineate treatment targets and types, and a pluralistic approach to case formulation and intervention is needed^{267,311}. Big data research reinforces the importance of holding our diagnoses of psychiatric disorders lightly, and providing explanations of these conditions humbly⁵⁴.

Conversely, a fourth lesson emerging from the work reviewed here is that some apparent findings from big data analyses may in fact reflect insufficient attention to clinical matters. Thus, for example, findings that different mental disorders have overlapping genetic architectures may be a result of participants in genomic studies not being deeply enough phenotyped, so that comorbid conditions are overlooked^{6,312}. Analogously, a greater focus on individual patient imaging data may give impetus to large-scale neuroimaging having clinical relevance^{179,186}. Clinicians often adopt a pluralistic stance; big data should similarly aim for better integration of biological, psychological and societal variables. Ongoing involvement of clinicians in the design of big data projects may help enhance the quality of the work, strengthen the reproducibility of findings, and increase clinical relevance.

Throughout our review we also considered the relevance of big data research for clinical training. We not only need to train clinicians to appropriately apply the findings of big data research in the clinic. We also need to build capacity to conduct such investigations, training the next generation of researchers on relevant big data methods and analyses. Such training should include exposure to transdisciplinary work and teams, and to different kinds of collaborations, and working together with individuals with lived experience. Clinical trainees need to understand the possibilities and limitations of big data approaches, including the need to rigorously evaluate AI tools before implementing them in practice. Additionally, clinical trainees need to be aware of how big data research triggers a range of ethical, legal and social implications³¹³.

Our review suggests a promising future for psychiatry research. Going forward, there is enormous scope for further building databases relevant to the investigation of mental disorders and mental health. Furthermore, there are growing opportunities to link different databases with one another, and to supplement such databases with a range of additional multimodal data. However, a fifth lesson emerging from the work reviewed here is that big data collection and analysis needs to give impetus to and be accompanied by conceptual advances. Advances in conceptual models and asking the right questions are as valuable as having a lot of data to test them. We need conceptual advances in key areas such as neuronal development and degeneration, integrating molecular and social determinants of mental disorder, and evolutionary aspects of psychiatry³¹⁴⁻³¹⁶. From this perspective, big data can be the source for both hypothesis generation and hypothesis testing.

The full impact of big data on psychiatry remains to be seen. With future advances in psychiatric big data collections, methods and analyses, it is possible that pioneering conceptual frameworks and practical clinical tools will emerge. Big data have made prom-

ising but as yet preliminary contributions to understanding the principles of brain organization across multiple scales, to transdiagnostic and dimensional approaches in psychiatry, and to some practical AI tools³¹⁷⁻³²⁰. The work reviewed here indicates that psychiatry research has a strong track record of large collaborative studies, and so is well placed to not only benefit from advances in big data, but also to help drive such work. Still, the initial enthusiastic support for big data by some clinicians should be tempered by a more mature skepticism, that reflects a better understanding of their strengths as well as limitations. Calls for a paradigm shift to big data should raise a warning flag that hype may be exceeding hope³²¹.

Several limitations in our review should be acknowledged. We have addressed only a small number of the many large databases, including web-based collections, that are now available for psychiatric research. Relatedly, there are a range of areas of big data efforts in basic and clinical psychiatric research that we did not address here, including large-scale attempts to map the molecular and cellular architecture of the brain, applications of machine learning in animal and human behavioral and cognitive neuroscience, and work on integrative bioinformatics, complexity theory, or computational psychiatry^{11,322,323}. We have also not discussed in detail progress in different areas of machine learning, such as deep learning^{324,325}. We have relied heavily on existing systematic reviews and meta-analyses, rather than conducting such work ourselves.

In summary, a balanced view of big data in psychiatry is appropriate. Big data should certainly not be viewed as a panacea to the challenges of psychiatry, given the depth of these challenges and the constraints of any scientific approach. Still, some of the pejorative resonance of the term “big data” is undeserved, and may be based on an overly nostalgic view of prior small-scale work. On careful reflection, both small-scale and large-scale work can be deeply useful and provide new insights, but also have crucial assumptions, biases and limitations that must be acknowledged and addressed. Ongoing triangulation of small-scale and large-scale work should lead to ongoing iterative and integrative advances in psychiatric research and practice.

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The promise of big data: don't fence me in

Stein et al¹ provide a timely overview of the opportunities and challenges created by the emergence of “big data”. It may be tempting during times of change to announce the “end of days” for this or that practice, but the authors provide us with a laboriously curated atlas of the new frontier, outlining the areas where it holds the most promise as well as those where we should keep our movement firmly grounded on the territory we know. Here I focus on the “bookends” of the “big data” production line: primary data quality and data linkage.

With respect to data quality, given the multilayered production processes involved in the creation of “big data”, it is unlikely that researchers not directly involved will have a basic understanding of what the data really mean. This is concerning, because having a thorough understanding of data quality is the cornerstone of validity for any result. Understanding does not guarantee validity (the research question and methodology need to be sound), but without understanding how our data capture our object, there is nothing we can do later to increase validity.

Two characteristics make “big data” particularly unwieldy: a) multiple sites/organizations involved in data collection; and b) many multimodal variables.

A key strength of high-quality surveys or registers is the uniform nature of instruments and protocols, which allows for centralized pooling and analysis. However, different sites mean different teams, clinical settings, cultural practices, and sometimes languages, leading to on-the-ground adaptations that modify data capture, requiring complex data labeling, cleaning, imputation, and quality control mechanisms. These nuances are poorly understood by external researchers who may access the final dataset, which may lead to fundamental misunderstandings about the meaning of variables.

In addition to heterogeneous data capture practices, electronic health records (EHRs) contain multiple dimensions – e.g., scales, free-text notes, laboratory results, images, drug-dispensation information. To make these data available, (very) simplified pooled datasets are created (e.g., hospital discharge data, physician billing data, drug dispensation data) that extract a minute subset of standardized fields (e.g., ICD diagnostic code, date of admission and discharge, prescription drug name and daily dose). Importantly, qualifying or contradictory information contained in other fields remains unknown: accessing these much more nuanced EHR data requires a level of interdisciplinary expertise that is usually unavailable.

Personal digital devices add further layers of complexity – e.g., inconsistency of data capture practices at the individual, app/software, and operating system levels; massive data cleaning and imputation challenges; and high complexity of access to and interpretability of multimodal data. In addition to highly specialized expertise, research teams need close partnerships with developers able to faithfully implement the capabilities required. Since these tools are frequently developed outside of public or health organizations, issues of data privacy, confidentiality, intervention effec-

tiveness and safety become paramount and generate additional risks, not to mention concerns related to equity, access, and profit motive.

So, these “big datasets” are usually the result of very complex processes that are unknown to external researchers who analyze them. The section on surveys and registers of Stein et al's paper includes a good example of the “opaque” nature of many “big datasets”: the Global Burden of Disease (GBD) database, a strange bedfellow here, since it consists of analytic outputs, not primary data². These estimates result from the GBD meta-regressions, which leverage sparse primary inputs (e.g., community surveys and facility registers) from multiple countries, which are cleaned, adjusted and imputed, yielding a homogeneous set of global estimates grounded on multiple assumptions and methodological decisions. External researchers are unfamiliar with these assumptions and methodologies, hence the results obtained and the conclusions drawn risk being severely biased³. These limitations of the GBD “big data” are not dissimilar to those of the large repositories that do contain primary data.

Let me focus now on the opportunities offered by data linkage: many de-identified health data sources can be linked at the individual level with both health and non-health sources. The scope and the linkage type vary, but the opportunities available in regions with public centralized systems, where health-related datasets are available along with non-health datasets, is remarkable. For example, in Canada, non-health datasets include environmental exposures, tax-filing-based socioeconomic status, child development/educational outcomes, corrections, immigration, occupation, housing, disability benefits, coroner's reports, and others⁴. Further, these datasets are universal (i.e., census samples without selection bias), and linkable at the individual level in a deterministic manner (i.e., through unique identifiers), ensuring linkage reliability and population-level validity.

The promise held by multimodal, linkable, census data cannot be overstated. However, all the requirements described earlier apply: ensuring quality and integrity of the dataset through transparent cleaning and imputation techniques; safeguarding privacy and confidentiality; and convening interdisciplinary expertise to ensure data validation, methodological rigor, nuanced conceptual frameworks, and relevant research questions^{5,6}.

An additional layer is that they require digital platforms that are secure (i.e., prevent re-identification or spurious use), reliable, and versatile. Several jurisdictions have developed such platforms, and impactful analyses offer insights to researchers, providers, and decision-makers, including for example on public health emergencies such as the COVID-19 pandemic and the opioid overdose crisis^{7,8}.

However, the full potential of these datasets is still far away: cumbersome processes to access secure environments discourage researchers from using individual-level data (relying instead on publicly-available aggregations) or from linking multimodal datasets (e.g., using only structured health datasets). Various expe-

riences are underway in which external data, from EHRs or from independent research projects, are uploaded to public platforms and individually linked to available datasets to illuminate specific questions. For example, discharge summaries from patients admitted due to overdose or brought by police due to agitation can be analyzed by the hundreds of thousands with large language models and linked to structured datasets to gain a nuanced understanding of which aspects are associated with improved outcomes, or predict readmission or death. Subsets of patients receiving interventions that are not captured in the available datasets can be grouped into a cohort, studied retrospectively and prospectively. Repeated brain imaging data from separate projects can be uploaded and individually linked to health utilization data to obtain detailed, objective insights of overdose impact on brain structure, health system utilization, and characteristics of death during any given period.

In summary, “big data” offer untold opportunities but also require a higher level of transparency in data capture and aggregation practices, of content and methodological expertise and interdisciplinarity, and availability of state-of-the-art platforms. Indeed, the need to ensure that population-level data are accessible becomes critical from a policy-making perspective. This hosting role has been fulfilled by governments, semi-public organizations, and academia, all of which have their pros and cons. Sometimes the entry barriers are prohibitive: researchers have to physically go to a secure environment to run analyses; or must pay per data extract to an in-house analyst. Further barriers include lengthy, opaque, arbitrary requirements by data stewards or committees. Such ap-

proaches make it very difficult that the promise held by these datasets is fulfilled.

On the other hand, some jurisdictions are making these datasets available for researchers with minimum barriers, without unwarranted delays or arbitrary requirements, through well-funded and expertly run platforms. In the “population health” market, and considering the different types of economic “goods” (private, common, club, and public), in the wrong hands “big data” function like “private goods”: when poor infrastructure restricts simultaneous access by multiple researchers, data become rivalrous and, if significant paywalls exist, excludable. In contrast, with adequate infrastructure, “big data” function like “club goods”: access is non-rivalrous (i.e., many researchers can access without interfering with each other), and tolls are reasonable. But, ideally, “big data” could be treated like “public goods”: any researcher meeting reasonable criteria and following rational transparent processes could access secure platforms at cost, maximizing societal impact.

Daniel Vigo

Department of Psychiatry and School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada

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Big data research: the importance of the data-generating process and domain expertise

Stein et al¹ provide an insightful overview of the opportunities and challenges that arise with the emergence of “big data” as a driver of progress in psychiatric research. As they point out, the concept of “big data” itself has been used to mean different things. In particular, it is important to distinguish the opportunities and challenges associated with scale (large sample size) from those associated with scope (i.e., high dimensionality and multimodality of variables within a dataset). For hypothesis-driven research, expanding sample size enables greater precision (i.e., less error) of effect estimates, and this, in turn, can improve the robustness and replicability of findings. The availability of high-dimensional and multimodal data can support truly novel and potentially transformative data-driven research.

The prospects for advancing mental health research using big data are formidable. Massive genomic and other “omic” datasets are revealing biological pathways and functional genomic mechanisms that implicate causal biology and novel therapeutic targets. The vast scale of electronic health records (EHRs) provides a real-world data resource for high-throughput phenotyping as well

as the development of predictive algorithms for risk stratification and treatment matching. Multimodal technologies for measuring brain structure and function can help map the pathophysiology of psychiatric illness and identify novel predictive or prognostic biomarkers. The dense measurements of behavior enabled by digital phenotyping and wearable sensors can identify dynamic trajectories of risk and treatment outcomes.

At the same time, as Stein et al discuss, bigger is not always better. If we are to capitalize on the accelerating availability of large-scale datasets, we must confront a broad range of methodological challenges. Here I focus on one issue that underlies many of the challenges raised in Stein et al’s paper: the importance of attending to the data-generating process. The value of our models depends on how well they track this process. So, we must always ask: “What underlying processes gave rise to the data we observe?” And the answer to this question requires attention to both the technical and statistical aspects of the data as well as the human factors involved in their measurement.

Statisticians and data scientists understand the appropriate use

and limitations of data types and modeling approaches – e.g., what assumptions apply to statistical and machine learning methods; what statistical techniques are appropriate for handling missing data. But the data are not merely numbers to be taken at face value. Psychiatric domain experts can bring a crucial awareness of how human behavior shapes the kind of observations that we can make. And the integration of computational and clinical domain knowledge is especially critical if we are to translate discoveries to clinical practice. Predictive models (whether based on EHR, genomic, imaging or digital data) are doomed to failure if the computational workflows are mis-specified. At the same time, we can build sophisticated data-driven models that perform beautifully but, without an understanding of human factors, they may have no chance of being clinically useful. As the saying goes, “garbage in, garbage out”.

Consider one of the major classes of big data that Stein et al review: the availability of massive real-world EHR data, which has provided new opportunities to phenotype and predict psychiatric outcomes using machine learning and other data science methods. This work can go astray without an understanding of how the documentation of health care encounters works in clinical practice.

Clinicians know that EHR notes often include text and diagnoses that are carried forward from prior encounters, compromising data validity. For example, we and others have used EHR data to develop algorithms that predict suicide-related behaviors². Because prior suicide attempt is one of the best-established predictors of a future attempt, we wanted to include documented attempts as a model feature. However, in an extensive EHR chart review, we discovered that more than 80% of consecutive suicide attempt codes given on different days were non-independent – that is, they referred to the same suicide attempt event³. Including the earlier attempt as a predictor would result in a form of “data leakage” in which the target outcome is included among the features used for the prediction, leading to substantial inflation of apparent model performance. Addressing this hidden threat required the development of a data selection rule that minimized the problem.

EHR-based data are also susceptible to problems with interpreting missing data. The absence of a diagnostic code does not necessarily imply absence of disease. For example, primary care and mental health clinicians may have different thresholds for documenting diagnoses or social determinants of health, and patients may receive their mental health care outside the given health care system. EHRs encode clinician behavior, not just biomedical facts.

Clinical domain knowledge may also be important for avoiding bias in the development of EHR predictive algorithms. A landmark study⁴ showed that a widely-used algorithm to predict health care needs was biased because health care costs were used as a proxy for health status. Because Black patients incurred lower health care costs than White patients, the algorithm was less likely to identify Black patients as needing additional health care resources. However, the lower costs were actually the result of less care being provided to Black patients (e.g., due to reduced access) than White patients for a given level of illness burden. In this case, inattention to

the data-generating process yielded a biased algorithm that risked reinforcing, rather than mitigating, existing health disparities.

In the realm of neuroimaging, innovations in data analytic methods have produced important discoveries about the relationships between mental disorders and brain structure and function. Statistical and technical insights have also been important for handling potential artifacts, such as variance produced by differences in scanner field strength and data pre-processing across sites in multi-site consortia, as well as inflated Type I error due to “double-dipping” when features (voxels or regions) are selected on the basis of their association with an outcome and then the same features are used to estimate statistical significance⁵.

But the neuroimaging literature also provides telling examples of how attention to behavioral and clinical features that shape the data-generating process is essential for valid inference. For example, neuroimaging findings initially interpreted as disorder-related have later been shown to be confounded by unrecognized features of the data generating process, including systematic group differences in head motion (e.g., in patients with attention-deficit/hyperactivity disorder) and antipsychotic exposure in schizophrenia^{6,7}.

Analogous issues arise with genomic data. The ongoing development of statistical genetic methods has facilitated the discovery and mapping of genetic influences across psychiatric disorders, and the development of polygenic scores that capture clinically-relevant risk. Statistical methods are also essential in accounting for potential confounds (e.g., population structure), multiple testing, and other threats to valid inference.

But equally important is an understanding of how phenotypic assessment shapes the findings of genetic analyses. For example, “depression” defined by a brief survey can be very different from the entities captured by EHRs or clinical diagnostic interviews. Indeed, large-scale genomic studies have shown that the depth of phenotyping has substantial effects on locus discovery, heritability estimates, and genetic overlap with other phenotypes⁸.

Digital phenotyping enables dense, person-specific measurement of real-world behavior that was previously difficult or impossible to capture at scale. Valid modeling of the factors underlying the generation of digital data again require technical, statistical and clinical expertise. Optimal methods for analyzing high-dimensional and time-varying smartphone and wearable sensor data are an active area of methods development, often requiring data science sophistication. But the design and interpretation of such studies also require domain expertise. For example, understanding the drivers of participant engagement – including social forces and the impact of psychiatric symptoms – are essential for interpreting missing data⁹.

The advent of multimodal big data resources will undoubtedly drive substantial advances in precision psychiatry. Psychiatric phenotypes are notoriously heterogeneous, and big data provide the scale and scope that are needed to embrace rather than avoid this heterogeneity as we endeavor to address unmet needs for diagnosis, prevention and treatment. But fulfilling this promise will require attending to the data generating process, as well as thoughtful and close collaboration between data scientists and

clinical domain experts.

Jordan W. Smoller

Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA; Department of Psychiatry, Harvard Medical School, Boston, MA, USA; Center for Precision Psychiatry, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA; Center for Suicide Research and Prevention, Mass General Brigham Department of Psychiatry, Boston, MA, USA

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From emulation to implementation: next steps for big data research in psychiatry

Stein et al¹ deliver a panoramic and admirably even-handed account of what big data have done – and have not yet done – for psychiatric science and care. Their central lesson is appropriately sober: scale is not a synonym for truth, and the translation from large datasets to clinical value demands rigor, transparency and theory, not only terabytes. Yet, the review also points to a concrete pathway where psychiatry can move fastest from promise to patient benefit: use of electronic health records (EHRs) to emulate target trials^{2,3}, distill provisional precision treatment rules, and then validate them prospectively in pragmatic designs. Here we sketch that loop in operational terms, and suggest how large language models (LLMs) can accelerate each step – while respecting the review's cautions about data quality, harmonization, fairness, and clinical humility.

EHRs already contain the ingredients for causal questions that mental health clinicians face daily – e.g., admission vs. discharge with rapid follow-up for suicidal presentations; esketamine vs. alternative augmentation in treatment-resistant depression; continuation electroconvulsive therapy vs. medication alone after index response. Stein et al's paper notes that EHR data, complemented by measurement-based care and natural language processing (NLP) of notes, can support target-trial emulations when randomized trials are infeasible (e.g., for rare outcomes such as suicide). That logic should be encoded into a pre-registration-ready template: define the clinical strategies; pin down time-zero to avoid immortal-time bias²; declare inclusion/exclusion and washout rules; and fix follow-up windows and outcomes (e.g., 30/90-day attempts or rehospitalizations; standardized symptom change where routine scales exist; adverse events)⁴.

EHRs can carry both structured fields and patient-reported outcomes. Stein et al's paper emphasizes their growing integration for risk prediction and monitoring – those same elements must be pre-declared as outcomes and covariates in the emulated trial. Confounding control should be specified up front: doubly robust estimators or high-dimensional propensity models; negative-control outcomes and exposures to probe residual bias; clinician and facility fixed effects to handle local practice styles. LLMs can make this prescriptive by: a) auto-abstracting eligibility, exposures, and outcomes from free-text notes into structured variables

with verifiable provenance; and b) drafting the trial-emulation protocol from a library of vetted templates⁵. All LLM outputs must be checked against ground-truth structured data and must be auditable, which aligns with the paper's insistence on transparency and reproducibility.

Stein et al's paper is clear about why models trained in one system may stumble in another: coding fragmentation (ICD-9/10 variants; non-standard medication/procedure vocabularies), variable documentation practices, and privacy constraints. The solution is not cosmetic post-hoc recalibration, but design-stage harmonization: map to a common data model where feasible; when raw pooling is impossible, keep data in place and use federated learning⁶ with meta-analytic combination of site-level models. LLMs can accelerate this step by: a) aligning local synonyms in notes to standard terminologies (e.g., mapping “passive wish not to wake up” to suicidal ideation phenotypes), with site-specific calibration reports; b) generating explainable phenotyping rules that combine structured codes and note phrases, which can then be validated against chart-review subsamples; and c) assisting common data model mapping by proposing code-to-code correspondences and flagging unmapped or ambiguous fields for expert review.

Emulated trials deliver average causal effects; clinicians need individualized advice. The next step is an auditable precision treatment rule that estimates conditional average treatment effects while honoring clinical guardrails. The paper's emphasis on fairness, transport and interpretability in EHR modeling suggests three constraints. First, uplift calibration – do not only report area under the curve (AUC) values; show that predicted benefit maps to realized benefit across bins, so decision thresholds are meaningful. Second, safety overrides – codify non-negotiables (e.g., active suicidal intent with high-lethality plan → recommend admission regardless of modeled advantage for outpatient care). Third, invariance and equity – select predictors whose associations are stable across sites and subgroups. LLMs can add two pragmatic pieces here: a) counterfactual narratives⁷ that translate uplift into a short, evidence-anchored explanation (“Given X, Y, Z in this chart, admission reduces your 90-day attempt risk by ~N per 100 patients; main drivers are A and B”), and b) model restriction to citing only facts that are actually present in the EHR (i.e., constrain retrieval-augmented generation),

which lowers the risk of fluent but unfounded explanations and directly addresses the authors' concern about "black box" models and trust.

LLMs can then weave the loop into clinical practice. Stein et al point to an early exemplar: a target-trial-derived rule for suicidal patients that is now entering pragmatic evaluation⁸. That should be the template, generically: embed cluster step-wedge or patient-level randomization into routine care; present the rule via clinical decision support that displays an individualized absolute risk, a counterfactual benefit (e.g., "predicted reduction in 90-day attempt risk if admitted"), and an uncertainty band; and require a one-click clinician response ("accepted/overridden + reason") to create learning labels. LLMs can operationalize: a) live eligibility screening and safety-override checks by reading the active note and medication list; b) summarization of the relevant risk context (recent attempts, access to firearms, housing instability) from the past 12 months; and c) provision of patient-facing explanations of options in plain language. LLMs can also monitor calibration drift, set fairness triggers to prompt review, and schedule periodic recalibration with a public version ledger. The authors' discussion of trial emulation, pragmatic trials, and the promise – and pitfalls – of artificial intelligence (AI) decision support fits naturally into this "closed-loop" quality-improvement posture.

Big data can miss the forest (big picture) for the trees (features) unless the goal is explicit. The rule should be judged against a small set of pre-specified utility metrics. In the suicide example, attempts prevented per 1,000 patients seen, psychiatric admissions avoided, days not hospitalized, clinician time saved per decision, and, where feasible, cost per quality-adjusted life year (QALY). The review's epidemiological synthesis offers two anchors. First, the World Mental Health Survey finding that only 26.1% of people are helped by the first professional, but 90.6% by the eighth, implies that an algorithm which expedites effective care (not just any care) could plausibly move a patient with greater speed and certainty across that gradient⁹; "helpfulness" rates and persistence costs are therefore legitimate utility targets. Second, the call to "hold diagnoses lightly" argues for stratification by symptom burden and function rather than categorical labels in both emulations and pragmatic trials. LLMs can measure the operational side – e.g., time saved by auto-drafting discharge safety plans, or reduction in avoidable bed-days by earlier identification of low-benefit admissions – so

that utility is not only clinical, but also system-relevant.

Finally, clinical decision support and generative tools should be treated like a drug. Algorithms that influence admission, discharge, or high-risk prescribing deserve the same procedural safeguards as therapeutics. An expert oversight group should review drift, fairness, and adverse event signals; patient-facing materials should explain how models use their data and how overrides work; and health systems should commit to sunseting or refitting models that fail pre-declared performance tolerances. For LLMs specifically, we should require: distinction of retrieval-only generation from verifiable EHR facts; citation of data sources; and red-teaming (i.e., using independent groups to deliberately probe, stress-test, and try to break the model by thinking like an adversary to uncover vulnerabilities and failure modes). These safeguards align directly with the review's emphasis on ethical, legal and social implications, as well as clinician training in AI-enabled practice.

In summary, the paper by Stein et al provides the *why* and *where* of big data research in psychiatry. The field now needs the *how*: a closed-loop, auditable, LLM-augmented, utility-anchored pipeline that a health system can adopt. Adding a prescriptive template for EHR target-trial emulation, a constrained precision-rule specification with explanation fidelity checks and updating rules incorporating iterative integration with clinician judgment, and a pragmatic validation plan with predefined utilities and LLM governance, are among the next steps to be taken to enable big data in psychiatry to deliver big gains for mental health.

Murray B. Stein¹, Martin P. Paulus²

¹Department of Psychiatry and School of Public Health, University of California San Diego, La Jolla, CA, USA; ²Laureate Institute for Brain Research, Tulsa, OK, USA

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Next generation of big data in psychiatry: more theory, more within-person data, and better integration of artificial intelligence

Stein et al¹ provide a thoughtful, thorough and forward-looking review of some of the key critiques and considerations on the burgeoning use of "big data" in psychiatry. As they note, psychiatry transitioned over the last century from a psychoanalytic to a neuroscientific perspective. It has now entered a digital era, in which the use of "big data" promises to lead to great advances in the description, prediction and treatment of mental disorders.

One could argue, however, that we have gone from a state of "all theory and no data" to one of "all data and no theory". Freud and others working from a psychoanalytic perspective used verbal explanations based largely on unobservable and unmeasurable factors (e.g., id, ego, superego) to guide the understanding and treatment of the conditions affecting their patients. The pendulum has swung, and psychiatry can now rely on biobanks, electronic health

records (EHRs) and digital devices that provide enormous amounts of person-level data. However, such data are typically used in whatever form they are made available, and superficially mined in a search for predictors of important mental health outcomes. Theories (explanations of how or why something happens) and even models (general representations of how things work) have taken a backseat to atheoretical predictive research in psychiatry.

Building on several key points raised by Stein et al, I argue that “big data” in psychiatry will generate even more progress if collected and used in a more planful manner than is being currently done in our field. I highlight three proposed directions: a) greater consideration of theory in the use of big data; b) development of idiographic psychiatry; and c) integration of generative artificial intelligence (AI) into psychiatric research and practice.

First, a greater focus on using big data to test, and inform, theories of mental disorders will facilitate progress toward better understanding and treatment. Current approaches to analyzing big data have a limited ability to advance the understanding of how mental disorders emerge, change over time, and may be best prevented and treated (most prominently reflected in the use of “black box” approaches). For instance, prediction models that use numeric ICD codes available in EHRs can help us better identify which patients in a health care system are at greatest risk of suicide attempt², but cannot inform on how, why or when suicidal thoughts and behaviors emerge – or how best to treat them. Most of the data available to researchers via big data sources (e.g., biobanks, EHRs, smartphone sensors) were not collected for the purpose of testing models of psychopathology and are not well-suited for such a task, posing a major limitation to predictive research in psychiatry.

How can we make things better? Interestingly, while much of the field has been focused on using big data to improve prediction and prevention efforts, another segment of the field is illustrating how theoretical and modeling research in other disciplines can help advance psychiatry. A recent paper³ on the future of the biopsychosocial model put forward by G. Engel 50 years ago – the most often-invoked organizing structure in the field – proposes an update of this model via connections with work on systems science. In this restructuring, the model is shown to be a helpful tool for synthesizing data from various biological, psychological and social sources to explain how mental disorders unfold and change over time.

Indeed, there have been increasing calls to incorporate formal theory and dynamical systems approaches, which have been fruitful across so many areas of science (e.g., ecology, climate change), to help explain the network of factors that interact across different time scales to give rise to the symptoms of mental disorders³⁻⁵. There is broad agreement that mental disorders are caused by complex, time-varying interactions of biological, psychological and social factors – but this is not reflected in our current analysis of big data. Future efforts should focus on specifying and testing our theories and models using the big data sources available, and on creating new sources of big data that better enable such tests.

Second, the collection and analysis of intensive *within-person* big data is likely to facilitate progress toward better understanding

and treatment. Such approaches are wildly underused and should represent a much larger part of the “big data” armamentarium moving forward. The earliest experimental psychologists (Ebbinghaus, Pavlov, Wundt) demonstrated that idiographic methods which use the intensive study of individual organisms over time could produce dramatic advances in psychological understanding⁶. The recent availability of deep digital phenotyping provides unprecedented opportunities to significantly strengthen these designs⁷. Here too, advances are most likely to come from proactively planning for the collection of data that can answer specific questions (e.g., how do different components of suicidal thinking vary over minutes, hours and days) rather than simply making use of all data that may be available from a particular data stream via default settings (e.g., all phone sensor data)^{8,9}.

Third, the systematic examination of how best to use generative AI to address psychiatric conditions is vital to improving science and practice. We are in a moment of incredibly rapid development and deployment of AI⁷. Psychologists and psychiatrists trained in understanding human intelligence and related mental traits/states are uniquely qualified to help ensure the safe development and delivery of these tools. Significant advances are needed on multiple fronts: a) understanding how AI can help us better understand humans (e.g., AI-supported analysis of big data); b) aiding clinicians in understanding and helping other humans (e.g., AI-enhanced clinical decision-making); and c) aiding patients directly (e.g., AI-supported chatbots as a complement to traditional care), with special attention to how, where and when humans should be involved most prominently in the loop. Scientists and clinicians have expressed concerns for many years about patients’ unmet need for care. Generative AI can help meet this need, though of course we must ensure that this need is met as safely and effectively as possible.

It has been exciting to see the advances resulting from the use of big data across several subfields of psychiatry. The next generation of research using big data in psychiatry promises even further progress with the incorporation of theory as a guide for leveraging data strategically, more intensive study of specific individuals, and more in-depth examination of the safe and effective ways to harness AI to advance the understanding and treatment of mental disorders.

Matthew K. Nock

Department of Psychology, Harvard University, Cambridge, MA, USA; Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

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Rethinking biomarkers in psychiatry: from etiological uncertainty to actionable prediction

Stein et al¹ provide an integrative overview of the expanding landscape of biomarker research in psychiatry. They emphasize the importance of a nuanced perspective on the strengths and limitations of large-scale analytics, and the need for advancements in methodology, study design, and the conceptualization of mental illness.

With a still limited understanding of core pathological processes, psychiatry actually faces a particularly pronounced challenge among medical fields in identifying biomarkers with robust and clinically meaningful performance – a difficulty underscored by recent large-scale evaluations showing that even advanced machine-learning approaches fail to yield generalizable neuroimaging-based diagnostic biomarkers for major depressive disorder².

Influenced by yet unresolved conceptual questions and the availability of large retrospective datasets, psychiatric biomarker research has often utilized case-control designs, which, despite their methodological validity, may be less informative regarding clinically actionable tasks such as treatment selection or relapse prediction.

In other medical fields, including oncology and cardiology, biomarker and predictive research is embedded in more clearly defined biological substrates and, importantly, in established intervention frameworks – factors that, as noted by Stein et al, critically influence the clinical utility of large-scale data analytics. This raises the question of whether psychiatry faces a uniquely intractable complexity in biomarker discovery and clinical translation, or whether valuable insights can be drawn from the translational trajectories of these other disciplines.

In oncology, biomarker research is anchored in an arguably more obvious cellular pathology compared to psychiatry, yet faces similar challenges due to pronounced biological heterogeneity³. For example, individual cancer types may harbor multiple histological and molecular subtypes, limiting prediction from available samples. Despite this, numerous highly effective oncological biomarkers, approved by the US Food and Drug Administration (FDA) – predominantly genomic and molecular companion diagnostics – are being used in clinical practice⁴.

Their clinical translation illustrates a conceptual shift from a “mechanism-complete” perspective towards clinically actionable endpoints and an iterative refinement of etiological understanding. Newer markers with direct patient benefit may inform therapeutic decisions – for example, mutations conferring sensitivity or resistance to targeted therapies. These advancements, rooted in the acceptance of biological heterogeneity as an inherent limitation, may provide psychiatry with a blueprint where translational strategy is directed towards clinical applicability and an iterative refinement of etiological understanding.

A further example for a “non-linear” translational pathway is offered by developments in cardiology, where the utility of multi-modal artificial intelligence (AI) algorithms for risk of heart failure or arrhythmia was driven by the *a priori* definition of useful clinical

decision points. Focusing on who would benefit from intensified monitoring or anticoagulation evaluation, rather than diagnosing the underlying pathophysiology, facilitated the development of FDA-cleared, AI-assisted electrocardiographic models for prediction of atrial fibrillation risk that are available for use in clinical practice⁵. Similarly, emerging AI applications for heart-failure risk stratification target clinically actionable endpoints, such as the need to initiate or escalate guideline-directed therapy. The clinical translation of these applications was supported by intervention pathways that were already established, even if the underlying pathophysiology was only partially understood.

A third example comes from pediatrics, where growth charts have long had high clinical utility despite not being tied to disease-specific mechanistic understanding. These are used to compare measures such as body mass index, height, or head circumference against age- and sex-specific reference distributions. Clinically meaningful deviations from typical developmental trajectories then guide decisions about further diagnostic evaluation or intervention. While the analogous “normative modeling” approaches are widely used in neuroscience, linking them to concrete clinical decision rules could be an important step towards their future clinical application.

Unlike conventional, supervised machine learning, normative models capture reference distributions and usually do not contain information on clinical endpoints directly. In psychiatry, where different deviations may be associated with the same clinical phenomenon, normative models may capture clinically relevant change better than direct prediction, allowing them, as suggested by Stein et al, to generate real clinical value.

Although personalized medicine frameworks from other medical disciplines may not be directly applicable in psychiatry, directing biomarker discovery more towards clinical action may be an important step to facilitate translation. As emphasized by Stein et al, advances in reproducible and standardized data acquisition are needed to support multi-site analytics and longitudinal robustness. This should go hand-in-hand with the definition of concrete, clinically actionable endpoints⁶, such as early treatment switching, or intensified monitoring to prevent relapse. These endpoints need to be operationalized regarding their application contexts, intervention pathways, and expected benefits and risks.

Baseline risks under usual care can inform the required effect of a predictive model to have a positive impact on clinical practice. This can guide the definition of actionable decision thresholds – e.g., based on the predicted non-response probability. AI model performance metrics can be supplemented with measures more closely tied to the clinical application contexts.

For example, the frequently used area under the curve (AUC) measures the ability of a model to differentiate between individuals in different outcome groups at all possible model thresholds. However, in practice, decisions are made at specific thresholds, and

the metric does not indicate whether such decision would meaningfully change the outcome probability for a given patient. The evaluation of clinical relevance requires additional absolute risk-based measures at specific decision thresholds, complemented by decision-analytic concepts, such as the net benefit, that summarize whether model-guided decisions are likely to improve patient outcomes⁷. Similarly, positive and negative predictive values indicate how reliably high- or low-risk classifications translate into true outcomes in the population to which the model is applied.

These examples illustrate that the clinical utility of AI models depends on the context of their application and the underlying event rate in the population where they find application. Considering this already during study design could allow aligning model development more closely to clinical decision making. Linking predictions to actionable clinical endpoints also supports the interpretability of AI model outputs at the clinical level, which is an important requirement for successful clinical translation⁸.

The methodological standardization alluded to by Stein et al will then form a critical element for staged validation schemes where AI models need to be tested in comparable external cohorts, followed by prospective clinical trials. These validation strategies will profit from early engagement with regulatory bodies, to ensure alignment with emerging qualification pathways and conformity requirements for AI-based clinical tools, laying the groundwork for integration into electronic health records, clinical guidelines, and reimbursement structures⁹.

Assessments of patient benefit should actively incorporate patient perspectives, for example through co-development with patient representative groups, to ensure that clinical decisions sup-

ported by AI tools align with patient values and priorities. They should also be accompanied by a deep understanding of the consequences of false positive and false negative predictions, that can only be established in representative and sufficiently heterogeneous target populations.

Advances made through a structured translational strategy focused around clinically actionable endpoints may lead to more rapid implementation of tools with real benefit for affected individuals and, in parallel, to an iterative conceptual refinement of mechanistic theories of mental disorders. As Stein et al argue, AI and related big-data methodologies will function as powerful instruments only to the extent that they are coupled with a clearly articulated and effective translational strategy.

Andreas Meyer-Lindenberg^{1,2}, Emanuel Schwarz^{1,3}

¹Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; ²German Centre for Mental Health, partner site Mannheim-Heidelberg-Ulm, Mannheim, Germany; ³Hector Institute for Artificial Intelligence in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

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Big data, disease mechanisms and clinically actionable discovery

Stein et al¹ provide a comprehensive synthesis of the advances, challenges and future directions for big data approaches in psychiatry. Their review highlights impressive technological and methodological progress, but also reflects the breadth of the field. Here I build on their arguments by considering how big data can be made more relevant to severe mental illness, and how new resources could further shift the field from observational insight to clinically actionable discovery.

Large community cohorts, population-based biobanks and routine data linkages have generated major advances in psychiatric research. By integrating genetic, neuroimaging, molecular and digital phenotyping data at scale, they have transformed our understanding of the architecture of common mental disorders. Although these cohort studies are rarely motivated by improving the care of people with severe mental illness, they have nevertheless reshaped the landscape of psychiatric research and improved the evidential base of the field.

The shift to large-scale mental health data science has been indispensable for testing, as well as generating, hypotheses. Prior to the availability of big data, psychiatry was dominated by small, underpowered studies that produced unreliable findings and con-

tributed to a replication crisis in neuroscience².

Genomics illustrates the scale of this transition. Between 2013 and 2025, the availability of population cohorts – such as UK Biobank, Generation Scotland, and the Norwegian Mother and Child Cohort Study (MoBa) – accelerated the identification of replicated genetic signals for major depression from zero to almost 700 independent loci³. These discoveries revealed causal mechanisms, enabled imaging-genetics studies, and opened pathways to molecular biomarker development and novel drug targets.

Moreover, one of the unexpected benefits of larger-scale genetic studies has been their ability to identify potentially modifiable experimental and lifestyle risk factors for mental illness. By comparing the genetic findings of different traits, studies have further evidenced a causal link between obesity and major depression. These results have implications for health and social policies that aim to reduce illness risk and improve population mental health.

Comparable progress has been made in our genetic understanding of almost all severe and common mental disorders⁴. While some advances have been made by substantially broadening the definitions of mental illness used, there is overwhelming evidence that discoveries remain relevant to people who have more severe

symptoms and less favourable outcomes.

The considerable progress in our genetic understanding of mental illness has been enabled by the development of large international consortia and by the Psychiatric Genomics Consortium (PGC) in particular. This collaborative approach to accelerating genetic discovery has been consistently productive since its inception. While the many genetic discoveries made do not yet account for the heritability of these conditions, progress is accelerating, with no sign of a plateau.

Stein et al ask whether big data can now be made more clinically relevant. Their concern is justified. Large cohorts under-sample individuals with severe mental illness, reducing generalizability to those groups and limiting clinical translation. They are also known to under-represent individuals who are less socially fortunate, a key risk factor for many conditions. However, despite these limitations, large population-based samples and cohorts remain valuable. They can, for example, be used to dissect the genetic architecture of complex mental disorders and to understand intermediate biological phenotypes in unaffected individuals, using samples unconfounded by medication exposure or chronic illness.

Big data approaches can also strengthen imaging studies that are individually underpowered. The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium⁵ exemplifies how meta-analytic methods can transform psychiatric neuroimaging through the accumulation of samples across continents in increasingly diverse populations. This has enabled consistent hypothesis testing and replication, and led to novel discoveries and methodological innovations. Arguably, one of ENIGMA's greatest achievements has been to foster global collaboration. Nevertheless, while ENIGMA's scientific successes are considerable, they too have not yet been translated into improved patient outcomes.

This divergence between rapid scientific progress and limited clinical benefit is evident across psychiatry. In oncology and other areas of medicine, genetic and epidemiological discoveries have more rapidly yielded mechanistic insights and targeted therapies. Psychiatry must now learn the lessons of other fields and adapt its methods to close this translation gap.

The last 20 years demonstrate that progress requires scale, collaboration and harmonized data, not small single-site studies. Small unreplicated studies that reported novel findings often produced excitement but advanced the field little and did not serve patients. Nevertheless, they taught us many lessons that we forget at our patients' cost. Contemporary research must be large enough to generate replicable findings. To achieve this, researchers must make data available to others so that they can interrogate and replicate published findings and leverage the resources to test their own novel hypotheses and methods. Publicly funded data are collected to deepen our scientific understanding and improve patient outcomes. There is an overwhelming argument for facilitating trustworthy access to publicly funded research when it is in pursuit of future patient benefit.

Recent national efforts in the UK, including the Mental Health Platform⁶ and the data science infrastructure provided through DATAMIND⁷, seek to address these challenges by changing the way in which research is conducted from the outset. Cross-disciplinary

collaborative work is encouraged and nurtured, and the resulting data are harmonized and made available for others to develop new diagnostics and therapies. These initiatives seek to make researchers less siloed and enable data to be found and made available to others. Input from people with lived experience of mental illness is proactively sought to improve research quality, feasibility and impact. Involving and engaging people with mental illness in research can help develop novel hypotheses, helps build trust and transparency, and guides researchers to the scientific questions that matter most to patients.

Experience from other domains of medicine indicates that transforming "big data" discoveries into new therapies requires experimental systems that psychiatry currently lacks. Lack of ready access to mechanistically relevant living brain tissue from affected individuals is a clear and understandable barrier to progress. Other vital approaches that have accelerated progress elsewhere include molecular and cellular disease models, the development of model organisms, and access to large, deeply phenotyped clinical samples. These resources often include minimally invasive fluid biopsies (commonly blood or saliva) to identify potential biomarkers. Many studies now include the potential to recall participants for clinical trials or future investigations, based on their individual characteristics. This capability is essential if we are to move from diagnosis-based towards personalized treatment and reform the diagnostic categories that have dominated our field for over a century.

Psychiatry does not yet have cohorts of extensively characterized patients with severe mental illness at the scale of UK Biobank. This once unimaginable possibility is now feasible. The motivation, infrastructure and passive phenotyping capabilities (e.g., electronic health records, digital data streams) are now in place to support population-scale clinical cohorts.

Major funders, including UK Research and Innovation, National Institute for Health and Care Research (NIHR)⁸, and the UK Office for Life Sciences⁹, have recognized this and are beginning to invest in transformative clinical cohorts. These resources have the potential to address many of the limitations highlighted by Stein et al, combining the statistical power and generalizability of big data approaches with the focus, depth and clinical relevance of patient-facing research.

Achieving this vision will require cultural and methodological shifts, alongside investment in training and capacity building. Future progress depends not only on building larger datasets, but on orienting those resources toward mechanistic discovery, biomarker validation and intervention development. Big data must not simply describe severe mental illness at scale; they must help explain it and ultimately change its trajectory.

Andrew McIntosh

Division of Psychiatry, University of Edinburgh, Edinburgh, UK

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Is bigger better?

Psychiatrists sense an enormous opportunity arising from the application into practice of findings from large population datasets. Such “big data” analytic approaches can accommodate the diversity and complexity of mental health problems and have potential to parse the subtle, cumulative effects of multiple adversities in the evolution of psychological distress and mental disorder. However, there is continuing uncertainty about the *added* value to *clinical* psychiatry of findings obtained from hypothesis-light analyses of extensive databases, when compared to insights derived from hypothesis-driven investigations in smaller samples. Put more simply, it is not yet clear whether “bigger is better”.

Stein et al, in their magisterial review, provide illustrations of this persisting uncertainty. They note, for example, that polygenic risk scores have not proved sufficiently predictive to merit translation into routine practice; that very few biological markers have demonstrated consistent utility in clinical settings; and that individual differences in neuroimaging measures of brain structure and function account for only a small proportion of the variance in mental disorders. Overall, they contend that overenthusiastic support for big data approaches must be tempered with a balanced understanding of their strengths and weaknesses¹.

Sometimes, “small is beautiful”. Single-case (“n-of-1”) methods based on serial measurement in an individual can be useful for testing theories and evaluating interventions, and have identified beneficial personalized interventions relating to drug and alcohol use, sleep, eating, and treatment adherence. Detailed consideration of individual narratives through incorporating qualitative research methods generates considerable insights into the lived experience of patients with psychiatric illness, to an extent not achievable by merely quantitative approaches². And the finding, mentioned by Stein et al, of little difference in severity, impairment and comorbidity between generalized anxiety disorder of 6-month duration and generalized anxiety symptoms of shorter durations, emerging from analysis of big data in community surveys involving 17 countries and 85,052 individuals, was established contemporaneously in a single-centre cohort comprising just 591 participants³.

The proponents of using big data approaches to direct strategic decisions in business management cite their beneficial key attributes of volume, variety, velocity and veracity in enhancing impact. But, in clinical management, the availability of databases which are large, multi-faceted and swiftly accessible may not necessarily inform the care of individual patients impactfully. Patient preference, clinician confidence, and local service availability are all relevant considerations, and insights derived from distantly accumulated datasets which cannot account for sometimes idiosyncratic and parochial concerns may have limited utility in determining treatment

choices in clinical practice. Hence, an important challenge to implementing treatment decisions informed by big data approaches is how best to incorporate the views and opinions of patients and to acknowledge the practice-based experience and internalized tacit “mindlines” of clinicians⁴.

Much of the anticipated success of big data approaches rests on securing widespread access to electronic health records in routine clinical practice. Stein et al provide some persuasive examples of the value of big data approaches centred on the records of treatment-seeking individuals, in enhancing clinical practice (as examples, improved accuracy in prediction of suicide risk), and in implementation of psychotherapies for common mental health problems. But, as with other areas of medicine, there are persisting doubts about such records in psychiatric services. What is recorded is influenced by patient, clinician, service and societal factors. Individuals and cultures differ in their idioms for expressing distress; patients offer psychological complaints to clinicians in variable, reflexive ways, depending on their perception of support within the encounter; and reporting of symptoms is affected by illness-related cognitive difficulties and emotion-processing biases. Furthermore, health professionals differ in their assiduousness when asking questions about pivotal symptoms for accurate diagnosis: as an example, a national audit in England revealed marked variation between and within mental health services in the comprehensiveness of patient assessment⁵.

Other considerations regarding the use of electronic health records in big data analysis include representativeness, comprehensiveness and privacy. Socioeconomically deprived individuals are disadvantaged in gaining access to services, yet are more likely to experience mental health difficulties, and similar problems are seen in the disproportionately low recruitment of individuals from marginalized communities into mental health research. Data analyses based on treatment-receiving and research-participating patients may, therefore, have reduced applicability in some populations. Health records tend to focus on measurable processes such as consultations and prescriptions, but may neglect important determinants of mental well-being, such as childhood adversity, trauma, diet, exercise, joblessness and family breakdown: experience from oncology research indicates that accurate characterization of this influential “exposome” is a substantial challenge⁶. In addition, there are widespread concerns about privacy protection when sharing health-related data. Although strategies such as “federated learning” (training statistical models whilst keeping data localized) are a potential solution, there is often a “trade-off” between maintaining privacy and optimizing model performance.

It is frequently stated that patients with psychiatric illness and their attending mental health professionals yearn for more appro-

priately targeted, individually tailored clinical care, designed to obviate “trial-and-error” treatment approaches, to enhance response rates, to alter the trajectory of illness, and to improve other clinical and personal outcomes. This “precision psychiatry” has the commendable goal of getting the right treatment to the right patient at the right time. Its questioning critics contend that, although well-intentioned, its underlying premises are flawed and bemoan its reductionist approach to mental suffering⁷. Its advocates, by contrast, anticipate that additional insights from big data analysis will enhance understanding of the effects of adversity and the attributes of resilience, increase the validity and accuracy of psychiatric diagnosis, and so transform clinical practice; and they emphasize the pivotal importance of identifying biomarkers derived from such analyses and their subsequent widespread integration into practice⁸.

In Alzheimer’s disease, biomarker identification and evaluation has refined diagnosis, modified clinical staging, informed drug development, and contributed to the approval of novel treatments. The chances of similar success in other psychiatric disorders will rest on establishing that any identified biomarkers have optimal sensitivity and specificity, reflect presumed pathophysiological processes, and can predict outcome trajectories accurately. Other pivotal characteristics of future biomarkers should include their acceptability to patients, their ease of incorporation into practice, and their being sufficiently cost-effective in refining clinical decisions. A biomarker might be adopted widely if it could be used easily and inexpensively.

Stein et al allude to some methodological developments in big data science which may not be widely known among practising psychiatrists. The challenge of linking data from small surveys to those within larger case-based registers can be met by algorithmic imputation of missing data when creating a “synthetic dataset” which can mimic real data, with sufficient granularity and variability whilst maintaining confidentiality. Electronic health records

can permit “emulated target trials,” which overcome formal randomization by comparing observational data from similar groups of patients given differing treatments⁹. Such an approach may permit evaluations of real-world comparative effectiveness and acceptability, and may also provide supportive data which might underpin subsequent trials of potentially repurposable medicines.

The opportunity provided by big data analytics, if welcomed with curiosity and flexibility but balanced by caution, could lead to a reconceptualization of psychiatric diagnosis, fuller understanding of pathophysiological processes, enhanced characterization of patients, delineation of personalized treatments, and – hopefully – improved clinical and personal outcomes. We can envisage a circular path of discovery, in which novel findings from explorations of big data confer an additional impetus to hypothesis-driven mechanistic investigations, the insights from which lead in turn to further pre-specified and pre-registered explorations in extensive datasets. But it would be essential to ensure that the explanatory models which emerge from such a process are both complex enough to represent reality yet simple enough to prove useful in psychiatric practice.

David S. Baldwin

University Department of Psychiatry, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

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Can big data answer the big questions about specific mental disorders? The example of obsessive-compulsive disorder

Stein et al¹ outline recent advances and current constraints in the use of “big data” in psychiatry. Here we provide a brief overview of these advances and constraints using the example of a specific mental disorder on which research has been particularly active in the last decades: obsessive-compulsive disorder (OCD). Three main questions continue to challenge research on this disorder: a) what are its causes; b) which treatments work best for whom; and c) how to increase access to evidence-based care. Big data approaches are being used to address each of these questions.

The question of what causes OCD spans multiple levels of explanation, from genetic and environmental risk factors operating across development, to alterations in brain circuits and cognitive processes that give rise to symptoms. Big data approaches are uniquely positioned to address this complexity if they are applied

within a clear causal framework that distinguishes etiology from pathophysiology.

Etiology refers to the causal processes that lead an individual to develop OCD. The prevailing model posits that genetic vulnerability interacts with environmental factors across development to shape risk. Genome-wide association studies and rare variant analyses are only now reaching sample sizes sufficient to identify robust genetic associations with OCD². Yet, gene discovery is only the first step. Understanding how genetic risk contributes to OCD requires tracing gene effects on the developing brain through transcriptomic, proteomic and metabolomic processes, leveraging experimental systems and translating to humans. Environmental factors (e.g., perinatal complications, infection and inflammation, trauma, toxins, cultural context) have also been implicated in OCD

risk³. Capturing these influences systematically over time presents substantial challenges. Thus, unraveling OCD etiology requires not only many different types of data, but also statistical models that can accommodate high-dimensional, longitudinal, multilevel data and represent interactions among genes, environments, and developmental processes. This is not merely a challenge of larger samples, but of clear hypotheses about causal pathways, robust data collection across multiple levels of analysis, and analytic frameworks capable of integrating diverse data types while remaining interpretable.

Pathophysiology refers to the brain and behavioral mechanisms through which OCD symptoms are expressed and maintained. Many studies have documented alterations in cognitive and affective processes (e.g., executive function, fear extinction, reward valuation) and in brain structure and function, implicating cortico-striato-thalamo-cortical circuits⁴. Despite the volume of research, robust and clinically actionable biosignatures of obsessive-compulsive (OC) clinical profiles have been difficult to identify, making the links between brain alterations and OC symptoms tenuous. Moreover, prior studies often recruited small samples and used heterogeneous methods, leading to findings that proved difficult to replicate. Importantly, brain alterations observed in individuals with OCD should be understood as intermediate phenotypes – mechanisms shaped by upstream etiologic processes and likely altered by disease duration and treatment – rather than causes in their own right.

Large-scale collaborative efforts have begun to address these limitations, attempting to link etiology and pathophysiology. By combining neuroimaging data from studies conducted around the world, the ENIGMA-OCD consortium has assembled very large samples, enabling meta- and mega-analyses of structural and functional neuroimaging data from individuals with OCD and healthy controls⁵. The findings reveal that some previously reported effects are small but reproducible, while others do not replicate at scale or appear to be medication effects, helping to recalibrate expectations about effect sizes and improve rigor in the field.

ENIGMA-OCD relies on retrospectively pooled data: clinical and imaging protocols were not harmonized across sites. This heterogeneity introduces substantial between-site variance and limits more fine-grained analyses focused on brain-behavior associations, including efforts to identify clinically meaningful subgroups.

To address this limitation, the Global OCD Study harmonized clinical, neurocognitive and neuroimaging methods across five international sites, recruiting 250 unmedicated adults with OCD and 250 matched healthy volunteers⁶. Using multimodal neuroimaging and targeted cognitive tasks designed to probe cortico-striato-thalamo-cortical circuits, the study seeks to identify reproducible biosignatures associated with OC clinical profiles rather than diagnosis *per se*. Preliminary findings suggest relatively few case-control brain differences, but more informative associations between specific brain and cognitive measures and OC clinical profiles, supporting a brain-behavior rather than brain-diagnosis framework.

While the Global OCD Study provides deep, harmonized phenotyping, its sample size limits the use of more flexible, data-driven

approaches that seek to discover latent or novel brain-behavior features without imposing *a priori* assumptions about diagnostic categories, symptom structure, or neural circuits⁷. To meet this need, a new initiative, MEGA-OCD (R01MH138569), leverages the complementary strengths of ENIGMA-OCD and Global OCD Study by combining large-scale samples with rich phenotyping, and applying multivariate approaches such as multimodal fusion, normative modeling, and symptom-anchored clustering, to identify brain signatures that relate to clinical phenotype, predict treatment outcome, and reflect gene expression.

While etiologic and pathophysiologic research advances, individuals with OCD require effective treatment now. First-line interventions – serotonin reuptake inhibitors (SRIs) and cognitive-behavioral therapy (CBT) with exposure and response prevention – enable up to half of patients to achieve minimal symptoms⁸. For the remainder, clinicians turn to a wide range of pharmacological, psychotherapeutic, neuromodulatory and surgical options, with treatment selection largely guided by trial-and-error.

Big data approaches offer the potential to reduce this uncertainty by identifying predictors, moderators and mediators of treatment response. An ambitious ongoing trial in China (clinicaltrials.gov NCT04539951) exemplifies this strategy, enrolling 1,600 treatment-naïve individuals with OCD to determine optimal pharmacotherapy strategies following first-line SRI treatment. As the largest OCD trial to date, this is powered to detect clinically meaningful moderators and mediators of outcome. Findings from such large-scale studies can then motivate mechanistic follow-up studies to test causal pathways.

At the same time, larger trials are not inherently better. With very large samples, small differences can achieve statistical significance without clinical relevance, and interventions that benefit only specific subgroups may fail to replicate if heterogeneity is not explicitly anticipated in the study design. This requires *a priori* hypotheses about which treatment will work best for whom, along with measures and analytic models capable of testing these questions directly. Thus, big data approaches in treatment research should be hypothesis-driven and clinically-anchored toward integrating clinical, behavioral and biological information to pave the way to precision psychiatry, rather than identifying a single “best” treatment for all patients.

Advances in understanding and treatment will only improve public mental health if individuals with OCD can access evidence-based care. Yet most do not, due to barriers at the system, clinician and patient levels⁹. Big data approaches can help identify and address these gaps. Analyses of electronic health records have documented substantial gaps in OCD care (e.g., <https://iocdf.org/ocdcarecrisis>), while artificial intelligence (AI)-informed digital platforms for screening, measurement-based care, and care matching are rapidly evolving (e.g., www.springhealth.com) and can be adapted to close these gaps in OCD care.

National initiatives, such as Sweden’s use of digital platforms to deliver exposure and response prevention at scale (www.internetpsykiatri.se), demonstrate how technology can transform access without sacrificing fidelity. Emerging AI tools can also support scalable ways to train clinicians to deliver exposure and re-

sponse prevention, and to monitor their fidelity. As with all big data applications, these innovations must be evaluated carefully to ensure that they augment rather than replace clinical judgment and do not exacerbate existing inequities.

In summary, the example of OCD research shows that big data are not an end in themselves, but a tool. When applied strategically, guided by theory, grounded in clinical reality, and evaluated with humility, they can help address the big questions concerning specific mental disorders. The promise of big data lies not in ever-larger datasets alone, but in integrating causal understanding, methodological rigor, and clinical insight to improve the lives of people with mental illness.

Helen Blair Simpson, Melanie Wall

Department of Psychiatry, Columbia University Irving Medical College, New York, NY, USA; New York State Psychiatric Institute, New York, NY, USA

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Evidence-based atlas of risk and protective factors for psychotic disorders: an umbrella review to inform personalized prognosis and prevention

Claudia Aymerich^{1,3}, Michele De Prisco^{3,6}, Antonio Melillo^{7,8}, Borja Pedruzo^{2,3,9,10}, Ana Catalan^{2,3,9,10}, Dominic Oliver^{8,11-14}, Kelly Diederer¹⁵, James MacCabe^{15,17}, Ricardo Twumasi¹⁵, Rudolf Uher¹⁸, Cathy Davies^{8,19}, Luis Alameda^{15,20,21}, Celso Arango^{22,23}, Eduard Vieta^{3,6}, Christoph U. Correll^{24,27}, Crick Lund^{28,29}, Merete Nordentoft^{30,31}, Thomas A. Pollak¹⁵, Dong Keon Yon³², Samuele Cortese^{33,37}, Laura Fusar-Poli^{38,39}, Stefano Damiani³⁸, Sameer Jauhar⁴⁰, Luigi Grassi^{41,42}, Alessio Maria Monteleone⁷, Manuel Capra³⁹, Ilaria Stirpe³⁹, Giovanni de Girolamo⁴³, Gonzalo Salazar de Pablo^{1,44,45}, Simon Cervenka^{46,47}, Marco Solmi^{27,48-50}, Matteo Tonna^{51,52}, Robin Murray^{15,44}, Oliver Howes^{15,53}, Joaquim Radua^{8,54}, Paolo Fusar-Poli^{8,38,55,56}

¹Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; ²Biobizkaia Health Research Institute, OSI Bilbao-Basurto, University of Basque Country, Bilbao, Spain; ³Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain; ⁴Institute of Neurosciences, Department of Medicine, Faculty of Medicine and Health Sciences, Universitat de Barcelona, Barcelona, Spain; ⁵Bipolar and Depressive Disorders Unit, Hospital Clínic de Barcelona, Barcelona, Spain; ⁶Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; ⁷Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy; ⁸Early Psychosis: Interventions & Clinical-detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; ⁹Department of Psychiatry, Basurto University Hospital, Osakidetza, Bilbao, Spain; ¹⁰Department of Neuroscience, University of Basque Country, Leioa, Spain; ¹¹Department of Psychiatry, University of Oxford, Oxford, UK; ¹²NIHR Oxford Health Biomedical Research Centre, Oxford, UK; ¹³OPEN Early Detection Service, Oxford Health NHS Foundation Trust, Oxford, UK; ¹⁴Institute for Mental Health and Centre for Human Brain Health, University of Birmingham, Birmingham, UK; ¹⁵Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; ¹⁶NIHR Biomedical Research Centre for Mental Health South London and Maudsley NHS, London, UK; ¹⁷National Psychosis Service, South London and Maudsley NHS Foundation Trust, London, UK; ¹⁸Department of Psychiatry, Dalhousie University, Halifax, NS, Canada; ¹⁹Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; ²⁰Service of General Psychiatry, Treatment and Early Intervention in Psychosis Program, Lausanne University Hospital, Lausanne, Switzerland; ²¹Department of Psychiatry, Hospital Universitario Virgen del Rocío, Universidad de Sevilla, Sevilla, Spain; ²²Hospital Universitario La Paz, Madrid, Spain; ²³CIBERSAM, School of Medicine, Universidad Autónoma de Madrid, Madrid, Spain; ²⁴Division of Psychiatry Research, Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA; ²⁵Department of Psychiatry and Molecular Medicine, Zucker School of Medicine Hofstra/Northwell, Hempstead, NY, USA; ²⁶Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Manhasset, NY, USA; ²⁷Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin Berlin, Berlin, Germany; German Center for Mental Health, partner site Berlin, Berlin, Germany; ²⁸Centre for Global Mental Health, Health Service and Population Research Department, King's College London, London, UK; ²⁹Alan J. Fisher Centre for Public Mental Health, Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa; ³⁰Copenhagen Research Center for Mental Health, Copenhagen University Hospital - Mental Health Services, Copenhagen, Denmark; ³¹Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; ³²Department of Pediatrics, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, Republic of Korea; ³³Developmental EPI (Evidence synthesis, Prediction, Implementation) Lab, Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK; ³⁴Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK; ³⁵Hampshire and Isle of Wight Healthcare Foundation NHS Trust, Southampton, UK; ³⁶Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, NY, USA; ³⁷Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro", Bari, Italy; ³⁸Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy; ³⁹IRCCS Istituto Clinico Scientifici Maugeri, Pavia, Italy; ⁴⁰Centre for Affective Disorders, Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; ⁴¹Institute of Psychiatry, Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy; ⁴²Department of Mental Health and Pathological Addiction, Local Health Trust and Sant'Anna University Hospital, Ferrara, Italy; ⁴³Unit of Epidemiological Psychiatry and Digital Mental Health, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy; ⁴⁴South London and Maudsley NHS Foundation Mental Health Trust, London, UK; ⁴⁵Institute of Psychiatry and Mental Health, University Hospital "G. Marañón", Madrid, Spain; ⁴⁶Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, and Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden; ⁴⁷Department of Medical Sciences, Psychosis Research and Preventive Psychiatry, Uppsala University, Uppsala, Sweden; ⁴⁸SCI-ENCES lab, Department of Psychiatry, Faculty of Medicine, University of Ottawa, ON, Canada; ⁴⁹Department of Mental Health, Ottawa Hospital, Ottawa, ON, Canada; ⁵⁰Ottawa Hospital Research Institute, Ottawa, ON, Canada; ⁵¹Department of Medicine and Surgery, Psychiatric Unit, University of Parma, Parma, Italy; ⁵²Department of Mental Health, Local Health Service, Parma, Italy; ⁵³Psychiatric Imaging Group, Institute of Clinical Sciences, Faculty of Medicine, Imperial College London, London, UK; ⁵⁴Imaging of Mood- and Anxiety-Related Disorders Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer, CIBERSAM, University of Barcelona, Barcelona, Spain; ⁵⁵Outreach and Support in South-London Service (OASIS), South London and Maudsley NHS Foundation Trust, London, UK; ⁵⁶Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Munich, Germany

Identifying updated, evidence-based risk and protective factors for psychotic disorders is essential to advancing scientific and clinical knowledge of their etiology. Since the most recent umbrella review published in this journal, the evidence base has expanded substantially. Following a pre-registered protocol, we searched the Web of Science for systematic reviews with meta-analyses of observational studies published between the search date of the last umbrella review (February 1, 2017) and March 31, 2025, examining associations of sociodemographic, parental, perinatal, and later factors or antecedents with ICD/DSM (any version) diagnoses of non-organic psychotic disorders. We graded associations between each putative factor and psychotic disorders using standardized international classification criteria: convincing (class I), highly suggestive (class II), suggestive (class III), and weak (class IV). We also conducted sensitivity analyses: a) lowering the classification criterion requiring more than 1,000 cases to 500 cases, b) restricted to prospective studies (class I-II factors), and c) testing more robust estimates of uncertainty (Hartung-Knapp-Sidik-Jonkman method). Then, we estimated the population attributable fraction (PAF) for potentially modifiable class I-III factors. Study quality was assessed with a MeaSurement Tool to Assess systematic Reviews (AMSTAR). A total of 69 systematic reviews and meta-analyses were included, reporting on 970 individual studies and 221 risk or protective factors for psychotic disorders. Six risk factors showed convincing (class I) evidence of association: Black-African ethnicity in England (odds ratio, OR=4.89, 95% CI: 4.04-5.92), South Asian ethnicity in England (OR=2.15, 95% CI: 1.69-2.73), paternal age <20 years (OR=1.34, 95% CI: 1.20-1.50), birthweight under 2,000 g (OR=1.77, 95% CI: 1.48-2.13), birthweight under 2,500 g (OR=1.50, 95% CI: 1.38-1.64), and maternal history of three or more previous pregnancies (OR=1.32, 95% CI: 1.20-1.45). Eighteen additional factors were highly suggestive (class II): maternal psychosis, Black-Caribbean ethnicity in England, any maternal mental health disorder, ethnic minority status in a low ethnic density area, first-generation immigrant status, cannabis use 5 to 7 days per week, Toxoplasma gondii IgG positivity, history of attention-deficit/hyperactivity disorder (ADHD), trait anhedonia, olfactory identification ability, premorbid IQ, and seven factors pertaining to minor physical anomalies. Two additional factors were upgraded from class IV to class II in our sensitivity analyses: clinical high-risk for psychosis (CHR-P) state, and soft neurological signs. Twenty-six factors (including four protective factors) were suggestive (class III), 75 were weak (class IV), and 96 were non-significant. Sensitivity analyses restricted to prospective studies downgraded some of the above factors, but only total minor physical anomalies became non-significant. The largest PAFs (>10%) were found for childhood adversities (40.69%), Toxoplasma gondii IgG positivity (20.47%), cannabis use 5-7 days per week (12.75%), and CHR-P state (12.68%). The sensitivity analyses employing robust uncertainty estimates confirmed that, among class I factors, Black-African ethnicity in England, birthweight under 2,000 g, and birthweight under 2,500 g retained their level of evidence. The

mean AMSTAR score was 7.73 ($SD=2.09$). These findings provide an evidence-based, updated atlas of risk and protective factors for psychosis, advancing epidemiological knowledge, refining precision psychiatry, identifying targets for preventive intervention, and guiding global public health research.

Key words: Psychosis, risk factors, sociodemographic factors, parental factors, perinatal factors, later factors, antecedents, preventive intervention, public health

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Psychotic disorders have an early onset in young people¹, and are marked by a profound disruption in the lived experience and sense of self², and a significant social and occupational impairment³. They are one of the leading causes of disability worldwide, accounting for a significant part of the burden associated with mental and substance use disorders⁴.

The etiology of psychotic disorders is complex and only partially understood, involving genetic and environmental factors, as well as their direct interplay³. Heritability estimates for these disorders range between 40 and 79%^{5,6}, and several genetic markers have been identified⁷. However, decades of research have also implicated various environmental risk factors. The consistency and magnitude of the evidence for environmental risk and protective factors for psychosis have largely remained scattered, with limited impact on clinical practice.

To address this gap, in an earlier publication in this journal⁸, we appraised the consistency and magnitude of non-purely genetic risk and protective factors for psychosis by conducting the first umbrella review (i.e., a meta-analysis of meta-analyses) summarizing the evidence. However, since that study (January 2017), the body of evidence on risk and protective factors for psychosis has expanded exponentially, leading to several novel systematic reviews and meta-analyses being published in international databases⁹.

Advances in etiopathological knowledge require reappraising prior evidence to confirm previously identified factors and investigate additional risk factors that reflect emerging scientific trends and discoveries. A regular mapping of evidence-based risk and protective factors for psychotic disorders is an essential step to inform scientific, clinical and public health knowledge at several levels. For example, the incorporation of precision psychiatry into real-world clinical practice is currently hampered, among various factors, by a fragmented and heterogeneous knowledge about the most robust predictors of outcomes. Identifying evidence-based predictors is pivotal for developing and validating individualized clinical prediction models to forecast clinical outcomes in psychotic disorders.

Similarly, the development of effective screening strategies and preventive interventions relies on an accurate understanding of which factors are plausible targets for modification and at which developmental stage they may be most relevant. With many, and often conflicting, findings, even across different meta-analyses on the same topic, this information is not readily available.

Third, at the public health level, preventive resources are limited, and there is uncertainty about which targets should be prioritized. Estimating the population attributable fraction (PAF) of

potentially modifiable risk factors¹⁰, based on umbrella review evidence, would be essential for identifying higher-yield targets and guiding a more cost-effective allocation of preventive efforts at the population level.

The present umbrella review aims to address these epidemiological, precision psychiatry, preventive, and public health gaps by systematically synthesizing the updated evidence on risk and protective factors for psychotic disorders, providing quantified effect estimates, and grading their credibility using established bias-sensitive criteria¹¹. We also estimated the PAF for the most robust, potentially modifiable factors, indicating their potential population-level impact. The findings are then interpreted to inform epidemiology, clinical prediction modelling, preventive and public health strategies.

METHODS

The study protocol was pre-uploaded on Open Science Framework (<https://osf.io/cqjt7>).

The systematic search and data extraction were conducted in accordance with the Preferred Reporting Items for Overviews of Reviews (PRIOR)¹² recommendations and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines¹³ (see also supplementary information).

Search strategy and selection criteria

First, we retrieved the systematic reviews assessed in our previous umbrella review, which covered studies up to January 31, 2017. Next, we searched the Web of Science database (incorporating the Core Collection, the BIOSIS Citation Index, the KCI-Korean Journal Database, MEDLINE, the Russian Science Citation Index, and the SciELO Citation Index, as well as Cochrane Central Register of Reviews, and Ovid/PsycINFO databases) to identify additional systematic reviews and meta-analyses of observational studies examining the association between putative factors and psychotic disorders, published from February 1, 2017 to March 31, 2025, without language restrictions.

To ensure consistency, we used the same search strategy and databases as in the previous umbrella review (see also supplementary information): “systematic review” OR “meta-analysis” OR “meta-review” OR “meta-analytic” OR “meta-analyses” OR “metanalysis” OR “metanalyses” AND “psychosis” OR “psychotic” OR “schizophren*” OR “psychoses”. The electronic search was

complemented by a manual search of the reference lists of the included papers and by consulting experts in the field to identify any additional relevant studies.

Eligibility criteria were defined *a priori* as follows: a) systematic reviews and meta-analyses of observational studies (e.g., case-control, cohort or ecological studies) published in peer-reviewed journals; b) examining the association between sociodemographic, parental, perinatal, and later factors or antecedents and any non-organic ICD or DSM psychotic disorder (e.g., schizophrenia spectrum disorders, mood disorders with psychotic features); and c) including a comparison group of individuals not diagnosed with a psychotic condition. Papers were initially screened by title and abstract against these criteria. Full texts of potentially eligible studies were then assessed in detail. When the information reported was insufficient to identify the primary studies included in the review, we contacted the corresponding authors to request additional details.

In line with the previous umbrella review, we excluded: a) systematic reviews without a meta-analysis and meta-analyses not based on a systematic search; b) systematic reviews and meta-analyses focused exclusively on purely-genetic markers of psychotic disorders; c) systematic reviews and meta-analyses investigating biomarkers, since they would require specific methodological approaches and separate analyses; and d) publications not subject to peer review (i.e., conference proceedings, dissertations).

When two papers presented overlapping datasets on the same factor, we retained for the main analysis the paper including the largest dataset. In case of a tie, preference was given to the paper with the highest methodological quality (see below). We retained factors from the previous umbrella review² that were not replaced by new meta-analyses with a larger sample. We updated the associations for factors identified in the previous umbrella review for which larger meta-analyses were identified.

Each individual paper included in the meta-analyses was also assessed against the same inclusion and exclusion criteria, with the additional requirement that non-organic psychotic disorders were defined according to any edition of the ICD¹⁴ or the DSM¹⁵. Each full text was independently reviewed by two investigators (AM, BP), with disagreements resolved through discussion and arbitration by a third investigator (CA). In addition, DistillerSR AI Classifiers¹⁶ were used to flag potentially missed records from the title and abstract list, which were then manually re-assessed by one investigator (CA).

Putative risk and protective factors were categorized following our previous umbrella review⁸ into four groups: sociodemographic and parental (demographic background and parental characteristics), perinatal (conditions and exposures occurring during pregnancy, delivery, or the immediate neonatal period), later factors (environmental exposures and life events arising after the perinatal period), and antecedents (premorbid deviations in functioning or development that may reflect early expression or risk-modifying processes). Importantly, these categories have only descriptive value and do not affect the meta-analytic computation (i.e., we did not pool factors within the same category to estimate an overall effect size).

Data extraction and risk of bias (quality) assessment

Data extraction was performed independently by two investigators (AM, BP), and discrepancies were resolved by consensus under the supervision of a senior researcher (CA). Risk and protective factors were extracted as defined in the original meta-analyses, without splitting factors into subgroups or combining across similar factors. When both pooled and subgroup results were available, the pooled estimates were preferred because of larger sample sizes. After eligibility assessment, data were extracted at the level of individual studies included in each systematic review or meta-analysis.

For each individual study, we recorded the following variables: first author and year of publication, type of psychotic diagnosis and diagnostic criteria used, factor investigated, number of exposed and non-exposed cases and controls (or, when unavailable, overall sample sizes and the reported measure of association, preferentially unadjusted, with 95% confidence intervals, CIs), and study design (cross-sectional or longitudinal). For continuous variables (means and standard deviations), we assumed a continuous probability distribution and derived the corresponding frequencies of individuals in the groups required to calculate the odds ratios (ORs), following methods previously validated by meta-analyses in the field¹⁷. When data were reported only in graphical form, they were digitized and extracted using WebPlot-Digitizer¹⁸. Data were formatted according to the specifications of the *metaumbrella* R package¹⁹.

For consistency with the previous umbrella review, risk of bias was assessed using A MeaSurement Tool to Assess Systematic Reviews (AMSTAR)²⁰, a validated 11-item instrument that evaluates the methodological quality of systematic reviews of randomized and non-randomized studies. Additionally, risk of bias was also assessed using the latest version of the tool, AMSTAR-2²¹.

Statistical analyses

The meta-analytic calculations were performed using the R package *metaumbrella*, version 4.2.2¹⁹. Random-effects models were fitted using restricted maximum likelihood (REML). When REML analyses failed to converge, the Hartung-Knapp-Sidik-Jonkman method was applied instead²². All results were presented as equivalent ORs (eORs), a standardized metric that allows different effect size measures – e.g., risk ratios (RRs), incidence rate ratios (IRRs) – to be converted into a common OR scale, thereby facilitating comparability across factors⁸. Given that event rates in the included studies were generally below 10%, ORs provide a close approximation to RRs.

We assessed the credibility of each association using pre-established criteria¹¹. Associations were graded as convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), or non-significant. Class I evidence requires more than 1,000 cases, $p < 10^{-6}$, no evidence of small-study effects or excess of significance bias, a prediction interval excluding the null, the largest study nominally significant, and not large heterogeneity (i.e., $I^2 < 50\%$).

Class II requires more than 1,000 cases, $p < 10^{-6}$, and a nominally significant largest study. Class III requires more than 1,000 cases and $p < 10^{-3}$. Class IV requires only $p < 0.05$.

To assess the robustness of our results, three additional analyses were conducted. First, because psychosis is a relatively infrequent condition, we conducted a sensitivity analysis lowering the threshold on the criterion from more than 1,000 cases to 500 cases, as previously applied in studies in this field²³. Second, a sensitivity analysis was conducted for factors classified as class I-II, using only prospective studies (as defined in each individual study) to assess the temporal direction of the association and address potential reverse causation. Third, an additional analysis of all new factors was conducted using the Hartung-Knapp-Sidik-Jonkman method, which provides more conservative CI coverage, particularly when the number of studies is fewer than 10, or the between-study variance is large.

Finally, we estimated the PAF for modifiable (based on clinical

considerations) class I-III factors with reliable prevalence data, quantifying the proportion of disease cases in the population attributable to each risk factor. Under an ideal exposure scenario, the PAF equals the proportional reduction in population-level disease once a risk factor is fully addressed (i.e., totally eradicated, which is a hypothetical scenario)²⁴, which can help prioritize preventive targets.

The PAF was calculated using Levin's formula, which requires the relative risk estimate and the prevalence of the risk factor¹⁰. To obtain robust prevalence estimates with corresponding CIs, we applied a multistep approach previously validated in other studies in the field¹⁰: prevalence data were preferably sourced from the most recent version of the Global Burden of Disease Study; when unavailable, we prioritized global reports of population-level prevalence from international agencies, followed by meta-analyses or systematic reviews, and, as a last option, individual, representative population-based studies, acknowledging this¹⁰ (see also supplementary information).

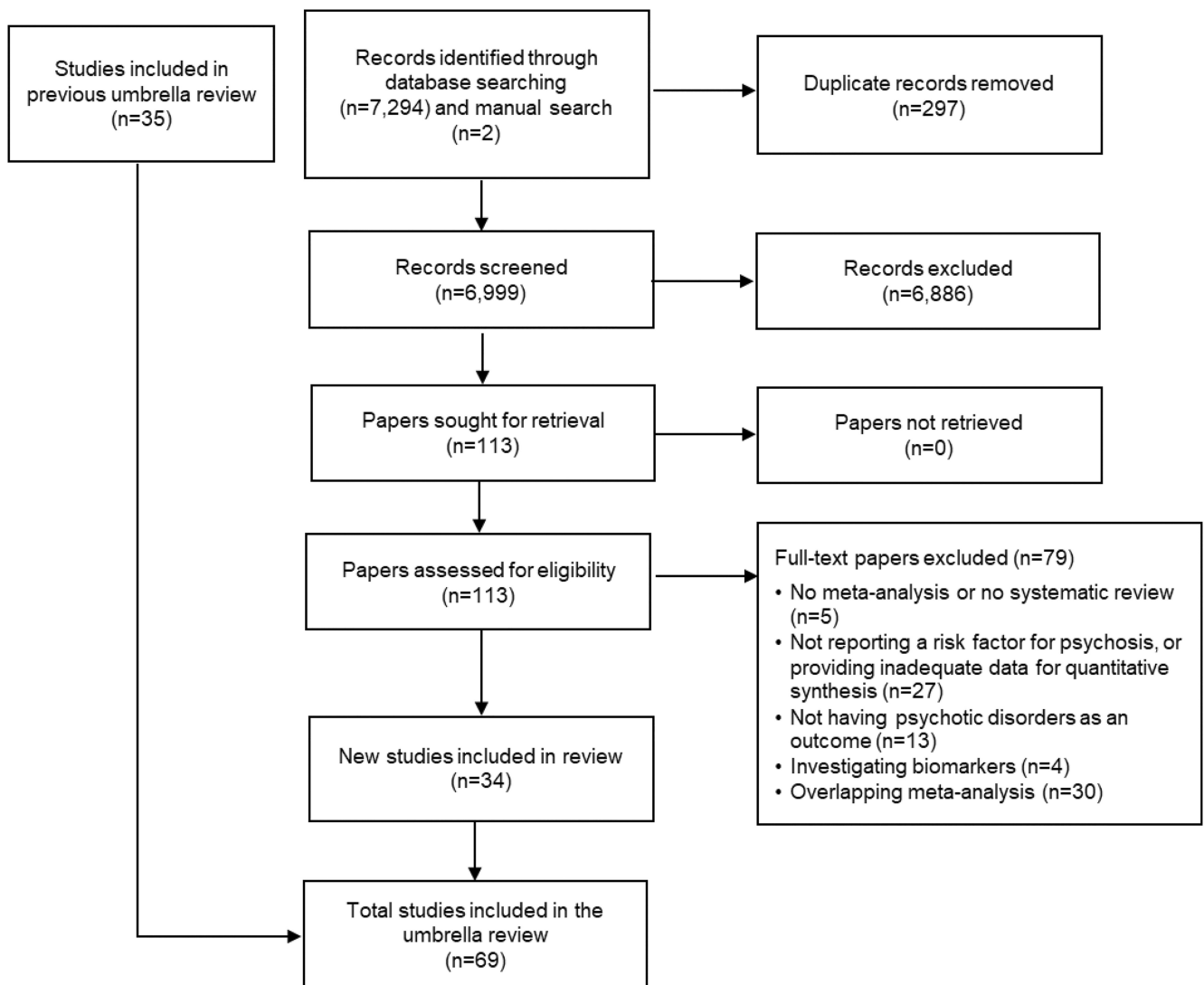


Figure 1 PRISMA 2020 flow chart

RESULTS

Retrieved records

Overall, 6,999 records were identified, of which 113 were screened for eligibility and 34 met inclusion criteria^{17,25-57}, including two studies identified through manual search and consultation with experts in the field^{56,57} (see also supplementary information). In addition, 35 studies were retained from the previous umbrella review⁵⁸⁻⁹², yielding a total of 69 studies included in the umbrella review (see Figure 1 and supplementary information). As in the previous review⁸, the clinical high-risk for psychosis (CHR-P) state was the only putative risk factor for which a healthy control group was not included, instead using help-seeking controls who underwent an assessment for CHR-P but did not meet the relevant criteria⁵⁶.

In total, 69 eligible meta-analyses, comprising 970 individual studies, reported 221 putative risk or protective factors for psychotic disorders. These studies spanned 48 countries across six continents; 351 (36.19%) were longitudinal, and 148 (15.26%) were prospective. Of the 221 factors, 135 were newly identified (101) or updated (34) from the previous review, as more comprehensive meta-analyses with a larger number of eligible studies had since been published, and 86 were confirmed compared to the earlier umbrella review.

Summary of associations

The number of cases exceeded 1,000 for 119 factors (53.85%). Of the 221 factors analyzed, 126 (57.01%) showed a statistically significant effect ($p < 0.05$) under the random-effects model, but only 46 (20.81%) reached the threshold of $p < 10^{-6}$. Large heterogeneity ($I^2 > 50\%$) was observed for 107 factors (48.42%), whereas the 95% prediction interval excluded the null for 40 factors (18.10%). Evidence of small-study effects and excess significance bias was detected in 21 (9.50%) and 29 (13.12%) factors, respectively.

Classification of the level of evidence of associations

Among the 221 factors, six risk factors showed a convincing level of association (class I). Three were sociodemographic or parental factors: Black-African ethnicity in England (OR=4.89, 95% CI: 4.04-5.92); South Asian ethnicity in England (OR=2.15, 95% CI: 1.69-2.73); and paternal age <20 years (OR=1.34, 95% CI: 1.20-1.50). Three were perinatal factors: birthweight under 2,000 g (OR=1.77, 95% CI: 1.48-2.13); birthweight under 2,500 g (OR=1.50, 95% CI: 1.38-1.64); and maternal history of three or more previous pregnancies (OR=1.32, 95% CI: 1.20-1.45) (see Table 1 and Figures 2-3).

For 18 risk factors, there was highly suggestive evidence of association (class II). Five were sociodemographic or parental factors: maternal psychosis (OR=7.64); Black-Caribbean ethnicity in England (OR=5.22); any maternal mental health disorder (OR=4.80); ethnic minority status in a low ethnic density area (IRR=3.71);

and first-generation immigrant status (OR=2.07). Two were later factors: cannabis use 5 to 7 days per week (OR=5.13) and Toxoplasma gondii IgG positivity (OR=1.97). Eleven were antecedents: history of attention-deficit/hyperactivity disorder (ADHD) (OR=5.63); trait anhedonia (eOR=4.41); minor physical anomalies (including anomalies of the mouth: eOR=4.63; head: eOR=2.97; craniofacial region: eOR=2.95; eyes: eOR=2.77; feet: eOR=2.51; peripheral anomalies: eOR=2.84; and total minor physical anomalies: eOR=3.94); premorbid IQ (eOR=0.47), and olfactory identification ability (eOR=0.19) (see Table 1, Figures 2-5, and supplementary information).

There was also suggestive evidence for association (class III) for 22 further risk factors. Ten were sociodemographic or parental factors: parental psychotic disorder (OR=3.83); any paternal mental health disorder (OR=2.94); Black ethnicity in the US (OR=2.49); mixed ethnicity in England (OR=2.28); North African immigrant status in Europe (IRR=2.22); urbanicity (OR=2.19); ethnic minority status in a high ethnic density area (IRR=2.11); second-generation immigrant status (OR=1.84); maternal age over 35 years (OR=1.26); and maternal age under 20 years (OR=1.15). Five were perinatal factors: smoking during pregnancy (OR=1.82); being small for gestational age (OR=1.48); birthweight between 2,500 and 2,999 g (OR=1.22); any maternal infection during pregnancy (OR=1.24); and winter season of birth (OR=1.05). Two were later factors: childhood adversities (OR=2.87); and any hospital-managed infection during childhood (OR=1.31). Five were antecedents: childhood social withdrawal (eOR=2.91); minor physical anomalies of the hand (eOR=2.88) and ears (eOR=2.79); non-right handedness (OR=1.58); and general academic achievement (eOR=0.61) (see Table 1 and Figures 2-5).

Additionally, we identified four protective factors with suggestive (class III) evidence: maternal age between 25 and 29 years (OR=0.92) or between 20 and 24 years (OR=0.93); and birthweight between 3,500 and 3,999 g (OR=0.90) or over 4,000 g (OR=0.86) (see Table 1 and Figures 2-3).

There was weak (class IV) evidence for a total of 75 factors, including cannabis use between 1 and 4 times per month, psychotic-like experiences, CHR-P state, obstetric complications, and neurological soft signs. The evidence was non-significant for 96 factors, including methamphetamine use disorder (see supplementary information).

Stability of the evidence across sensitivity analyses

After lowering the threshold for the number of cases from more than 1,000 to 500 in the sensitivity analysis, two factors were upgraded from weak (class IV) to highly suggestive evidence (class II): CHR-P state (RR=9.09) and neurological soft signs (eOR=7.59).

Sensitivity analyses restricted to prospective studies could not be conducted for nine associations initially categorized as class I-II in the overall analysis (cannabis use 5 to 7 days per week; minor physical anomalies of the mouth, head, craniofacial region, peripheral region, eyes and feet; trait anhedonia, and olfactory identification ability), and neurological soft signs, as no prospec-

Table 1 Class I-III associations of risk and protective factors with psychotic disorders, stratified by decreasing class of evidence and magnitude

	n	Effect size (95% CI)	Features used for the classification of the level of evidence							eOR	CE
			N	p random-effects	I ²	PI (95% CI)	SSE/ESB	LS			
Sociodemographic and parental factors											
Black-African ethnicity in England	8	RR: 4.891 (4.042-5.919)	2,228	8.15 × 10 ⁻⁶⁰	3%	3.500-6.835	No/No	Yes	4.891	I	
South Asian ethnicity in England	6	RR: 2.148 (1.69-2.731)	2,414	4.27 × 10 ⁻¹⁰	31%	1.568-2.943	No/No	Yes	2.148	I	
Paternal age <20 years	12	OR: 1.339 (1.198-1.496)	17,677	2.73 × 10 ⁻⁷	12%	1.181-1.516	No/No	Yes	1.339	I	
Maternal psychosis	6	OR: 7.645 (6.389-9.148)	33,979	3.10 × 10 ⁻⁹	62%	4.845-12.063	No/No	Yes	7.645	II	
Black-Caribbean ethnicity in England	10	RR: 5.224 (4.052-6.734)	2,580	2.82 × 10 ⁻³⁷	64%	2.443-11.169	No/No	Yes	5.224	II	
Maternal mental health disorder (any)	8	OR: 4.800 (2.988-7.711)	34,322	8.88 × 10 ⁻¹¹	96%	0.985-23.395	No/No	Yes	4.800	II	
Ethnic minority in low ethnic density area	5	IRR: 3.71 (2.47-5.58)	1,328	3.1 × 10 ⁻¹⁰	77%	0.950-14.430	Yes/No	Yes	3.71	II	
First-generation immigrant	19	RR: 2.069 (1.736-2.465)	184,589	4.37 × 10 ⁻¹⁶	95%	0.946-4.523	No/No	Yes	2.069	II	
Parental psychotic disorder	26	RR: 3.830 (2.18-6.72)	15,917	3.17 × 10 ⁻⁶	85%	0.317-46.140	No/No	Yes	3.830	III	
Paternal mental health disorder (any)	5	OR: 2.940 (1.805-4.788)	5,231	0.467 × 10 ⁻⁶	89%	0.637-13.574	No/No	Yes	2.940	III	
Black ethnicity in US	5	OR: 2.493 (1.671-3.719)	3,785	7.56 × 10 ⁻⁶	90%	0.738-8.424	No/No	Yes	2.493	III	
Mixed ethnicity in England	3	RR: 2.278 (1.426-3.638)	1,886	5.68 × 10 ⁻⁴	0%	0.815-6.367	No/No	Yes	2.278	III	
North African immigrant in Europe	12	IRR: 2.22 (1.58-3.12)	2,577	4.2 × 10 ⁻⁶	65%	0.77-6.41	No/NA	Yes	2.22	III	
Urbanicity	8	OR: 2.19 (1.55-3.09)	45,791	8.9 × 10 ⁻⁵	99%	0.62-7.77	No/No	Yes	2.19	III	
Ethnic minority in high ethnic density area	5	IRR: 2.11 (1.39-3.20)	1,328	4.3 × 10 ⁻⁴	58%	0.57-7.81	No/No	Yes	2.11	III	
Second-generation immigrant	10	RR: 1.845 (1.417-2.401)	140,925	5.30 × 10 ⁻⁶	96%	0.704-4.832	No/No	Yes	1.845	III	
Maternal age between 25 and 29 years	32	OR: 0.922 (0.896-0.947)	19,337	1.18 × 10 ⁻⁶	0%	0.891-0.953	No/No	Yes	0.922	III	
Maternal age >35 years	35	OR: 1.265 (1.102-1.453)	60,495	8.48 × 10 ⁻⁴	96%	0.729-2.197	No/Yes	Yes	1.265	III	
Maternal age <20 years	34	OR: 1.147 (1.058-1.244)	22,153	9.34 × 10 ⁻⁴	4%	0.939-1.401	No/No	Yes	1.147	III	
Maternal age between 20 and 24 years	31	OR: 0.932 (0.901-0.963)	19,286	3.56 × 10 ⁻⁵	0%	0.9-0.965	No/No	No	0.932	III	
Perinatal factors											
Birthweight under 2,000 g	17	OR: 1.773 (1.476-2.129)	7,492	9.38 × 10 ⁻¹⁰	0%	1.452-2.164	No/No	Yes	1.773	I	
Birthweight under 2,500 g	22	OR: 1.505 (1.377-1.644)	11,792	1.58 × 10 ⁻¹⁹	0%	1.369-1.654	No/No	Yes	1.505	I	
Three or more previous pregnancies	10	OR: 1.317 (1.197-1.449)	3,133	1.70 × 10 ⁻⁸	7%	1.179-1.470	No/No	Yes	1.317	I	
Smoking during pregnancy	7	OR: 1.820 (1.346-2.462)	1,798	1.01 × 10 ⁻⁴	53%	0.844-3.927	No/No	No	1.820	III	
Being small for gestational age	10	OR: 1.477 (1.256-1.737)	13,976	2.46 × 10 ⁻⁶	36%	1.029-2.119	No/No	Yes	1.477	III	
Birthweight between 2,500 and 2,999 g	14	OR: 1.224 (1.156-1.296)	8,169	2.53 × 10 ⁻⁶	0%	1.139-1.316	No/No	Yes	1.224	III	
Maternal infection during pregnancy (any)	3	OR: 1.239 (1.097-1.399)	12,142	5.53 × 10 ⁻⁴	32%	0.852-1.800	No/No	No	1.239	III	
Winter season of birth	35	OR: 1.050 (1.029-1.072)	10,065,331	2.43 × 10 ⁻⁶	17%	0.987-1.117	No/No	No	1.050	III	
Birthweight between 3,500 and 3,999 g	15	OR: 0.896 (0.852-0.943)	8,169	2.68 × 10 ⁻⁵	0%	0.847-0.948	No/No	Yes	0.896	III	
Birthweight over 4,000 g	15	OR: 0.857 (0.800-0.919)	8,201	1.35 × 10 ⁻⁵	0%	0.794-0.925	No/No	Yes	0.857	III	
Later factors											
Cannabis use 5 to 7 days per week	4	OR: 5.130 (3.283-8.047)	1,257	7.98 × 10 ⁻¹³	69%	0.820-31.853	No/No	Yes	5.130	II	
Toxoplasma gondii IgG+	43	OR: 1.970 (1.684-2.326)	7,628	1.67 × 10 ⁻¹⁶	60%	0.870-4.450	No/Yes	Yes	1.970	II	

Table 1 Class I-III associations of risk and protective factors with psychotic disorders, stratified by decreasing class of evidence and magnitude (continued)

	n	Effect size (95% CI)	Features used for the classification of the level of evidence							
			N	p random-effects	I ²	PI (95% CI)	SSE/ESB	LS	eOR	CE
Childhood adversities	20	OR: 2.87 (2.07-3.98)	2,363	2.50×10^{-14}	77%	0.75–11.01	No/Yes	No	2.87	III
Hospital-managed infection during childhood (any)	5	OR: 1.31 (1.12-1.53)	13,572	4.55×10^{-4}	87%	0.75–2.29	No/Yes	Yes	1.31	III
<i>Antecedents</i>										
Clinical high-risk for psychosis	22	RR: 9.09 (6.18-13.37)	609	3.76×10^{-29}	22%	3.157–26.156	Yes/Yes	Yes	9.09	II*
Neurological soft signs	7	g: 1.83 (1.28-2.38)	564	7.7×10^{-11}	93%	–0.15 to 3.81	Yes/No	Yes	7.59	II*
History of ADHD	8	OR: 5.631 (3.915-8.098)	12,683	1.15×10^{-20}	95%	1.881-16.854	No/No	Yes	5.631	II
Minor physical anomalies (mouth)	19	g: 0.845 (0.700-0.989)	1,525	1.71×10^{-30}	72%	0.289-1.400	No/No	Yes	4.635	II
Minor physical anomalies (total)	37	g: 0.756 (0.619-0.893)	3,290	3.54×10^{-27}	85%	0.100-1.018	Yes/Yes	Yes	3.944	II
Trait anhedonia	44	g: 0.820 (0.72-0.92)	1,601	9.2×10^{-57}	43%	0.37-1.27	No/Yes	Yes	4.415	II
Minor physical anomalies (head)	15	g: 0.600 (0.440-0.761)	1,243	2.39×10^{-13}	75%	0.015-1.186	No/Yes	Yes	2.973	II
Minor physical anomalies (craniofacial)	19	g: 0.597 (0.387-0.806)	1,865	2.40×10^{-8}	84%	–0.330 to 1.524	Yes/Yes	Yes	2.954	II
Minor physical anomalies (peripheral)	19	g: 0.573 (0.416-0.731)	1,594	9.75×10^{-13}	76%	–0.073 to 1.219	No/No	Yes	2.837	II
Minor physical anomalies (eyes)	23	g: 0.559 (0.445-0.672)	2,262	4.58×10^{-22}	64%	0.100-1.018	No/No	Yes	2.768	II
Minor physical anomalies (feet)	13	g: 0.508 (0.371-0.645)	1,063	3.75×10^{-13}	56%	0.074-0.941	No/No	Yes	2.512	II
Olfactory identification ability	55	g: –0.91 (–1.05 to –0.78)	1,703	4.00×10^{-41}	67%	–1.72 to –0.10	Yes/Yes	Yes	0.193	II
Premorbid IQ	16	g: –0.42 (–0.52 to –0.33)	4,459	1.10×10^{-18}	73%	–0.70 to –0.14	No/No	Yes	0.471	II
Childhood social withdrawal	15	g: 0.59 (0.33-0.85)	1,810	6.40×10^{-6}	93%	–0.44 to 1.62	No/No	Yes	2.91	III
Minor physical anomalies (hand)	15	g: 0.584 (0.345-0.822)	1,471	1.63×10^{-6}	90%	–0.402 to 1.569	No/No	Yes	2.88	III
Minor physical anomalies (ears)	22	g: 0.566 (0.354-0.778)	1,893	1.72×10^{-7}	86%	–0.436 to 1.567	Yes/Yes	No	2.79	III
Non-right handedness	41	OR: 1.58 (1.35-1.86)	2,652	2.00×10^{-8}	21%	0.99-2.54	No/No	No	1.58	III
General academic achievement	10	g: –0.271 (–0.426 to 0.116)	4,990	6.02×10^{-4}	92%	–0.82 to 0.278	No/No	Yes	0.61	III

CE – class of evidence, PI – prediction interval, SSE – small study effect, ESB – excess significance bias, LS – largest study with significant effects, eOR – equivalent odds ratio, RR – risk ratio, OR – odds ratio, IRR – incidence rate ratio, NA – not assessable, Ig – immunoglobulin, ADHD – attention-deficit/hyperactivity disorder. *After sensitivity analysis lowering the threshold for number of cases from more than 1,000 to 500.

tive studies were available.

Among the class I factors, three retained their level of evidence: birthweight under 2,000 g, birthweight under 2,500 g, and paternal age under 20 years. The remaining three class I factors were downgraded to class III (maternal history of three or more previous pregnancies) or class IV (Black-African ethnicity in England, and South Asian ethnicity in England), due to large heterogeneity, a low number of cases, or dilution of the p-value (see Table 2).

Within class II factors, only maternal psychosis, history of ADHD, CHR-P state, any maternal mental health disorder, and first-generation immigrant status maintained their level of evidence. The others were downgraded either to class IV (Black-Caribbean ethnicity in England, ethnic minority status in low ethnic density areas, and Toxoplasma gondii IgG positivity), or to non-significant (total minor physical anomalies) (see Table 2).

When re-analyzed using the Hartung-Knapp-Sidik-Jonkman

method, only three of the factors initially classified as class I retained their level of evidence: Black-African ethnicity in England, birthweight under 2,000 g, and birthweight under 2,500 g. Among class II factors, six remained stable: Black-Caribbean ethnicity in England, first-generation immigrant status, Toxoplasma gondii IgG positivity, minor physical anomalies affecting the mouth and the eyes, and total minor physical anomalies (see supplementary information).

Meta-analytic PAF of risk factors

Table 3 presents the meta-analytic PAFs for each potentially preventable class I-III risk factor with robust prevalence data, ordered by magnitude, alongside their prevalence estimates. Several class I-II risk factors were deemed not potentially modifiable and

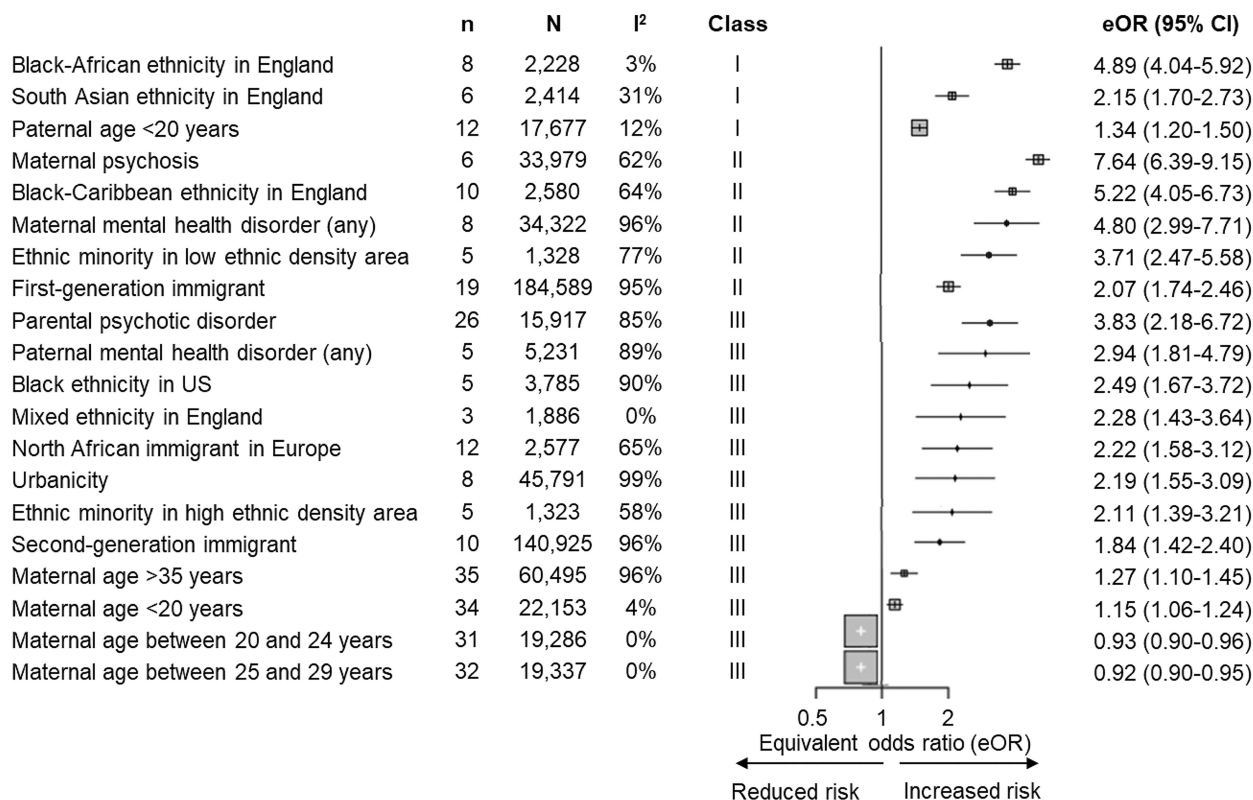


Figure 2 Forest plot for class I-III risk and protective sociodemographic and parental factors

thus excluded from the PAF analysis. All PAFs were calculated using global prevalence estimates, except for cannabis use (5 to 7 days per week), for which the most robust and representative prevalence data were available from US populations (PAFs stratified by country are provided in the supplementary information).

The largest PAFs (>10%) were observed for childhood adversities (40.69%, 95% CI: 28.03-52.54), *Toxoplasma gondii* IgG positivity (20.47%, 95% CI: 14.57-26.57), cannabis use (5 to 7 days per

week) (12.75%, 95% CI: 5.05-22.12), and CHR-P state (12.68%, 95% CI: 5.27-21.87, after sensitivity analysis lowering the threshold for number of cases). Smaller but still significant PAFs were found for being small for gestational age (7.20%, 95% CI: 3.91-10.82), birthweight under 2,500 g (6.88%, 95% CI: 5.16-8.72), birthweight under 2,000 g (4.30%, 95% CI: 2.64-6.19); maternal age over 35 years (3.84%, 95% CI: 1.49-6.36) or under 20 years (1.33%, 95% CI: 0.52-2.18); smoking during pregnancy (1.20%, 95% CI: 0.00-3.34), and

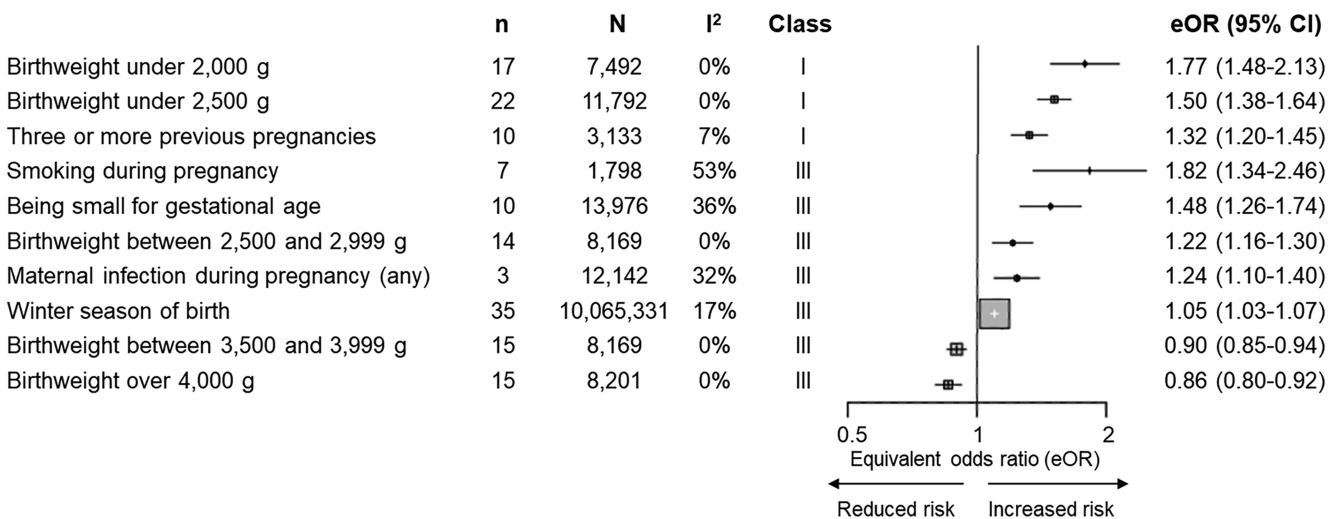


Figure 3 Forest plot for class I-III risk and protective perinatal factors

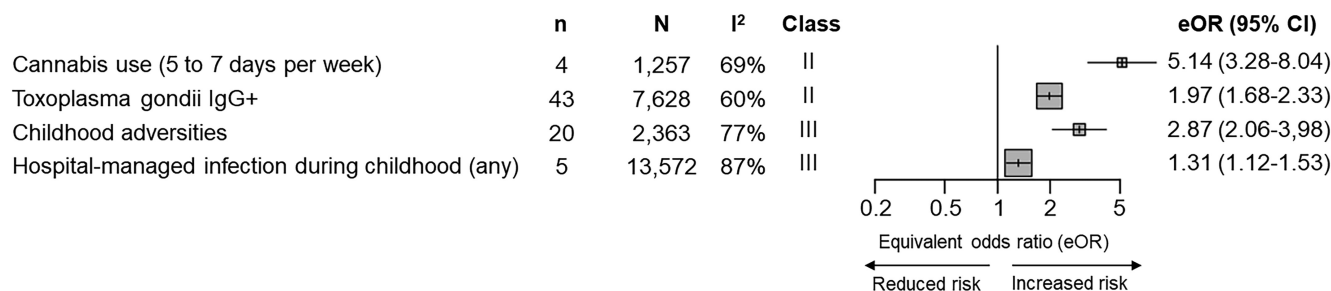


Figure 4 Forest plot for class I-III risk and protective later factors. Ig – immunoglobulin.

paternal age under 20 years (0.83%; 95% CI: 0.48-1.21).

Study quality

The AMSTAR scores ranged from 3/11 to 11/11, with a mean score of 7.73±2.09 out of 11. The main factor lowering the AMSTAR rating was the absence of a pre-registered protocol or other *a priori* design. Domain-level scores for AMSTAR and AMSTAR-2 are reported in the supplementary information.

DISCUSSION

To the best of our knowledge, this is the largest quantitative evidence synthesis of risk and protective factors for psychosis adopting an umbrella review approach with a robust evidence classification. We appraised 970 individual studies covering 221 putative risk or protective factors investigated globally, and conducted

several sensitivity analyses, including estimates of PAFs. We discuss below the significance of all class I-II factors identified by this study, and of some class III factors, based on clinical relevance.

The first finding of our analysis confirms several sociodemographic variables with strong evidence of association with psychosis, including Black-African (class I), South Asian (class I) and Black-Caribbean (class II) ethnicities in England. Other class III risk factors, while showing lower levels of association, further reinforce this finding, such as Black ethnicity in the US, mixed ethnicity in England, and North African immigrant status in Europe. Members of these communities are disproportionately exposed to discrimination and social adversity^{93,94}, which can increase psychosis risk via various pathways, including feelings of social defeat in those exposed to bullying and abuse^{95,96}, decreased self-esteem, and negative beliefs about the self, the world and others^{97,98}.

The effect is often amplified in areas of low ethnic density, itself a factor with highly suggestive (class II) evidence of association, supporting the notion that social isolation within the broader community contributes more than ethnicity *per se*. In addition, the cluster-

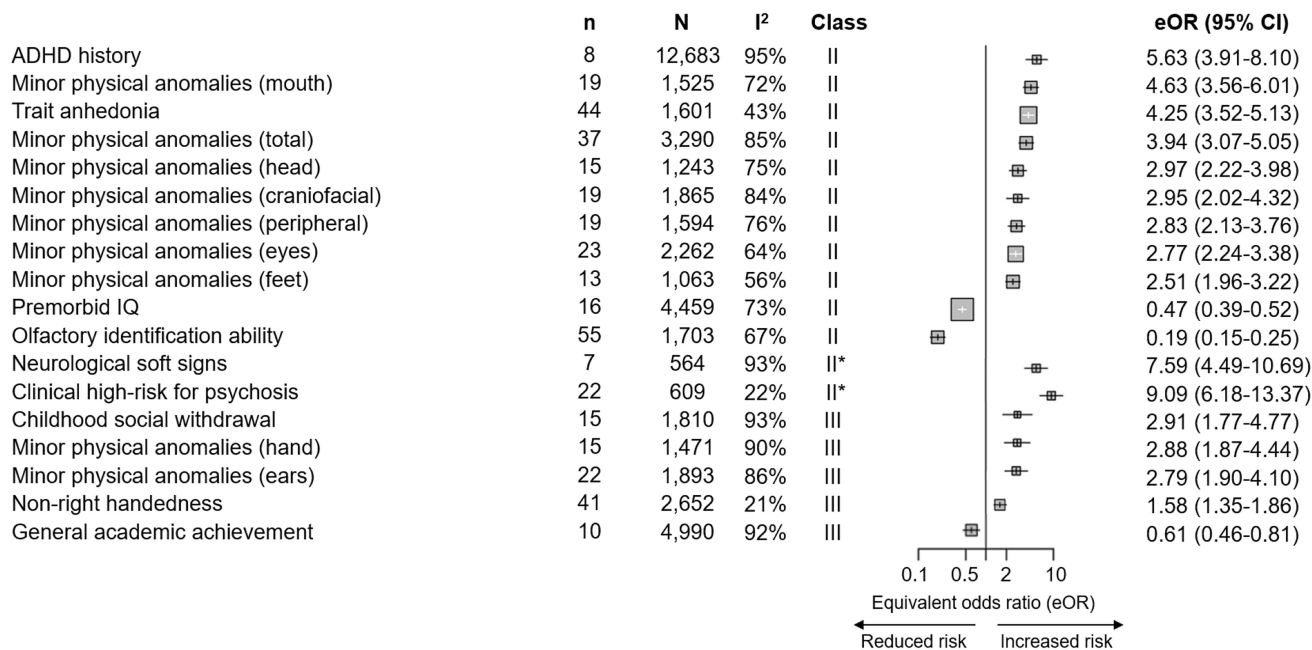


Figure 5 Forest plot for class I-III risk and protective antecedent factors. ADHD – attention-deficit/hyperactivity disorder. *After sensitivity analyses lowering the threshold for number of cases from more than 1,000 to 500.

Table 2 Sensitivity analysis for the associations of class I-II factors restricted to prospective studies

	CE	n	Effect size (95% CI)	N >1000	Features used for classification of the level of evidence						
					p random-effects	I ²	PI (95% CI)	SSE/ESB	LS	eOR	CES
Black-African ethnicity in England	I	2	RR: 5.77 (4.21-7.93)	No	1.88×10^{-27}	0%	0.74-44.96	NA/No	Yes	5.77	IV
South Asian ethnicity in England	I	2	RR: 2.04 (1.13-3.72)	Yes	0.019	47%	0.01-483.66	NA/No	Yes	2.04	IV
Birthweight under 2,000 g	I	5	OR: 1.80 (1.49-2.18)	Yes	1.16×10^{-9}	0%	1.38-2.38	No/No	Yes	1.80	I
Birthweight under 2,500 g	I	8	OR: 1.54 (1.40-1.69)	Yes	1.23×10^{-19}	0%	1.38-1.72	No/No	Yes	1.54	I
Paternal age <20 years	I	7	OR: 1.39 (1.23-1.57)	Yes	1.69×10^{-7}	31%	1.19-1.62	No/No	Yes	1.39	I
Three or more previous pregnancies	I	5	OR: 1.30 (1.16-1.45)	Yes	4.37×10^{-6}	0%	1.11-1.52	Yes/No	Yes	1.30	III
Clinical high-risk for psychosis	II*	22	RR: 9.09 (6.18-13.37)	No	3.76×10^{-29}	22%	3.157-26.156	Yes/Yes	Yes	9.09	II
Maternal psychosis	II	6	OR: 7.65 (6.39-9.15)	Yes	3.10×10^{-9}	62%	4.85-12.06	No/No	Yes	7.65	II
Neurological soft signs	II*	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
ADHD history	II	5	OR: 4.53 (2.87-7.15)	Yes	9.55×10^{-11}	93%	1.32-15.54	No/No	Yes	4.53	II
Black-Caribbean ethnicity in England	II	2	RR: 6.77 (3.91-11.70)	No	7.65×10^{-12}	89%	0.02-2,505.26	NA/No	Yes	6.77	IV
Cannabis use 5 to 7 days per week	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Maternal mental health disorder (any)	II	8	OR: 4.80 (2.99-7.71)	Yes	8.88×10^{-11}	96%	0.99-23.40	No/No	Yes	4.80	II
Minor physical anomalies (mouth)	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Trait anhedonia	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Minor physical anomalies (total)	II	2	g: 0.38 (-0.17 to 0.94)	No	0.178	80%	0-78,258	NA/No	No	2.00	n.s.
Ethnic minority in low ethnic density area	II	3	IRR: 4.27 (1.89-9.68)	No	4.9×10^{-4}	82%	0-75,335	Yes/No	Yes	4.27	IV
Minor physical anomalies (head)	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Minor physical anomalies (craniofacial)	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Minor physical anomalies (peripheral)	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Minor physical anomalies (eyes)	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Minor physical anomalies (feet)	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
First-generation immigrant	II	10	RR: 1.91 (1.58-2.32)	Yes	3.53×10^{-11}	95%	0.94-3.89	No/No	Yes	1.91	II
Toxoplasma gondii IgG+	II	2	OR: 1.64 (1.09-2.47)	No	1.83×10^{-2}	0%	0.12-23.38	NA/No	Yes	1.64	IV
Olfactory identification ability	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC

CE – class of evidence, PI – prediction interval, SSE – small study effect, ESB – excess significance bias, LS – largest study with significant effects, eOR – equivalent odds ratio, CES – class of evidence after sensitivity analysis, RR – risk ratio, OR – odds ratio, IRR – incidence rate ratio, NA – not assessable, Ig – immunoglobulin, ADHD – attention-deficit/hyperactivity disorder, n.s. – non-significant, NC – not calculable (no prospective studies to be analyzed). *After sensitivity analysis lowering the threshold for number of cases from more than 1,000 to 500.

ing of minoritized ethnic groups in socioeconomically deprived urban areas, together with barriers in education⁹⁹, housing¹⁰⁰, and employment¹⁰¹, may further compound the risk. Related to this, first-generation immigrant status has also been confirmed as a risk factor (class II) for psychosis.

Immigrant status often consists of a combination of pre-migra-

tion adversities (e.g., trauma, persecution, displacement)¹⁰², post-migration stressors (acculturative stress, language barriers, legal and housing precarity)⁹⁶, and reduced social capital in the host context¹⁰³. This elevated risk does not dissipate within the first generation; second-generation immigrant status also emerged as a risk factor for psychosis, albeit with lower evidence (class III), con-

Table 3 Meta-analytic population attributable fractions (PAFs) for class I-III modifiable risk factors

	PAF (95% CI)	Prevalence (95% CI)	Effect size (95% CI)	CE
Childhood adversities	40.69% (28.03-52.54)	38.80% (38.79-38.81)	OR: 2.870 (2.070-3.980)	III
Toxoplasma gondii IgG+	20.47% (14.57-26.57)	31.00% (27.80-34.20)	OR: 1.970 (1.684-2.326)	II
Cannabis use (5 to 7 days per week)	12.75% (5.05-22.12)	10.40% (9.21-11.51)	OR: 5.130 (3.283-8.047)	II
Clinical high-risk for psychosis	12.68% (5.27-21.87)	1.70% (1.00-2.90)	RR: 9.087 (6.177-13.366)	II*
Being small for gestational age	7.20% (3.91-10.82)	16.34% (14.86-18.94)	OR: 1.477 (1.256-1.737)	III
Birthweight under 2,500 g	6.88% (5.16-8.72)	14.70% (13.66-16.13)	OR: 1.773 (1.476-2.129)	I
Birthweight under 2,000 g	4.30% (2.64-6.19)	5.80% (5.20-6.40)	OR: 1.505 (1.377-1.644)	I
Maternal age >35 years	3.84% (1.49-6.36)	15.09% (15.08-15.10)	OR: 1.265 (1.102-1.453)	III
Maternal age <20 years	1.33% (0.52-2.18)	9.23% (9.23-9.23)	OR: 1.147 (1.058-1.244)	III
Smoking during pregnancy	1.20% (0.00-3.34)	1.70% (0.00-4.50)	OR: 1.820 (1.346-2.462)	III
Paternal age <20 years	0.83% (0.48-1.21)	2.50% (2.49-2.51)	OR: 1.339 (1.198-1.496)	I

All PAFs were calculated using global prevalence estimates, except for cannabis use, for which prevalence data from US populations were used. CE – class of evidence, OR – odds ratio, RR – risk ratio, Ig – immunoglobulin. *After sensitivity analysis lowering the threshold for number of cases from more than 1,000 to 500.

sistent with inter-generational effects of persistent minority stressors and structural inequalities¹⁰⁴.

The second finding is that parental characteristics and conditions constitute another cluster of risk factors for psychosis. For the first time, paternal age under 20 years has emerged as a risk factor with convincing evidence (class I), an association likely reflecting converging genetic, perinatal and social mechanisms, that has also been described in bipolar disorder¹⁰⁵. Adolescent fatherhood correlates with socioeconomic deprivation¹⁰⁶, unstable partnerships, higher rates of paternal and maternal substance use and psychopathology¹⁰⁷, younger maternal age, and reduced antenatal care¹⁰⁸, many of which also constitute independent risk factors for psychosis.

Regarding maternal age, we found that ages 20-29 years were protective (class III), while ages <20 or >35 were risk factors (class III). This finding is interesting and may indicate a non-linear (U-shaped) relationship, with elevated risk at younger and older extremes, which has also been described in large cohort studies¹⁰⁹. In settings where parenthood is increasingly delayed, the proportion of births falling within this low-risk window (i.e., 20-29 years) is shrinking¹¹⁰. Advanced maternal age often co-occurs with factors that heighten offspring vulnerability, such as cumulative environmental and medical exposures¹¹¹, while very young maternal age frequently correlates with socioeconomic adversity¹¹².

Although the neurodevelopmental risk for psychosis linked to advanced parental age is often hypothesized to operate through *de novo* mutations and perinatal complications^{113,114}, risk at the youngest end of the spectrum is more plausibly driven by contextual pathways, albeit genetic factors may also contribute. Notably, most available evidence on parental age and psychosis risk derives from high-income settings¹⁷, leaving essential gaps regarding whether these associations hold – or differ – in low- and middle-income countries, where patterns of maternal age, obstetric care, and social adversity may diverge substantially.

Additionally, both a history of maternal psychosis and a history

of any maternal mental health disorder emerged as risk factors (class II), with very large ORs. These associations highlight not only the role of family liability to psychotic disorders, but also a marked transdiagnostic heritable risk across mental disorders⁵⁷. The history of any paternal mental health disorder also constituted a risk factor for psychosis, although with a lower strength of association (class III). These findings may reflect a combination of genetic architecture and correlated prenatal and early-life environments, alongside later factors such as caregiving stress and/or childhood adversity¹¹⁵.

A third finding of this umbrella review, also in relation to the above, is the uncovering, for the first time, of a cluster of perinatal factors with convincing evidence, including low birthweight (class I) and a maternal history of three or more previous pregnancies (class I). There was a consistent negative relationship between birthweight and the risk of psychosis: infants weighing under 2,000 g at birth had higher ORs than those weighing under 2,500 g. At the other end of the spectrum, birthweights above 3,500 g may act as a protective factor, although the evidence of association is weaker (class III). Again, the positive protective effects increased progressively from 3,500 g to 3,999 g and over 4,000 g. Reduced birthweight is often considered a proxy for intrauterine growth restriction, a broad marker of the fetal environment at a time when adverse changes can induce long-lasting alterations in organ development, including the central nervous system¹¹⁶. However, the possibility of genetic confounding cannot be disregarded¹¹⁷. It is also important to note that low birthweight is also associated with other perinatal variables that we confirmed as independent risk factors for psychosis – albeit supported by weaker evidence – such as maternal smoking during pregnancy¹¹⁸, being small for gestational age, and maternal infections during pregnancy¹¹⁹ (all class III). These results confirm for the first time at the umbrella review level that the prenatal period constitutes the first developmental step towards psychosis¹²⁰.

A fourth core finding is the emergence of near-daily cannabis

use (5–7 days per week) as a risk factor (class II), with an OR above 5, one of the strongest associations identified across all factors. While the psychotogenic potential of cannabis is well established, this contrasts with the previous umbrella review⁸, where cannabis use only reached class IV evidence. A different operationalization of heavy cannabis use, along with several other elements, may account for this robust association: larger, higher-quality datasets; clearer exposure gradients; and improved confounder control. Notably, we observed a graded pattern: strong associations for near-daily use (OR=5), modest effects (OR<2) with weak evidence for weekly use (1–4 days per month), and no significant association for occasional use, consistent with dose-response and supporting causal plausibility¹²¹.

The psychotogenic effects of delta-9-tetrahydrocannabinol (THC) are modulated by dose and frequency of use, which is extensively documented pre-clinically¹²² and clinically¹²³. In this context, the rising potency of cannabis products¹²⁴ represents a major public health concern, as daily consumption of these compounds likely increases psychosis risk even further¹²⁵. Their mechanism of action may be mediated by altered dopamine activity in the mesostriatal pathway¹²⁶.

A fifth finding is that a history of ADHD emerged as a factor with a highly suggestive (class II) level of association with psychosis. This may reflect shared neurodevelopmental vulnerabilities, given that both ADHD and psychotic disorders have been linked to alterations in dopaminergic and fronto-striatal circuits¹²⁷. ADHD could also be considered an early developmental marker within a broader trajectory of neurodevelopmental disturbance that culminates in psychosis for a subset of individuals¹²⁸. Furthermore, part of the association may be attributable to diagnostic misclassification, particularly in early stages where symptoms overlap, including executive dysfunction, agitation or impulsiveness, particularly in young people. In addition, ADHD is frequently associated with conduct problems, academic failure¹²⁹, and substance misuse¹³⁰, all of which are known risk factors for psychosis and may partly mediate the association. Furthermore, it is not fully clear whether stimulant medication – the first-line pharmacological treatment for ADHD – can modulate the risk for psychotic symptoms and psychotic disorders¹³¹.

A sixth cluster of later factors and antecedents has emerged as class II risk factors. These include *Toxoplasma gondii* IgG positivity, trait anhedonia, olfactory identification ability, premorbid IQ, and seven factors related to minor physical anomalies. Among these, the only potentially modifiable factor is *Toxoplasma gondii* IgG positivity. This intracellular protozoan parasite, which infects approximately one-third of the global population, is typically acquired by ingesting contaminated meat or by exposure to oocysts shed by an infected cat¹³². While the infection is usually asymptomatic in immunocompetent individuals, the available evidence suggests its association with psychotic disorders, potentially via dysregulation of the hypothalamic-pituitary-adrenal axis¹³³ and alterations in dopaminergic signaling¹³⁴.

Taken together, the class II antecedent factors indicate a coherent neurodevelopmental liability profile. Subtle deviations apparent in early life, including lower premorbid IQ and minor physical

anomalies, suggest perturbations in embryonic and early cortical development¹³⁵. These developmental imprints appear to converge with early-emerging alterations in affect and sensory processing. Although largely non-modifiable, these factors strengthen risk stratification by capturing complementary factors of vulnerability to psychosis.

An innovation of the current paper is the introduction of PAF estimates for class I–III factors. Three factors showed a PAF over 10%. The largest PAF was observed for childhood adversities (40.69%). These adversities are not only linked to the onset of severe mental illness¹³⁶, but also to a wide range of chronic somatic conditions, including cancer and cardiovascular disease¹³⁷, as well as poorer educational attainment and employment prospects¹³⁸. Severe forms of abuse – such as emotional, physical and sexual abuse – carry substantial risk^{139,140}. Moreover, physical and emotional neglect is also detrimental, not only for psychosis onset¹⁴¹, but also for being associated with more pronounced negative symptoms and impairment of social functioning^{142,143}. These findings highlight the need to prevent, reduce and remediate childhood adversities, fostering safe, stable and nurturing relationships and environments for all children across multiple mental disorders and somatic conditions¹⁴⁴.

Notably, the second largest contributor by magnitude was IgG seropositivity to *Toxoplasma gondii*, with a PAF of 20.47%. This also emerged in our previous analysis⁸ as a robust risk factor for psychosis. The third largest PAF was associated with near-daily cannabis use (12.75%). Although the overall global prevalence of such high-frequency consumption is relatively low, there is wide variability across different settings (see supplementary information for our analysis stratifying the PAF across various countries worldwide).

One additional factor, CHR-P state, was supported by highly suggestive (class II) evidence in our sensitivity analyses. This state, based on subclinical symptoms of psychosis, has been consistently associated with a 20% risk for psychosis at two years^{145,146} and up to 46% at 14 years¹⁴⁷. Overall, it resulted in the largest association in this umbrella review (OR=9.09), translating into a clinically meaningful large PAF of 12.68%. The CHR-P approach, therefore, is confirmed as an established preventive strategy for reducing the risk of psychosis onset in help-seeking young people, with increasing implementation also outside Western countries¹⁴⁸.

Preventive approaches in CHR-P individuals are particularly suited to complement population-level preventive strategies, for example, those targeting cannabis abuse¹⁴⁹. Recent meta-analyses found no evidence to favor any active intervention for preventing the onset of psychosis¹⁴⁶, likely because of large uncertainty and beneficial effects of the needs-based interventions that are routinely offered to these individuals. Randomized controlled trials involving novel therapeutics (e.g., cannabidiol, pomaglumetad, MT1988¹⁵⁰) are being planned to refine novel preventive approaches for this group.

Although this updated umbrella review identified a considerable number of factors with convincing or highly suggestive evidence of association with psychotic disorders, several expected risk factors did not emerge or showed only weak or non-significant evi-

dence. This was the case, for instance, for substances of abuse other than cannabis, or for broader determinants such as air pollution and climate change, which have been linked to poor mental health outcomes¹⁵¹. This likely reflects a combination of limited statistical power across numerous primary studies – often small samples with few transitions to psychosis – together with substantial between-study heterogeneity and inconsistencies. Also, recent individual studies reporting on very large associations between substance use and schizophrenia-spectrum disorders from representative cohorts have not yet been included in systematic reviews¹⁵². In addition, exposure misclassification and low exposure contrast – such as reliance on ecological proxies for some outcomes, such as air pollution, rather than individual dose estimates – likely diluted true effects. Moreover, some factors that had attained class I evidence in our previous umbrella review⁸ – most notably the CHR-P state – have now been downgraded to lower evidence classes, owing to the emergence of newer, more heterogeneous data that prevents these associations from meeting the criteria for a convincing association.

The implications of this updated umbrella review are multiple. Taken together, these findings sharpen the epidemiological map of psychosis risk. By quantifying both the magnitude and credibility of the associations and, where possible, their PAFs, this updated umbrella review helps distinguish highly prevalent contributors (e.g., childhood adversities) from less prevalent but high-OR exposures (e.g., near-daily cannabis use). This more granular picture supports psychosis risk as developmentally contingent and context dependent, rather than uniform across populations, and thus provides an empirical foundation for stratifying risk at the individual and subgroup level.

The present umbrella review also offers key insights to guide the next generation of psychosis risk-prediction models, central to advancing precision psychiatry. Although around fifty such models currently exist¹⁵³, some showing promising performance¹⁵⁴, further refinement is needed to reliably identify individuals at the highest likelihood of developing a psychotic disorder. For example, risk-prediction algorithms could be expanded to capture broader familial vulnerability by considering not only a history of maternal psychotic disorder but also any maternal mental health condition, both emerging as class II risk factors for psychosis. Likewise, the inclusion of environmental and developmental factors, concurrently measured in a poly-environmental approach, could improve predictive precision¹⁵⁵.

Furthermore, several class I and II antecedents identified here, including premorbid IQ and minor physical anomalies, may represent feasible and scalable prognostic biomarkers. They are inexpensive, non-invasive, and relatively easy to assess, making them attractive candidates for integration into multivariate predictive frameworks. This is also the case for neurological soft signs (i.e., subtle deficits in sensory integration, motor coordination, and sequencing of complex motor acts¹⁵⁶), which were upgraded to class II in our sensitivity analyses. The incorporation of these variables into multimodal, population-level approaches – such as screening in offspring of patients with psychosis¹⁵⁷ or those presenting with subthreshold symptoms¹⁵⁸ – could substantially enhance early

identification and refine risk stratification beyond specialized clinical settings.

Translating these findings into preventive and early intervention strategies highlights a set of modifiable levers. Among them, near-daily cannabis use stands out as the most immediately actionable preventive target. Evidence from this umbrella review indicates a clear dose-response relationship, and, unlike many other exposures, effective harm-reduction measures already exist¹⁵⁹. In practice, curbing heavy, near-daily consumption – especially of high-THC products^{123,125} – may represent the most feasible strategy currently available to lower population-level psychosis risk. As policy liberalization increases accessibility and social acceptance of cannabis, the parallel rise in the incidence of schizophrenia¹⁶⁰ and the health care contacts for psychotic symptoms¹⁶¹ reinforces the urgency of this focus. However, universal preventive programs have achieved only modest and short-lived effects^{162,163}. Shifting toward a selective prevention paradigm that prioritizes daily users, therefore, appears to be a promising and more cost-effective approach.

Parental and early-life events also emerge as critical preventive targets. The trend toward older maternal age underscores the value of optimizing pre-conception and antenatal care to mitigate potentially modifiable pathways that could offset the loss of protection conferred by younger maternal age. Interventions at this life stage – such as folic acid supplementation during pregnancy¹⁶⁴ – have shown encouraging evidence in reducing neurodevelopmental disorders¹⁶⁴. However, their impact on psychosis incidence remains unproven, partly due to the delayed onset and low base rate of psychotic disorders¹⁶⁵.

Likewise, strategies aimed at reducing childhood adversities through family, school and community-based programs hold potential for broad transdiagnostic benefits, including possible downstream effects on psychosis risk. Other exposures with high PAF, such as *Toxoplasma gondii* IgG positivity, pose even more significant challenges. Reducing transmission of this pathogen at scale, outside specific high-risk periods such as pregnancy, is unlikely to be globally feasible or cost-effective. For now, preventive efforts should prioritize more tractable and modifiable factors. At the same time, future research should clarify whether targeted screening or health education interventions are justified for selected high-risk groups or settings.

For specific clinical populations, such as individuals with ADHD, this umbrella review offers additional preventive insights. While concerns about the emergence of potential psychotic symptoms are not, in general, grounds for withholding ADHD treatment, a multistep screening approach for psychosis risk should be adopted¹⁶⁶. The detection of significant risk factors for psychotic disorders – such as the presence of psychotic-like experiences or a family history of psychosis – should be followed by the administration of structured psychometric interviews traditionally used to detect a CHR-P state, such as the Comprehensive Assessment of At-Risk Mental States (CAARMS) or the mini-CAARMS¹⁶⁷.

From a public health perspective, the findings of this umbrella review provide a roadmap for a more rational and cost-effective allocation of preventive resources. By distinguishing risk factors

supported by strong, credible evidence and providing PAFs for the most robust, modifiable ones, these results can help prioritize which exposures warrant investment in large-scale prevention trials, policy interventions, or public-awareness campaigns. For highly prevalent factors with strong associations – such as childhood adversities¹⁶⁸ – even modest reductions may substantially decrease the population burden, whereas for less prevalent but high-impact factors – such as near-daily cannabis use – more selective interventions in specific subgroups are likely to be more efficient. Additionally, universal measures such as accurate potency and THC labeling, consumer warnings about psychosis risk with near-daily use, and age-appropriate education could help shift population-level exposure. Finally, the evidence gaps identified in this umbrella review, including limited data on specific exposures and on interactions between risk factors, can guide future research agendas and help refine global prevention strategies.

The findings of this umbrella review should be interpreted in the light of some limitations. Associations between risk or protective factors and psychotic disorders do not necessarily imply causality, and reverse causation remains a concern, although we have addressed this issue by conducting sensitivity analyses restricted to prospective studies. For some factors, we cannot entirely rule out the possibility of genetic confounding¹⁶⁹. In addition, the definition of healthy control groups may not always be accurate or may vary across the included papers, and the boundaries between sociodemographic, perinatal, and later factors and antecedents are not always clear-cut; however, these categories did not affect our meta-analytic computations. Moreover, our analyses evaluated one factor at a time, while – in real-world settings – individuals are often exposed to multiple, and sometimes opposing, factors. This limitation is currently addressed by the development of poly-environmental risk factors for psychosis that measure multiple exposures at the same time¹⁵⁵.

In addition, the quality of the systematic reviews and meta-analyses included in our umbrella review was heterogeneous, with a substantial proportion lacking a pre-registered protocol. To overcome this limitation, we manually reviewed and extracted data from each individual study to ensure their relevance and adherence to the inclusion criteria. This nevertheless underscores the urgent need for rigorous, high-quality evidence syntheses.

Finally, there are also some limitations inherent to the use of PAFs. They are static measures which assume that the removal of an exposure does not have downstream effects – an assumption that may not hold, particularly for early neurodevelopmental exposures¹⁷⁰. Estimates may also be affected by the limited availability of reliable prevalence data, which prevented us from calculating PAFs for some factors. In the case of daily cannabis use, we were unable to identify robust global prevalence estimates, which highlights the need for more reliable epidemiological data in this area at a worldwide level.

In conclusion, the findings of this umbrella review provide an evidence-based, updated atlas of risk and protective factors for psychosis, advancing epidemiological knowledge, refining precision psychiatry, identifying targets for preventive intervention, and guiding global public health research.

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Network analysis of the genetic relationships between twenty psychiatric and substance use disorders

Kenneth S. Kendler^{1,2}, Henrik Ohlsson³, Jan Sundquist^{3,4}, Kristina Sundquist^{3,4}

¹Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA; ²Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA; ³Center for Primary Health Care Research, Department of Clinical Sciences, Lund University, Malmö, Sweden; ⁴University Clinic Primary Care, Skåne University Hospital, Region Skåne, Sweden

We sought to clarify, using network analysis, the structure of genetic risk factors for a wide range of psychiatric and substance use disorders. Using split halves (N=1,510,974), we computed the family genetic risk scores (FGRSs) for 20 psychiatric and substance use disorders assessed in treated individuals from the entire Swedish population born between 1960 and 2000. We calculated a genetic correlation matrix for them to which we applied an EBICglasso network analysis. The network was dense, with five inter-connected clusters of genetic risks for internalizing, externalizing, neurodevelopmental, eating, and psychotic disorders. Genetic risks for four disorders were transitional across clusters: attention-deficit/hyperactivity disorder (ADHD) between neurodevelopmental and externalizing disorders; bipolar disorder (BD) between internalizing and psychotic disorders; obsessive-compulsive disorder (OCD) between internalizing and eating disorders; and autism spectrum disorder (ASD) between neurodevelopmental and psychotic disorders. The most central nodes in the network were genetic risks for major depression (MD) and drug use disorder. The strongest links of genetic risk for BD were with genetic risks for MD and schizoaffective disorder, with no direct link with schizophrenia. We then added genetic risks for borderline personality disorder (BPD), suicide attempt (SA) and suicide death (SD). Genetic risk for BPD had diverse links to genetic risks for SA, BD, internalizing, externalizing, and eating disorders. Genetic risks for SA and SD had their strongest edges with, respectively, genetic risks for drug use and alcohol use disorder. Our results were stable across split halves and when sampling only one sibling per family. Compared to standard factor analytic methods, network analyses can provide both confirmatory results and novel insights into the structure of genetic risks for a variety of psychiatric disorders.

Key words: Network analysis, genetic risk, national registers, bipolar disorder, major depression, borderline personality disorder, drug use disorder, suicide attempt, suicide death

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The study of the degree to which the familial/genetic risk for individual psychiatric disorders is shared versus disorder-specific goes back to the roots of psychiatric genetics in the early 19th century¹. This question has been examined in early pedigree², family^{3,4}, and twin^{5–7} studies, and most recently with molecular genetic methods^{8,9}. The initial studies were descriptive; then comparisons were made in risk of disorders among relatives of different proband groups.

Twin studies introduced the concept of genetic correlations between disorders, and these were first fit to pairs of disorders⁵ and then larger groups^{6,7}. From these, more complex factor analytic structural equation models were applied¹⁰. Finally, these methods were adapted to genetic correlations calculated from either genomic data^{8,9,11} or family-genetic risk scores (FGRSs)^{12,13}.

Such factor models specifically evaluate whether the correlations in genetic risk observed between a set of particular disorders – such as major depression (MD), generalized anxiety disorder (GAD) and phobic anxiety disorders (PAD) – could be well explained by a latent “internalizing disorder” genetic factor. If such a factor fits the data well, more advanced questions could then be posed, such as how that “internalizing disorder” latent factor might relate to an “externalizing” common genetic factor estimated from the genetic correlations between drug use disorder (DUD), alcohol use disorder (AUD) and attention-deficit/hyperactivity disorder (ADHD)¹².

While informative, such factor models can be complex to perform, involving decisions about numbers of factors to extract, the question of the indeterminacy of factor rotations¹⁴, and the relative roles of exploratory and confirmatory methods. They produce large number of estimates, including loadings of each disorder on

each factor, correlations between factors (if oblique rotations are used), and the proportions of risk for each disorder unaccounted for by the factors.

Network analyses applied to psychiatric disorders provide a different and more intuitive approach to examining multivariate relations that abandons the latent factor model and focuses on the direct relationships between disorders (technically called “nodes” connected by “edges”)¹⁵.

The information used for network analyses – a genetic correlation matrix – does not differ from that used for factor analyses. In network analyses, edges represent associations that remain after conditioning on all other nodes, and the resulting graph emphasizes relative proximity, clustering, and conditional independence rather than dimensional reduction as in factor analyses. Particularly, in our application to a genetic correlation matrix, edges are descriptive and “correlational” and do not imply causation.

The distinction between the two methods lies in their interpretative framing: whether shared genetic risk is conceptualized as arising from unobserved common liabilities “compressed” into factors or as a structured relational web of overlapping genetic influences among phenotypes as in network analysis.

Network analyses have, in the last decade, been frequently applied to psychopathology¹⁶, but few studies have applied this method to study genetic relationships between psychiatric disorders. These have either focused on small numbers of disorders¹⁷ or been applied to local analysis of specific associations¹¹.

While complementary to traditional factor methods, network analyses present several attractive features, including: a) an easily grasped spatial representation of results; b) a focus on the degree of “connectivity” between disorders; c) estimates of the “central-

ity” of individual nodes; d) delineation of disorder clusters; and e) the capacity to identify “transitional” disorders between clusters.

In this study, we began by fitting a network model to the genetic correlation matrix for 20 psychiatric and substance use disorders assessed in treated individuals from the entire Swedish population born between 1960 and 2000, and described the findings in detail. We then expanded our network by adding genetic risks for borderline personality disorder (BPD), suicide attempt (SA), suicide death (SD), and two measures of cognitive functioning: low educational attainment (LEA) and intellectual disability (ID).

METHODS

We used data from Swedish population-based registers with nationwide coverage (see supplementary information). Each individual’s unique personal identification number was pseudonymized by Statistics Sweden using a serial number to ensure confidentiality. Ethical approval was obtained from the Regional Ethical Review Board in Lund (no. 2008/409 and subsequent amendments). Participant consent was not required.

The study cohort consists of all individuals born between 1960 and 2000 in Sweden to Swedish born parents (N=3,021,948) (48.7% female), who were followed up to a mean age of 40.9±10.5 years in 2018. The analysis focused on FGRSs for 25 phenotypes with diagnoses based on ICD-8, ICD-9 or ICD-10 codes from primary care, specialist outpatient care, and inpatient hospital records (see supplementary information). The FGRSs were calculated using morbidity risks among first- through fifth-degree relatives, while accounting for cohabitation effects (for details, see supplementary information). In contrast to molecular genetic measures, FGRSs quantify familial phenotypic liability.

We estimated a sparse Gaussian graphical model using the EBICglasso procedure¹⁸. This approach shrinks small edges toward zero and selects the optimal model using the extended Bayesian information criterion, thereby penalizing excessive model complexity. The model was estimated from Pearson correlations; however, the resulting edge weights correspond to partial correlations, reflecting conditional associations between variables after adjusting for all other nodes in the network. For each node, we report the most easily interpreted of the centrality metrics, strength¹⁹, calculated as the sum of absolute edge weights for each node²⁰. Edge-specific 95% confidence intervals (CIs) were obtained using non-parametric bootstrapping with 1,000 replications.

To examine the network’s community structure, we applied the Spinglass algorithm, which identifies partitions that best capture densely interconnected groups of nodes. To evaluate the robustness of these communities, we iteratively re-estimated the Spinglass solution and computed a node-level stability measure, quantifying how consistently each node was assigned to the same cluster across 1,000 repetitions²¹.

We performed several robustness checks. First, we randomly split the cohort in half and replicated the model in the second subsample, using a confirmatory network model²². Second, to partially address non-independence arising from the large num-

ber of related individuals contributing to many probands’ FGRS values, we repeated the analysis using one randomly selected sibling per sibship. To evaluate temporal stability, we conducted separate analyses for individuals born between 1960 and 1980, and between 1981 and 2000.

Finally, we replicated all analyses using a refined version of the FGRS that incorporates improved statistical properties (PA-FGRS)^{23,24}. All robustness comparisons were performed using the network comparison test, which assesses network structure invariance, global strength invariance, and differences in individual edge weights, using 1,000 permutations²⁵. All other statistical analyses were conducted using R version 4.3.1²⁶.

RESULTS

Table 1 presents the population prevalence rates and the male/female ratio for the examined phenotypes. The prevalence varies widely from a minimum of 0.12% for conduct disorder (CD) to a

Table 1 Lifetime prevalence and sex ratio for the phenotypes examined in the study

	Lifetime prevalence	Sex ratio of prevalence (M/F)
Acute psychosis (AP)	0.38%	1.11
Alcohol use disorder (AUD)	4.49%	2.14
Anorexia nervosa (AN)	0.36%	0.05
Attention-deficit/hyperactivity disorder (ADHD)	2.56%	1.24
Autism spectrum disorder (ASD)	1.09%	1.56
Bipolar disorder (BD)	1.43%	0.55
Borderline personality disorder (BPD)	0.54%	0.16
Bulimia nervosa (BN)	0.23%	0.04
Conduct disorder (CD)	0.12%	1.46
Delusional disorder (DD)	0.22%	1.40
Drug use disorder (DUD)	4.78%	2.24
Generalized anxiety disorder (GAD)	2.42%	0.49
Intellectual disability (ID)	0.92%	1.18
Major depression (MD)	17.02%	0.55
Nicotine dependence (ND)	1.85%	0.62
Obsessive-compulsive disorder (OCD)	1.01%	0.62
Panic disorder (PD)	4.10%	0.56
Phobic anxiety disorders (PAD)	1.94%	0.68
Post-traumatic stress disorder (PTSD)	5.66%	0.42
Psychosis not otherwise specified (PNOS)	0.60%	1.26
Schizoaffective disorder (SAD)	0.15%	0.86
Schizophrenia (SZ)	0.33%	1.68
Suicide attempt (SA)	4.89%	0.95
Suicide death (SD)	0.24%	2.25

maximum of 17.02% for MD. The male/female sex ratio ranges from 0.04 for bulimia nervosa (BN) to 2.25 for SD.

Primary model

Our primary model examining the relationships between genetic risks for 20 psychiatric and substance use disorders is presented in Figure 1. The edge strengths for each disorder are provided in Table 2 and in the supplementary information. Of the many features of the model, we emphasize six.

First, a cluster of genetic risks for internalizing disorders – MD, GAD, panic disorder (PD), PAD, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) – is seen in the upper left quadrant of the network, with the strongest edges occurring between MD and GAD (estimate = 0.15, 95% CI: 0.14-0.15), MD and PD (estimate = 0.13, 95% CI: 0.12-0.13), MD and PTSD (estimate = 0.17, 95% CI: 0.17-0.18), PD and PAD (estimate = 0.13, 95% CI: 0.13-0.13), and PD and GAD (estimate = 0.15, 95% CI: 0.15-0.16).

Second, the genetic risks for substance use and externalizing disorders – nicotine dependence (ND), AUD, DUD, ADHD and CD – are depicted in the lower left quadrant of the network, with the

strongest edges between ND and AUD (estimate = 0.14, 95% CI: 0.14-0.14), AUD and DUD (estimate = 0.35, 95% CI: 0.34-0.35), DUD and ADHD (estimate = 0.16, 95% CI: 0.16-0.17), and CD and ADHD (estimate = 0.08, 95% CI: 0.08-0.09).

Third, the genetic risk for autism spectrum disorder (ASD), in the right lower section of the network, has a very strong edge with the risk for ADHD (estimate = 0.26, 95% CI: 0.25-0.26), and a modest edge with genetic risk for schizophrenia (SZ) (estimate = 0.09, 95% CI: 0.09-0.10).

Fourth, at the far right of the network, we see a tightly clustered group of genetic risks for four non-affective psychotic disorders – delusional disorder (DD), acute psychosis (AP), psychosis not otherwise specified (PNOS), and SZ – as well as schizoaffective disorder (SAD), with strong inter-linking edges (e.g., estimate = 0.21, 95% CI: 0.21-0.22 between SZ and PNOS; estimate = 0.21, 95% CI: 0.20-0.22 between SZ and SAD; estimate = 0.14, 95% CI: 0.14-0.15 between SZ and DD).

Fifth, genetic risks for the two eating disorders – BN and anorexia nervosa (AN) – are seen at the bottom of the network, with a moderately strong edge between them (estimate = 0.08, 95% CI: 0.08-0.09), but without strong edges to other disorders.

Sixth, the genetic risk for BD has a unique place in the network, with its strongest edge with MD (estimate = 0.14, 95% CI: 0.14-0.15), followed by SAD (estimate = 0.14, 95% CI: 0.13-0.14). It has weaker edges to two other psychotic disorders – PNOS (estimate = 0.08, 95% CI: 0.08-0.08) and AP (estimate = 0.07, 95% CI: 0.07-0.08) – and no unique edge with SZ.

The confirmatory network analysis suggested a good fit, with root mean square error of approximation of 0.002 (95% CI: 0.002-0.002).

Figure 2 illustrates the centrality analysis for our primary model, utilizing strength. The three most central nodes in the network are genetic risks for MD, DUD and ADHD.

Figure 3 presents the Spinglass solution identifying five clusters, all showing high stability (>0.85), indicating that the corresponding community assignments were consistently recovered across bootstrap replications. This figure also reports the stability of the individual nodes across replications, which are quite high (≥ 0.94), with the exception of AN and BN (both 0.83). The resulting clusters could easily be labeled genetic risks for internalizing disorders (MD, PTSD, PAD, PD, GAD and OCD), psychotic disorders (SZ, SAD, PNOS, AP, DD and BD), externalizing disorders (AUD, DUD and ND), neurodevelopmental disorders (ADHD, ASD and CD), and eating disorders (BN and AN).

Genetic risks for four disorders can be considered transitional across clusters: ADHD between neurodevelopmental and externalizing disorders, BD between internalizing and psychotic disorders, OCD between internalizing and eating disorders, and ASD between neurodevelopmental and psychotic disorders.

Expanded model

The expanded model network is seen in Figure 4, and maintains the basic structure of our primary model. The edge strengths

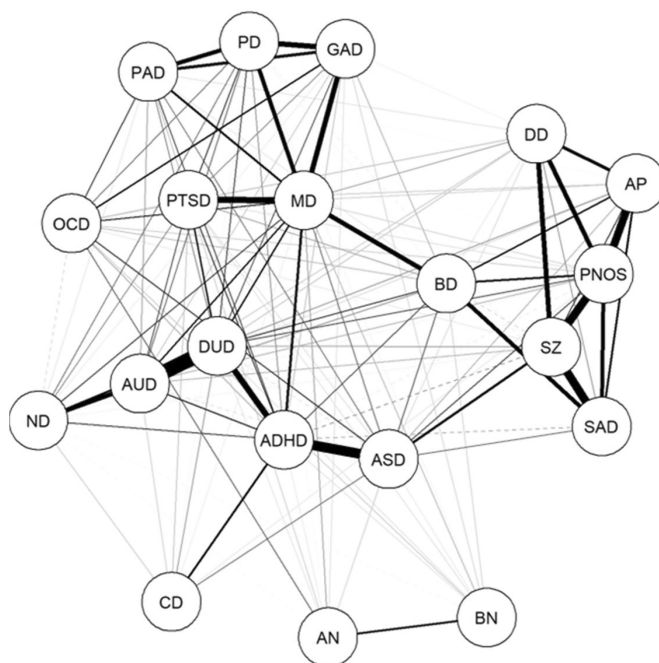


Figure 1 Primary model network. The strength of the edges is reflected by the thickness of the lines. Positive edges are solid and negative edges are dotted. ADHD – attention-deficit/hyperactivity disorder, AN – anorexia nervosa, AP – acute psychosis, ASD – autism spectrum disorder, AUD – alcohol use disorder, BD – bipolar disorder, BN – bulimia nervosa, CD – conduct disorder, DD – delusional disorder, DUD – drug use disorder, GAD – generalized anxiety disorder, MD – major depression, ND – nicotine dependence, OCD – obsessive-compulsive disorder, PAD – phobic anxiety disorders, PD – panic disorder, PNOS – psychosis not otherwise specified, PTSD – post-traumatic stress disorder, SAD – schizoaffective disorder, SZ – schizophrenia.

Table 2 Strongest edges for the network of the primary model

Node	Strongest edges, estimate (95% CI)
ADHD	ASD: 0.26 (0.25-0.26); DUD: 0.16 (0.16-0.17); MD: 0.09 (0.09-0.09); CD: 0.08 (0.08-0.09)
AN	BN: 0.08 (0.08-0.09); OCD: 0.04 (0.04-0.04)
AP	PNOS: 0.20 (0.20-0.21); DD: 0.11 (0.11-0.12); SAD: 0.08 (0.07-0.09); BD: 0.07 (0.07-0.08)
ASD	ADHD: 0.26 (0.25-0.26); SZ: 0.09 (0.09-0.10)
AUD	DUD: 0.35 (0.34-0.35); ND: 0.14 (0.14-0.14); MD: 0.07 (0.07-0.08)
BD	MD: 0.14 (0.14-0.15); SAD: 0.14 (0.13-0.14); PNOS: 0.08 (0.08-0.08); AP: 0.07 (0.07-0.08)
BN	AN: 0.08 (0.08-0.09)
CD	ADHD: 0.08 (0.08-0.09)
DD	SZ: 0.14 (0.14-0.15); PNOS: 0.14 (0.14-0.15); AP: 0.11 (0.11-0.12)
DUD	AUD: 0.35 (0.34-0.35); ADHD: 0.16 (0.16-0.17); ND: 0.08 (0.08-0.08); PTSD: 0.07 (0.07-0.07); MD: 0.07 (0.06-0.07)
GAD	PD: 0.15 (0.15-0.16); MD: 0.15 (0.14-0.15); PAD: 0.10 (0.09-0.10); OCD: 0.07 (0.07-0.07)
MD	PTSD: 0.17 (0.17-0.18); GAD: 0.15 (0.14-0.15); BD: 0.14 (0.14-0.15); PD: 0.13 (0.12-0.13); ADHD: 0.09 (0.09-0.09); PAD: 0.08 (0.07-0.08)
ND	AUD: 0.14 (0.14-0.14); DUD: 0.08 (0.08-0.08)
OCD	GAD: 0.07 (0.07-0.07); MD: 0.06 (0.06-0.07); PAD: 0.06 (0.06-0.06); ASD: 0.05 (0.05-0.05); AN: 0.04 (0.04-0.04)
PAD	PD: 0.13 (0.13-0.13); GAD: 0.10 (0.09-0.10); MD: 0.08 (0.07-0.08)
PD	GAD: 0.15 (0.15-0.16); PAD: 0.13 (0.13-0.13); MD: 0.13 (0.12-0.13)
PNOS	SZ: 0.21 (0.21-0.22); AP: 0.20 (0.20-0.21); DD: 0.14 (0.14-0.15); SAD: 0.12 (0.11-0.13); BD: 0.08 (0.08-0.08)
PTSD	MD: 0.17 (0.17-0.18); DUD: 0.07 (0.07-0.07)
SAD	SZ: 0.21 (0.20-0.22); BD: 0.14 (0.13-0.14); PNOS: 0.12 (0.11-0.13); AP: 0.08 (0.07-0.09)
SZ	PNOS: 0.21 (0.21-0.22); SAD: 0.21 (0.20-0.22); DD: 0.14 (0.14-0.15); ASD: 0.09 (0.09-0.10)

ADHD – attention-deficit/hyperactivity disorder, AN – anorexia nervosa, AP – acute psychosis, ASD – autism spectrum disorder, AUD – alcohol use disorder, BD – bipolar disorder, BN – bulimia nervosa, CD – conduct disorder, DD – delusional disorder, DUD – drug use disorder, GAD – generalized anxiety disorder, MD – major depression, ND – nicotine dependence, OCD – obsessive-compulsive disorder, PAD – phobic anxiety disorders, PD – panic disorder, PNOS – psychosis not otherwise specified, PTSD – post-traumatic stress disorder, SAD – schizoaffective disorder, SZ – schizophrenia. The estimates for all the edges are available in the supplementary information.

for each phenotype are provided in Table 3 and in the supplementary information.

BPD is placed in between internalizing, eating and psychotic disorder clusters, with the strongest edges to SA (estimate = 0.09, 95% CI: 0.08-0.09), BD (estimate = 0.07, 95% CI: 0.07-0.08), and DUD (estimate = 0.06, 95% CI: 0.06-0.06).

SA sits between the externalizing and internalizing genetic clusters, with the strongest edges to AUD (estimate = 0.17, 95% CI: 0.17-0.17), DUD (estimate = 0.15, 95% CI: 0.15-0.16), and BPD (estimate = 0.09, 95% CI: 0.08-0.09). SD is less strongly connected to psychiatric disorders, with strongest edges to AUD (estimate = 0.08, 95% CI: 0.08-0.09) and SA (estimate = 0.06, 95% CI: 0.05-0.06).

Genetic risk for LEA is closely related to ND (estimate = 0.15, 95% CI: 0.15-0.15), AUD (estimate = 0.11, 95% CI: 0.11-0.11), and ADHD (estimate = 0.11, 95% CI: 0.11-0.11), while genetic risk for ID is most strongly linked to ASD risk (estimate = 0.11, 95% CI: 0.11-0.12).

The confirmatory network analysis suggested a good fit, with root mean square error of approximation of 0.003 (95% CI: 0.003-0.003). Figure 5 presents the centrality analysis for our expanded model, which resembles closely that seen for the primary model.

DISCUSSION

In this study, we applied network analysis to the long-debated question of the nature of the genetic relationships between diverse psychiatric and substance use disorders. While well established, few network analyses have been conducted on the genetic risk factors for a broad range of psychiatric disorders.

Importantly, we adopted a sampling frame for these analyses that, through the use of FGRSs, based our genetic risk calculations on all treated patients from the population of Sweden, with high quality and relatively uniform register data. Thus, we could avoid the use of the typically heterogeneous case-control samples from multiple investigative teams, with often widely varying diagnostic assessments, that now form the basis of most molecular genetic multivariate models of psychopathology. Furthermore, our sample size was large enough to enable inclusion of uncommon disorders rarely considered in other multivariate genetic studies (e.g., SAD, PD, AP, CD, BN and DD).

The first question to address regarding our findings is the degree to which they are congruent with those obtained using more traditional factor analytic methods in other samples. Indeed, our

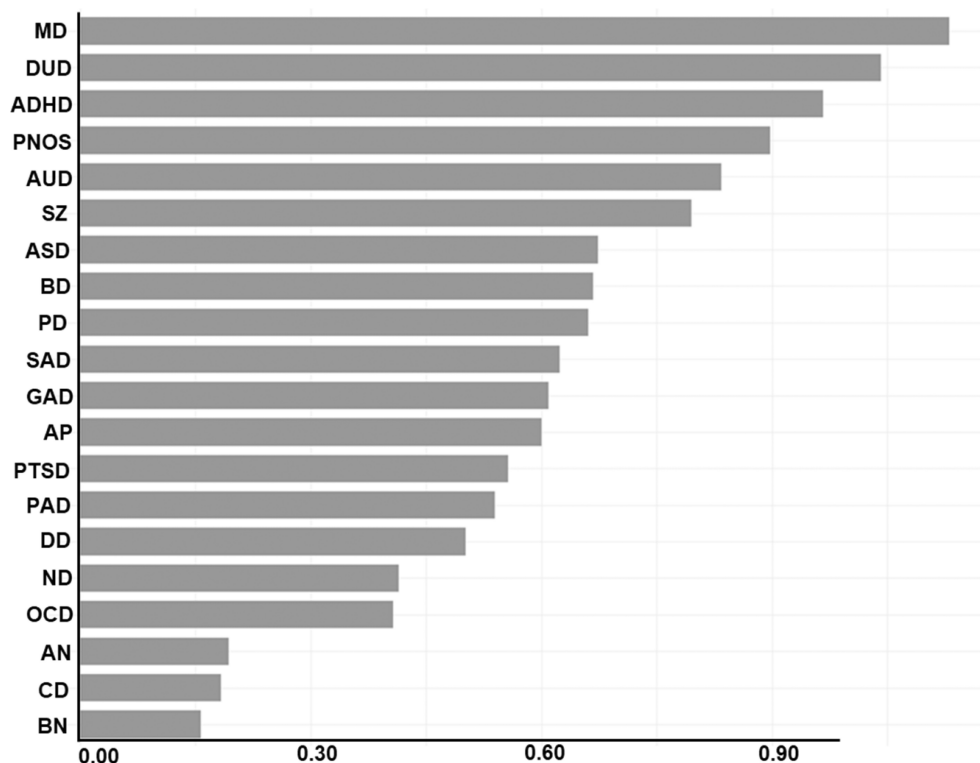


Figure 2 Centrality of each node in the primary model. ADHD – attention-deficit/hyperactivity disorder, AN – anorexia nervosa, AP – acute psychosis, ASD – autism spectrum disorder, AUD – alcohol use disorder, BD – bipolar disorder, BN – bulimia nervosa, CD – conduct disorder, DD – delusional disorder, DUD – drug use disorder, GAD – generalized anxiety disorder, MD – major depression, ND – nicotine dependence, OCD – obsessive-compulsive disorder, PAD – phobic anxiety disorders, PD – panic disorder, PNOS – psychosis not otherwise specified, PTSD – post-traumatic stress disorder, SAD – schizoaffective disorder, SZ – schizophrenia.

results are similar to several prior twin studies showing distinct genetic factors for internalizing and externalizing psychiatric and substance use disorders^{10,27-29}. Our findings have even greater resemblance to a multivariate genetic factor analysis based on genome-wide genetic correlations of 14 disorders¹¹. That study identified five genetic factors with high homology to the clusters detected in our analysis: compulsive disorders, schizophrenia/bipolar disorder, neurodevelopmental disorders, internalizing disorders, and substance use disorders.

Some even more striking resemblances are noteworthy. In broad congruence with our results, that study¹¹ found that both AN and OCD loaded together within the compulsive disorder factor; MD and PTSD both loaded within the internalizing disorder factor; and ADHD loaded both on the substance use and neurodevelopmental disorder factors. Given the substantial differences in statistical methods and sampling frame, this level of congruence represents evidence of triangulation³⁰. One point of non-replication is noteworthy. While that study¹¹ found BD and SZ to be highly genetically correlated and load together on a single factor, we found BD to be more closely related to MD than to SZ.

It is of particular interest to compare our findings with those obtained by genetic factor analytic methods applied to the same Swedish population sample¹³, although our network analyses contained two additional disorders (ND and CD). At a high level, the overall patterns of results from the two methods are similar.

For example, our confirmatory factor analytic model produced six factors for externalizing, neurodevelopmental, anxiety, mood, psychotic and eating disorders, while our network community structure showed four clusters very similar to four of those six factors. However, our internalizing cluster largely combined the anxiety and mood disorders factors from the factor analysis.

Equally important, a number of noteworthy differences were seen in these two studies, which reflected the differences in interpretative framing of the two statistical methods. There was no parallel in the factor analyses for our centrality analyses, showing MD, DUD and ADHD to be the most “connected” disorders in our model. The factor analytic model also had no way of capturing subtleties of some of our network results, of which we provide four examples.

First, our network analysis provides greater granularity in the depiction of the internalizing disorders. The edge with MD is strongest for GAD, intermediate for PD and weakest for PAD, consistent with prior twin studies³¹⁻³³. Our findings also suggest, consistent with clinical experience, that the genetic correlation between PAD and MD is likely mediated by genetic risk for PD.

Second, we see a quite interesting contrast in the edges from BD and ASD to the psychotic cluster. The edge from ASD to SZ is much stronger than any other edge for ASD to other members of the psychotic cluster. The pattern for BD is entirely different, with strongest edges to SAD, PNOS and AP, all psychotic disorders char-

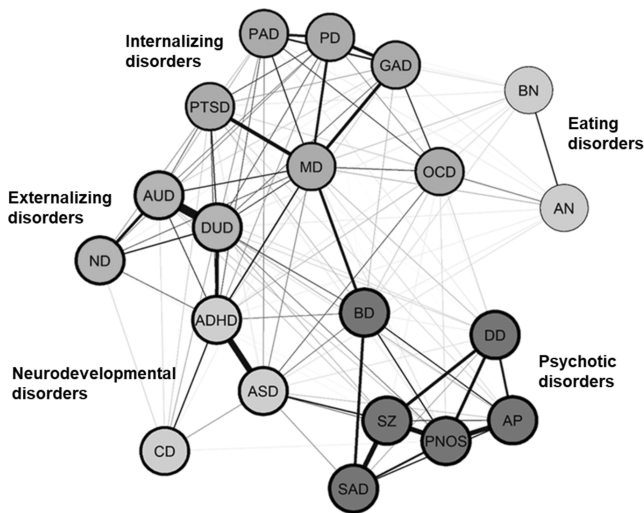


Figure 3 Community structure of the network of the primary model. Nodes with their stability: ADHD – attention-deficit/hyperactivity disorder (0.98), AN – anorexia nervosa (0.83), AP – acute psychosis (1.00), ASD – autism spectrum disorder (0.98), AUD – alcohol use disorder (0.99), BD – bipolar disorder (1.00), BN – bulimia nervosa (0.83), CD – conduct disorder (0.97), DD – delusional disorder (1.00), DUD – drug use disorder (0.99), GAD – generalized anxiety disorder (0.94), MD – major depression (0.94), ND – nicotine dependence (0.99), OCD – obsessive-compulsive disorder (0.94), PAD – phobic anxiety disorders (0.94), PD – panic disorder (0.94), PNOS – psychosis not otherwise specified (1.00), PTSD – post-traumatic stress disorder (0.94), SAD – schizoaffective disorder (1.00), SZ – schizophrenia (1.00).

acterized by prominent affective symptoms and/or a relapsing recurrent course.

Third, while modest, the edge from OCD to AN is four times stronger than the edge to BN, consistent with the evidence that obsessive and perfectionist traits are considerably more common in AN than BN^{34,35}.

Fourth, both our factor and network models show that, genetically, BD is more closely related to MD than to psychotic disorders. However, network analyses show a subtler but intriguing pattern. BD has no direct edge with SZ, but has a strong edge to SAD, which in turn has a substantial edge with SZ. This suggests that the genetic association between BD and SZ might be substantially mediated through SAD. However, it should be noted that our clustering algorithm assigned BD to the psychotic disorder cluster, likely due to strong edges of BD with SAD, PNOS and AP.

Finally, we would suggest that, at a global level, the spatial representation of the genetic relationships between the disorders in our network models are more intuitively accessible than the complex path diagrams and loading presented in multivariate genetic analyses.

The design of adding five phenotypes to our primary model provides an independent and therefore particularly useful opportunity to assess the informativeness of our network structure. Consistent with prior twin modeling³⁶, BPD has a large number of modest genetic edges to a diverse set of disorders, the top six of which were SA, BD, DUD, ADHD, PTSD and BN. This range of disorders gives additional insight into what has been termed³⁷ the

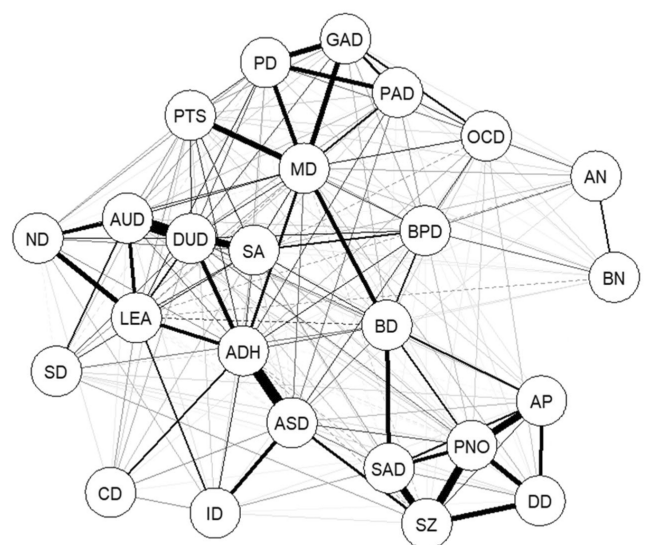


Figure 4 Expanded model network. The strength of the edges is reflected by the thickness of the lines. Positive edges are solid and negative edges are dotted. ADHD – attention-deficit/hyperactivity disorder, AN – anorexia nervosa, AP – acute psychosis, ASD – autism spectrum disorder, AUD – alcohol use disorder, BD – bipolar disorder, BN – bulimia nervosa, BPD – borderline personality disorder, CD – conduct disorder, DD – delusional disorder, DUD – drug use disorder, GAD – generalized anxiety disorder, ID – intellectual disability, LEA – low educational attainment, MD – major depression, ND – nicotine dependence, OCD – obsessive-compulsive disorder, PAD – phobic anxiety disorders, PD – panic disorder, PNOS – psychosis not otherwise specified, PTSD – post-traumatic stress disorder, SA – suicide attempt, SAD – schizoaffective disorder, SD – suicide death, SZ – schizophrenia.

predisposition to “impulsivity, emotion sensitivity, suicidal behavior [and] aggression” related to risk for BPD.

While both considered paradigmatic suicidal phenotypes, the positions of SA and SD in our network are quite different and only modestly inter-linked. SA is much more widely inter-connected in the network (18 non-zero edges) than SD (7 non-zero edges), and the top edges for SA are considerably stronger than the top edges for SD. These results support, from a novel perspective, concerns about using genetic risk for SA as a strong proxy for SD genetic risk³⁸⁻⁴⁰.

Finally, while both ID and LEA are generally considered to be indices of cognitive ability, the placement of these two phenotypes within our primary network model are very different. ID’s strongest edge is with ASD, with which LEA had no significant relationship. LEA has relatively strong edges with AUD and DUD, while ID has no significant edges with these two key substance use disorders. These findings are not entirely unexpected, as LEA has been shown to index a range of personality traits in addition to cognitive ability⁴¹.

These results should be interpreted in the context of six potential limitations. First, the validity of our findings depends on the quality of the Swedish register diagnoses, which reflect an averaging of the diagnostic approach of Swedish psychiatric clinicians over decades. The validity of the AUD and DUD diagnoses are supported by the high rates of concordance across ascertainment

Table 3 Strongest edges for the network of the expanded model

Node	Strongest edges, estimate (95% CI)
ADHD	ASD: 0.24 (0.24-0.25); DUD: 0.14 (0.14-0.14); LEA: 0.11 (0.11-0.11); MD: 0.09 (0.08-0.09); CD: 0.08 (0.07-0.08)
AN	BN: 0.08 (0.08-0.09)
AP	PNOS: 0.20 (0.20-0.21); DD: 0.11 (0.11-0.12); SAD: 0.08 (0.07-0.09); BD: 0.07 (0.07-0.07)
ASD	ADHD: 0.24 (0.24-0.25); ID: 0.11 (0.11-0.12); SZ: 0.09 (0.08-0.09)
AUD	DUD: 0.29 (0.29-0.29); SA: 0.17 (0.17-0.17); LEA: 0.11 (0.11-0.11); ND: 0.11 (0.11-0.11); SD: 0.08 (0.08-0.09); MD: 0.06 (0.06-0.06)
BD	MD: 0.14 (0.13-0.14); SAD: 0.13 (0.13-0.14); PNOS: 0.08 (0.07-0.08); BPD: 0.07 (0.07-0.08); AP: 0.07 (0.07-0.07)
BN	AN: 0.08 (0.08-0.09)
BPD	SA: 0.09 (0.08-0.09); BD: 0.07 (0.07-0.08); DUD: 0.06 (0.06-0.06); ADHD: 0.05 (0.05-0.06); PTSD: 0.05 (0.04-0.05); BN: 0.04 (0.03-0.04)
CD	ADHD: 0.08 (0.07-0.08)
DD	SZ: 0.14 (0.14-0.15); PNOS: 0.14 (0.14-0.15); AP: 0.11 (0.11-0.12)
DUD	AUD: 0.29 (0.29-0.29); SA: 0.15 (0.15-0.16); ADHD: 0.14 (0.14-0.14); LEA: 0.07 (0.07-0.08); BPD: 0.06 (0.06-0.06); ND: 0.06 (0.06-0.06)
GAD	PD: 0.15 (0.15-0.16); MD: 0.15 (0.14-0.15); PAD: 0.10 (0.09-0.10); OCD: 0.07 (0.07-0.07)
ID	ASD: 0.11 (0.11-0.12); LEA: 0.08 (0.08-0.08); ADHD: 0.6 (0.06-0.06)
LEA	ND: 0.15 (0.15-0.15); AUD: 0.11 (0.11-0.11); ADHD: 0.11 (0.11-0.11); ID: 0.08 (0.08-0.08); DUD: 0.07 (0.07-0.08)
MD	PTSD: 0.17 (0.16-0.17); GAD: 0.15 (0.14-0.15); BD: 0.14 (0.13-0.14); PD: 0.13 (0.12-0.13); ADHD: 0.09 (0.08-0.09); PAD: 0.08 (0.07-0.08)
ND	LEA: 0.15 (0.15-0.15); AUD: 0.11 (0.11-0.11); DUD: 0.06 (0.06-0.06)
OCD	GAD: 0.07 (0.07-0.07); MD: 0.06 (0.06-0.06); PAD: 0.06 (0.06-0.06)
PAD	PD: 0.13 (0.12-0.13); GAD: 0.10 (0.09-0.10); MD: 0.08 (0.07-0.08)
PD	GAD: 0.15 (0.15-0.16); PAD: 0.13 (0.12-0.13); MD: 0.13 (0.12-0.13)
PNOS	SZ: 0.21 (0.21-0.22); AP: 0.20 (0.20-0.21); DD: 0.14 (0.14-0.15); SAD: 0.12 (0.11-0.13); BD: 0.08 (0.07-0.08)
PTSD	MD: 0.17 (0.16-0.17); SA: 0.06 (0.06-0.06)
SA	AUD: 0.17 (0.17-0.17); DUD: 0.15 (0.15-0.16); BPD: 0.09 (0.08-0.09); MD: 0.06 (0.06-0.07); PTSD: 0.06 (0.06-0.06); SD: 0.05 (0.05-0.06)
SAD	SZ: 0.21 (0.20-0.22); BD: 0.13 (0.13-0.14); PNOS: 0.12 (0.11-0.13); AP: 0.08 (0.07-0.09)
SD	AUD: 0.08 (0.08-0.09); SA: 0.06 (0.05-0.06); DUD: 0.05 (0.04-0.05); BD: 0.03 (0.03-0.04); MD: 0.03 (0.02-0.03); SZ: 0.02 (0.02-0.03)
SZ	PNOS: 0.21 (0.21-0.22); SAD: 0.21 (0.20-0.22); DD: 0.14 (0.14-0.15); ASD: 0.09 (0.08-0.09)

ADHD – attention-deficit/hyperactivity disorder, AN – anorexia nervosa, AP – acute psychosis, ASD – autism spectrum disorder, AUD – alcohol use disorder, BD – bipolar disorder, BN – bulimia nervosa, BPD – borderline personality disorder, CD – conduct disorder, DD – delusional disorder, DUD – drug use disorder, GAD – generalized anxiety disorder, ID – intellectual disability, LEA – low educational attainment, MD – major depression, ND – nicotine dependence, OCD – obsessive-compulsive disorder, PAD – phobic anxiety disorders, PD – panic disorder, PNOS – psychosis not otherwise specified, PTSD – post-traumatic stress disorder, SA – suicide attempt, SAD – schizoaffective disorder, SD – suicide death, SZ – schizophrenia. The estimates for all the edges are available in the supplementary information.

methods^{42,43} and the similarity of patterns of resemblance across relatives to studies using personal interviews^{44,45}. Chart review analyses support the validity of Swedish hospital diagnoses of SZ and BD⁴⁶⁻⁴⁸. The validity of MD and anxiety disorder diagnoses are based on their prevalence, sex ratio, correlations in relatives, and associations with psychosocial risk factors^{49,50}. The Swedish diagnosis of ADHD is validated by its close relationship with stimulant medication prescription⁵¹. While we are unaware of validation efforts for Swedish register diagnoses of AN and BN, they have been used in a number of research studies^{e.g., 52-54}.

Second, FGRSs derive from diagnoses in extended pedigrees. We corrected for shared environmental effects of both parent-offspring and sibling relationships, with the validity of this method supported by simulations⁵⁵. We have formally compared, both empirically and via simulations, FGRSs and polygenic risk scores^{23,24}, showing that both scores behave (i.e., predict out-

comes and intercorrelate) as measures of additive genetic liability consistent with expected levels of measurement error.

Third, no easy correction was available for the non-independence of our results across the Swedish population. The CIs presented in this paper are almost certainly too small but, given our large sample size, this limitation is likely minimal. To evaluate the possible biases we might have introduced, we re-analyzed our data by selecting only one sibling at random from each sibship. The primary network model thereby obtained did not differ from the one reported above ($p=0.643$).

Fourth, we tested the stability of our findings in two ways. First, the overall network structure for our primary model did not differ significantly across our split-halves ($p=0.083$) (see supplementary information). More ambitiously, we tested the similarity of our primary model fitted to individuals born in Sweden in 1960-1980 versus 1981-2000. The overall differences were significant ($p=0.001$)

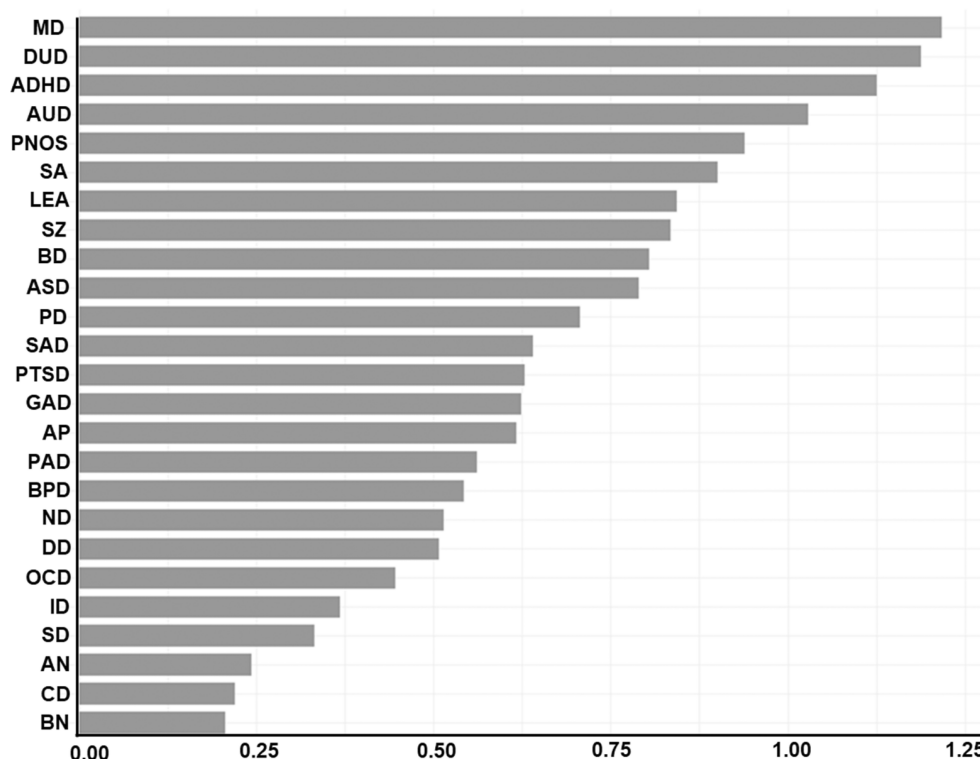


Figure 5 Centrality of each node in the expanded model. ADHD – attention-deficit/hyperactivity disorder, AN – anorexia nervosa, AP – acute psychosis, ASD – autism spectrum disorder, AUD – alcohol use disorder, BD – bipolar disorder, BN – bulimia nervosa, BPD – borderline personality disorder, CD – conduct disorder, DD – delusional disorder, DUD – drug use disorder, GAD – generalized anxiety disorder, ID – intellectual disability, LEA – low educational attainment, MD – major depression, ND – nicotine dependence, OCD – obsessive-compulsive disorder, PAD – phobic anxiety disorders, PD – panic disorder, PNOS – psychosis not otherwise specified, PTSD – post-traumatic stress disorder, SA – suicide attempt, SAD – schizoaffective disorder, SD – suicide death, SZ – schizophrenia.

and, as detailed in the supplementary information, the most striking findings were due to increasing edges with and centrality for DUD, rates of which began to climb substantially in Sweden in the late 1970s⁵⁶.

Fifth, unlike polygenic risk scores, FGRSs, where the number of relatives in a pedigree typically range from 10 to 50, have a skewed distribution, which is often worse with rare disorders because many pedigrees contain no affected individuals. Skewness typically attenuates correlations which are basic to network analyses. To evaluate the robustness of our solution, we re-ran our exploratory factor analysis using a Yeo-Johnson transformation⁵⁷. The correlation with the edge weights from our original results was high (+0.88) (see supplementary information).

Sixth, we re-ran our network analyses using the PA-FGRS measures. The correlations between edge weights from our original results were very high (+0.98) (see supplementary information).

CONCLUSIONS

Network analyses provide a novel perspective on a very old question in psychiatric genetics: how genetic liabilities to the various disorders inter-relate. We applied this method to a genetic correlation matrix from 20 diverse psychiatric and substance use

disorders, assessed from high-quality registers from the Swedish population. Network analyses are more relational and intuitively accessible than the complex path diagrams and loading presented in prior multivariate genetic analyses.

Our results support many of the prior conclusions of factor-analytic multivariate twin and molecular genetic studies, but reveal some substantive differences, especially in the genetic relationship between SZ and BD, and point out a range of new subtler findings (for example, the striking differences in the edges of ASD and BD with the psychotic disorders).

We suggest that, going forward, network analyses should be considered an important tool in our continued effort to understand the complex genetic relationships between the various mental and substance use disorders.

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Mental health disparities in LGBTQIA+ populations: an umbrella review of systematic reviews and meta-analyses

Vincenzo Oliva^{1,4}, Joaquim Radua^{1,4}, Michele De Prisco^{1,4}, Matteo Cerioli^{1,3,5}, Marta Bort^{1,3}, Chiara Possidente^{1,3,6}, Lorenzo Bracco^{1,3,7}, Gerard Anmella^{1,4}, Gonzalo Salazar de Pablo⁸⁻¹⁰, Giovanna Fico^{1,3}, Eduard Vieta^{1,4}

¹Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain; ²Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; ³Bipolar and Depressive Disorders Unit, Hospital Clínic de Barcelona, Barcelona, Spain; ⁴Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain; ⁵Department of Biomedical and Clinical Sciences "L. Sacco", University of Milan, Milan, Italy; ⁶Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy; ⁷Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; ⁸Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; ⁹Child and Adolescent Mental Health Services, South London and Maudsley NHS Foundation Trust, London, UK; ¹⁰Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario "G. Marañón", Madrid, Spain

Lesbian, gay, bisexual, transgender, questioning, intersex, asexual (LGBTQIA+) populations face unique social, political, psychological and health care-related challenges that contribute to marked mental health disparities. However, the overall strength and credibility of evidence across mental disorders, mental disorder-related symptomatology, suicidal or self-harm behaviors, and access to mental health care have not been systematically assessed in these populations. We conducted an umbrella review of systematic reviews with meta-analyses (SRMAs) of observational studies investigating mental health outcomes in LGBTQIA+ populations. PubMed, Scopus and PsycINFO were searched from inception to April 23, 2025, with no language restrictions. Eligible SRMAs compared LGBTQIA+ populations with cisgender heterosexual populations (primary aim), or subgroups within LGBTQIA+ populations (secondary aim). Outcomes were categorized as diagnosed mental disorders, disorder-related symptomatology, suicidal or self-harm behaviors, and access to mental health care. The credibility of each association was evaluated according to standardized criteria, classifying evidence as convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), or not significant. We included 22 SRMAs encompassing 398 individual studies and 162 unique meta-analytic associations. Among these, eight associations reached convincing evidence (class I). Compared with cisgender heterosexual populations, LGB populations had a higher risk of depressive disorders (risk ratio, RR=2.05, 95% CI: 1.69-2.48) and suicidal behaviors, including suicide attempts (RR=2.51, 95% CI: 2.14-2.94) and suicidal ideation or attempts combined (odds ratio, OR=3.20, 95% CI: 2.65-3.86). Among adolescents, gay populations showed higher odds of eating disorder-related behaviors compared with heterosexual peers, including dieting (OR=3.10, 95% CI: 2.69-3.58) and purging (OR=5.40, 95% CI: 4.72-6.17). Within LGBTQIA+ populations, bisexual individuals had higher odds of anxiety symptoms (OR=1.73, 95% CI: 1.56-1.92) and non-suicidal self-injury (OR=2.24, 95% CI: 1.91-2.63) compared with lesbian and gay individuals. In addition, gay populations showed significantly lower body image disturbance than lesbian populations (standardized mean difference, SMD=-0.25, 95% CI: -0.32 to -0.19). Considering both class I and II evidence, body image disturbance showed a consistent gradient across sexual orientation, with higher levels among heterosexual women, followed by lesbian women, gay men, and heterosexual men. We conclude that mental health disparities affecting LGBTQIA+ populations are supported by highly credible evidence, particularly for depressive disorders, suicidality, and eating disorder symptoms, underscoring the urgent need for inclusive prevention strategies, targeted interventions, and structural reforms addressing stigma and discrimination in health care.

Key words: LGBTQIA+ populations, mental health disparities, depressive disorders, suicidal behaviors, eating disorder symptoms, body image disturbance, stigma, inclusive prevention strategies

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In more than 60 countries worldwide, consensual same-sex sexual acts or gender-diverse expressions remain criminalized, and at least seven countries explicitly apply the death penalty, underscoring the persistence of severe discrimination against lesbian, gay, bisexual, transgender, questioning, intersex, asexual (LGBTQIA+) populations¹. Beyond these settings, in recent years numerous countries have introduced laws restricting freedom of expression, limiting public visibility, and curtailing previously consolidated rights². Such regression has occurred even in contexts that had achieved substantial legal and social progress, reflecting broader patterns of resistance and backlash against sexual and gender diversity³.

This sociopolitical climate shapes the environments in which LGBTQIA+ populations live and seek care, with clear implications for public health. Structural stigma – defined as societal-level conditions, cultural norms, and institutional policies that constrain opportunities, resources and well-being⁴ – has emerged as a key driver of mental health disparities affecting LGBTQIA+ populations⁵. Evidence consistently links structural stigma to elevated risks of de-

pression, suicidality, substance use, and poorer self-rated health, highlighting the tangible health consequences of discriminatory legal and social frameworks⁵.

Disparities also arise from the complex interplay between interpersonal discrimination, individual, and health care system factors, as well as intersecting determinants. Specifically, interpersonal discrimination – including victimization, bullying, and family rejection – consistently increases the risk of depression, anxiety, post-traumatic stress, and suicidality^{6,7}. Individual factors – such as internalized stigma, expectations of rejection, and concealment of one's identity – further contribute to chronic stress and poorer mental health^{8,9}. Within health care system factors, lack of provider training, discriminatory attitudes, and the absence of inclusive clinical guidelines, can exacerbate disparities by limiting access to prevention and treatment¹⁰. Finally, intersecting determinants – such as ethnicity, migration status, socioeconomic position, and disability – may compound stigma-related risks, creating layered vulnerabilities within LGBTQIA+ populations¹¹.

Despite growing recognition of these issues, the scientific evi-

dence remains fragmented. Previous systematic reviews and meta-analyses (SRMAs) have only examined specific mental health outcomes in specific sexual and gender minorities. Two umbrella reviews identified substantial mental health disparities, but they only focused on restricted sub-populations, namely transgender and non-binary adults¹², and sexual and gender minority youth¹³. Moreover, these latter reviews did not apply formal credibility-grading frameworks to systematically assess the strength and reliability of the evidence across outcomes, limiting the generalizability and interpretability of their conclusions.

Our umbrella review aims to provide a comprehensive synthesis of the mental health outcomes of LGBTQIA+ populations across the full spectrum of sexual and gender minority identities and age groups, and to grade the certainty of evidence according to established criteria, by examining: a) differences between LGBTQIA+ and cisgender heterosexual populations, and b) disparities within LGBTQIA+ subgroups.

By integrating the available evidence and rigorously grading its credibility, this umbrella review seeks to clarify which mental health disparities affecting LGBTQIA+ populations are supported by the most robust data, and which areas remain uncertain. This work is intended to provide a reliable evidence base to guide clinicians, researchers and policy makers in identifying priority needs, reducing preventable inequalities, and informing more inclusive and effective mental health interventions.

METHODS

This paper followed the rules for umbrella reviews¹⁴, and the Preferred Reporting Items for Overviews of Reviews (PRIOR) guidelines¹⁵. The protocol was registered on the Open Science Framework (see supplementary information). We systematically searched PubMed, Scopus and PsycINFO from inception until April 23, 2025, with no language restrictions. The full search strings are provided in the supplementary information.

Inclusion and exclusion criteria

We included SRMAs, defined as systematic reviews that conducted an explicit, structured and reproducible search in at least one biomedical database, with clearly reported selection criteria, and that performed a quantitative synthesis of study results through meta-analytical techniques. Eligible SRMAs were based on observational studies (cross-sectional and longitudinal) investigating mental health in LGBTQIA+ populations of any age groups.

Comparisons were of two types: a) those examining differences between LGBTQIA+ populations and cisgender heterosexual populations (primary aim), and b) those examining disparities across LGBTQIA+ subgroups (secondary aim), using the comparator groups defined by each original SRMA rather than a pre-defined control group. Eligible outcomes comprised four categories: diag-

nosed mental disorders; mental disorder-related symptomatology; suicidal or self-harm behaviors; and access to mental health care services. All outcomes were considered as operationalized in the original studies and synthesized in the included SRMAs, in line with previous umbrella reviews¹⁶.

We excluded SRMAs without a comparison group, SRMAs of interventions, systematic reviews without meta-analysis, and meta-analyses not preceded by a systematic search.

Data extraction and quality assessment

Four authors (MB, LB, MC, CP) independently screened titles, abstracts and full texts of potentially eligible SRMAs. Discrepancies were resolved by discussion; when consensus was not reached, two senior authors (VO and MDP) were consulted. Two authors (VO and MC) independently extracted data from each eligible SRMA; in case of discrepancies, a third author (MDP) was consulted.

At the SRMA level, we extracted first author, publication year, number of included studies, age group of participants, LGBTQIA+ population examined, comparison group, mental health outcomes, and time frame of the outcome (e.g., current or lifetime). When reported by the SRMAs, we also extracted information at the individual study level, including first author, year, country, design, sample size of the population examined and the control group, and either the effect sizes with 95% confidence intervals (CIs) or the corresponding measures of variance, event rates, or means and standard deviations required to calculate them.

For the purposes of this umbrella review, each association was defined as the combination of the LGBTQIA+ population examined, the comparator group, the age group (i.e., adolescents, adults, mixed), the mental health outcome, and the time frame of the outcome. If two SRMAs presented data on the same association, we applied a hierarchical decision rule to avoid duplication: we prioritized inclusion of the SRMA that included the largest number of individual studies and, in case of a tie, the most recent SRMA.

Two authors (VO and MC) independently assessed the methodological quality of each included SRMA using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2)¹⁷, with discrepancies resolved by a third author (MDP). Methodological quality was categorized as “high” if no critical weaknesses and no more than one non-critical weakness was found, “moderate” if no critical weaknesses and more than one non-critical weakness was found, “low” if one critical weakness was found, and “critically low” if more than one critical weakness was found¹⁷.

Data analysis

We conducted all analyses using the R package *metaumbrella*, which re-meta-analyzes the data to produce harmonized meta-analytic estimates and diagnostics¹⁸. The credibility of each association was assessed according to recognized international crite-

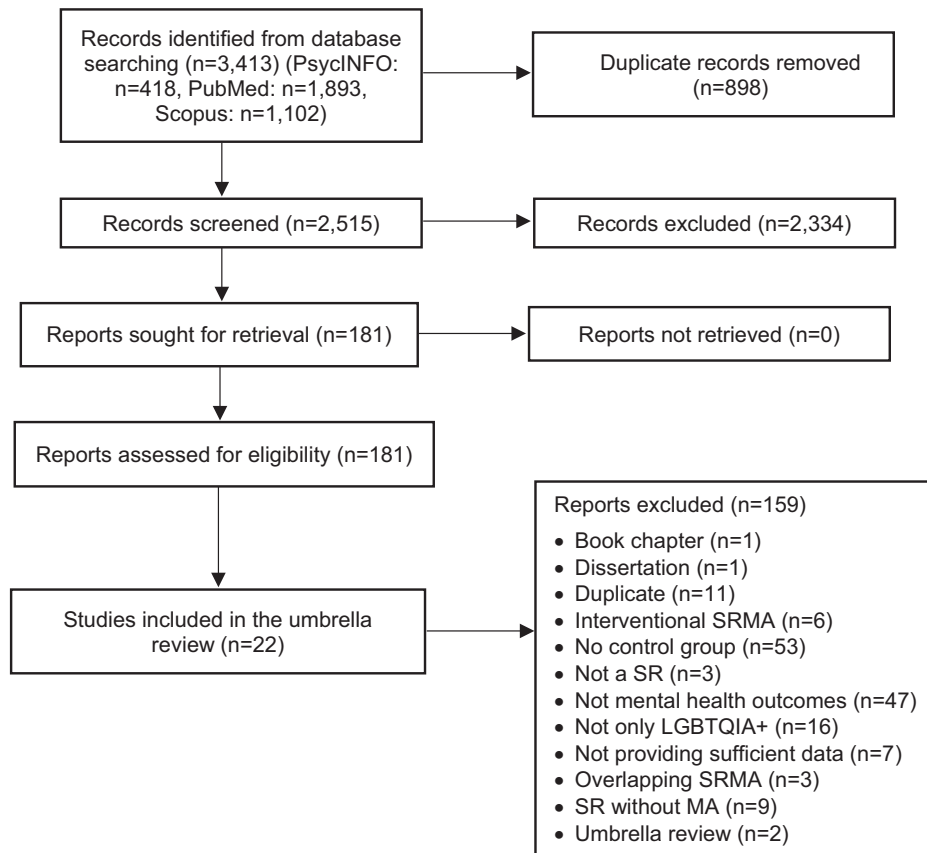


Figure 1 PRISMA flow chart. SR – systematic review, MA – meta-analysis, LGBTQIA+ – lesbian, gay, bisexual, transgender, questioning, intersex, asexual

ria¹⁶, classifying the evidence as convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), or not significant. For significant associations, class I required more than 1,000 cases, $p < 10^{-6}$, no evidence of small-study effects or excess significance bias, a prediction interval not including the null, the largest study being significant, and $I^2 < 50\%$. Class II required more than 1,000 cases, $p < 10^{-6}$, and the largest study being significant. Class III required more than 1,000 cases and $p < 10^{-3}$. Class IV required $p < 0.05$.

We also conducted sensitivity analyses for both primary and secondary aims, removing the >1,000-cases criterion to account for the under-representation of LGBTQIA+ populations in primary studies, and restricting analyses to individual studies conducted within the same continent to explore potential geographical heterogeneity.

RESULTS

Our systematic search identified 3,413 records. After removal of 898 duplicates, 2,515 records were screened at title and abstract level, of which 2,334 were excluded. We assessed 181 full-text reports for eligibility. Twenty-two SRMAs met inclusion criteria and were included in the umbrella review (see Figure 1 and supplementary information)¹⁹⁻⁴⁰.

plementary information)¹⁹⁻⁴⁰.

The included SRMAs were published between 2006 and 2024. Eighteen (81.8%) of them examined mixed age groups (adolescents and adults), one (4.6%) focused exclusively on adults, and three (13.6%) exclusively on adolescents. Twenty-two (100%) SRMAs compared LGBTQIA+ populations with cisgender heterosexual populations (primary aim), and eight (36.4%) investigated differences across LGBTQIA+ subgroups (secondary aim). Regarding the outcomes, nine (40.9%) SRMAs reported on diagnosed mental disorders, 10 (45.5%) on mental disorder-related symptomatology, and 11 (50.0%) on suicidal or self-harm behaviors, whereas none addressed access to mental health care services.

The included SRMAs encompassed a total of 398 individual studies. Among the studies for which information on geographical distribution was available ($n = 268$, 67.3%), 195 (72.8%) were conducted in North America, 40 (14.9%) in Europe, 16 (6.0%) in Asia, 13 (4.8%) in Oceania, two (0.7%) in Africa, and two (0.7%) in South America. Regarding study design, information was available for 251 studies (63.1%). Of these, 226 (90.0%) were cross-sectional and 25 (10.0%) were longitudinal.

We identified 162 associations. Of these, 125 (77.2%) emerged from comparisons between LGBTQIA+ populations and cisgender heterosexual populations (primary aim), and 37 (22.8%) from comparisons between different subgroups within the LGBTQIA+

Table 1 Summary of associations with convincing (class I) evidence for mental health outcomes in LGBTQIA+ populations

Population	Comparator	Specific outcome	Estimate (95% CI)	p	n	N cases	N controls	PI	I ²	SSE/ESB	LS
<i>LGBTQIA+ vs. heterosexual cisgender, adolescents</i>											
G	Heterosexual boys	Dieting	OR=3.10 (2.69-3.58)	<10 ⁻⁶	3	145,578	50,381	Significant	26%	No/no	Yes
G	Heterosexual boys	Purging	OR=5.40 (4.72-6.17)	<10 ⁻⁶	5	26,664	186,801	Significant	0%	No/no	Yes
<i>LGBTQIA+ vs. heterosexual cisgender, mixed age groups (adolescents and adults)</i>											
LGB	Non-LGB	Depressive disorders (past year)	RR=2.05 (1.69-2.48)	<10 ⁻⁶	4	1,991	21,742	Significant	0%	No/no	Yes
LGB	Non-LGB	Suicide attempts (past year)	RR=2.51 (2.14-2.94)	<10 ⁻⁶	4	2,329	27,823	Significant	16%	No/no	Yes
LG	Heterosexual	Suicidal ideation or suicide attempts	OR=3.20 (2.65-3.86)	<10 ⁻⁶	8	46,314	110,191	Significant	26%	No/no	Yes
<i>Within LGBTQIA+ populations</i>											
B	LG	Anxiety symptoms (current)	OR=1.73 (1.56-1.92)	<10 ⁻⁶	4	3,224	8,319	Significant	0%	No/no	Yes
G	L	Body image disturbance	SMD=-0.25 (-0.32 to -0.19)	<10 ⁻⁶	16	3,838	2,870	Significant	23%	No/no	Yes
B	LG	Non-suicidal self-injury (lifetime)	OR=2.24 (1.91-2.63)	<10 ⁻⁶	9	2,291	1,443	Significant	29%	No/no	Yes

G – gay, B – bisexual, L – lesbian, T – transgender, Q – questioning, I – intersex, A – asexual, OR – odds ratio, RR – risk ratio, SMD – standardized mean difference, PI – prediction interval, SSE – small study effect, ESB – excess significant bias, LS – largest study with significant effects

community (secondary aim). Regarding outcomes, 50 associations (30.9%) concerned diagnosed mental disorders, 46 (28.4%) disorder-related symptomatology, and 66 (40.7%) suicidal or self-harm behaviors.

Within the 50 associations focusing on diagnosed mental disorders, 17 (34.0%) regarded anxiety disorders, 16 (32.0%) depressive disorders, 10 (20.0%) substance use disorders, five (10.0%) post-traumatic stress disorder (PTSD), one (2.0%) psychotic disorders, and one (2.0%) any mental disorder. Among the 46 associations focusing on mental disorder-related symptomatology, 29 (63.0%) regarded eating disorder-related symptoms, eight (17.4%) depressive symptoms, four (8.7%) anxiety symptoms, three (6.5%) post-traumatic stress symptoms, one (2.2%) autism spectrum disorder traits, and one (2.2%) psychotic experiences.

Of the 66 associations concerning suicidal and self-harm behaviors, 27 (40.9%) regarded suicide attempts, 19 (28.9%) self-harm, 16 (24.2%) suicidal ideation, three (4.5%) suicidal ideation or suicide attempts, and one (1.5%) mental health difficulties in LGBTQIA+ vs. cisgender heterosexual populations with experiences of self-harm or suicide.

Four SRMAs were rated as having “low” quality^{23,28,30,37}, and the others as having “critically low” quality according to AMSTAR-2 (see supplementary information).

There was convincing (class I) evidence for eight associations (4.9%) (see Table 1), and highly suggestive (class II) evidence for 46 associations (28.4%) (see Table 2). The evidence was classified as suggestive (class III) for 28 associations (17.3%), as weak (class IV) for 44 (27.2%), and as not significant for 36 (22.2%) (see supple-

mentary information).

Among the eight associations that reached convincing evidence (class I), five (62.5%) emerged from comparisons between LGBTQIA+ populations and cisgender heterosexual populations (see Table 1). Among adolescents, gay populations had higher odds of eating disorder-related symptoms compared with heterosexual populations, including both dieting (odds ratio, OR=3.10, 95% CI: 2.69-3.58) and purging (OR=5.40, 95% CI: 4.72-6.17). In mixed adolescent/adult samples, LGB populations had a higher past-year risk of depressive disorders compared with non-LGB populations (risk ratio, RR=2.05, 95% CI: 1.69-2.48). Moreover, LGB populations had a higher risk of past-year suicide attempts (RR=2.51, 95% CI: 2.14-2.94) and LG populations had higher odds of suicidal ideation or suicide attempts (OR=3.20, 95% CI: 2.65-3.86) compared with cisgender heterosexual populations.

Three further associations (37.5%) with convincing evidence emerged from comparisons within LGBTQIA+ subgroups (see Table 1). In mixed samples, bisexual populations had higher odds of current anxiety symptoms compared with LG populations (OR=1.73, 95% CI: 1.56-1.92). Gay populations reported lower body image disturbance compared with lesbian populations (standardized mean difference, SMD=-0.25, 95% CI: -0.32 to -0.19). Finally, bisexual populations had higher odds of lifetime non-suicidal self-injury compared with LG populations (OR=2.24, 95% CI: 1.91-2.63).

Considering both class I and II evidence, a consistent gradient of body image disturbance emerged across sexual orientation and gender groups. In fact, in addition to the above-mentioned lower

Table 2 Summary of associations with highly suggestive (class II) evidence for mental health outcomes in LGBTQIA+ populations

Population	Comparator	Specific outcome	Estimate (95% CI)	p	n	N cases	N controls	PI	I ²	SSE/ESB	LS
<i>LGBTQIA+ vs. heterosexual cisgender, adolescents</i>											
Sexual minority	Heterosexual	Depressive symptoms or disorders	OR=2.94 (2.27-3.80)	<10 ⁻⁶	6	19,348	68,735	Significant	93%	No/no	Yes
Sexual minority	Heterosexual	Depressive symptoms	SMD=0.40 (0.33-0.47)	<10 ⁻⁶	13	11,050	11,050	Significant	67%	No/yes	Yes
L	Heterosexual girls	Diet pills use (current)	OR=2.59 (1.99-3.36)	<10 ⁻⁶	3	150,097	46,356	Not significant	52%	No/no	Yes
B girls	Heterosexual girls	Purging	OR=2.32 (1.81-2.98)	<10 ⁻⁶	5	25,385	7,667	Not significant	82%	No/no	Yes
B	Heterosexual	Suicide attempts	OR=4.60 (3.46-6.12)	<10 ⁻⁶	9	559,720	1,346,709	Significant	99%	No/no	Yes
LGB	Heterosexual	Suicide attempts	OR=4.39 (2.61-7.38)	<10 ⁻⁶	6	119,495	147,116	Not significant	98%	No/no	Yes
Sexual minority	Heterosexual	Suicide attempts	OR=4.31 (3.51-5.28)	<10 ⁻⁶	24	738,506	1,747,949	Significant	98%	No/no	Yes
LG	Heterosexual	Suicide attempts	OR=4.14 (3.57-4.79)	<10 ⁻⁶	19	353,835	1,945,203	Significant	88%	No/no	Yes
<i>LGBTQIA+ vs. heterosexual cisgender, adults</i>											
LGB	Heterosexual	Psychotic experiences	OR=1.99 (1.54-2.57)	<10 ⁻⁶	4	29,281	87,540	Not significant	81%	No/no	Yes
<i>LGBTQIA+ vs. heterosexual cisgender, mixed age groups (adolescents and adults)</i>											
B	Heterosexual	Anxiety disorders	OR=2.84 (1.98-4.07)	<10 ⁻⁶	5	12,741	75,552	Not significant	79%	No/no	Yes
LG	Heterosexual	Anxiety disorders	OR=2.19 (1.76-2.72)	<10 ⁻⁶	9	108,296	91,127	Significant	82%	No/no	Yes
LB women	Non-LB women	Depressive disorders (past year)	RR=2.1 (1.60-2.76)	<10 ⁻⁶	4	1,349	11,826	Not significant	0%	No/no	Yes
LGB	Non-LGB	Depressive disorders (lifetime)	RR=2.03 (1.70-2.42)	<10 ⁻⁶	2	1,357	5,648	Not significant	0%	No/no	Yes
B	Heterosexual	Depressive disorders	OR=2.69 (2.27-3.20)	<10 ⁻⁶	15	75,141	314,994	Significant	86%	No/no	Yes
LG	Heterosexual	Depressive disorders	OR=1.98 (1.77-2.21)	<10 ⁻⁶	20	244,698	232,783	Significant	56%	No/no	Yes
T	Heterosexual/ cisgender	PTSD	OR=2.52 (2.22-2.87)	<10 ⁻⁶	7	24,494	49,608	Significant	78%	No/no	Yes
LGTBQ	Heterosexual/ cisgender	PTSD	OR=2.20 (1.86-2.60)	<10 ⁻⁶	22	118,527	177,698	Significant	91%	No/no	Yes
L	Heterosexual women	Body image disturbance	SMD=-0.14 (-0.20 to -0.08)	<10 ⁻⁶	22	3,757	44,936	Not significant	42%	No/no	Yes
G	Heterosexual men	Body image disturbance	SMD=0.35 (0.22-0.47)	<10 ⁻⁶	24	4,305	44,081	Not significant	81%	No/yes	Yes
B	Heterosexual	Depressive symptoms (current)	OR=2.33 (1.80-3.01)	<10 ⁻⁶	17	301,513	249,975	Not significant	91%	Yes/No	Yes
Non-binary	Cisgender	Depressive symptoms	SMD=0.52 (0.42-0.62)	<10 ⁻⁶	8	11,130	11,130	Significant	92%	No/no	Yes
Sexual minority women	Heterosexual women	PTSD symptoms	SMD=0.45 (0.31-0.59)	<10 ⁻⁶	20	5,535	5,535	Not significant	87%	No/no	Yes
LGBTQ+ with experiences of self-harm or suicide	Heterosexual/ cisgender with experiences of self-harm or suicide	Mental health difficulties	OR=3.30 (2.16-5.04)	<10 ⁻⁶	8	21,146	22,491	Not significant	95%	Yes/no	Yes

Table 2 Summary of associations with highly suggestive (class II) evidence for mental health outcomes in LGBTQIA+ populations (*continued*)

Population	Comparator	Specific outcome	Estimate (95% CI)	p	n	N cases	N controls	PI	I ²	SSE/ESB	LS
B	Heterosexual	Non-suicidal self-injury	OR=5.74 (4.26-7.73)	<10 ⁻⁶	8	25,718	108,577	Significant	95%	No/no	Yes
B	Heterosexual	Non-suicidal self-injury	OR=4.46 (3.19-6.24)	<10 ⁻⁶	12	15,675	38,169	Significant	80%	No/no	Yes
LGBTQI+	Non-LGBTQI+	Non-suicidal self-injury	OR=4.26 (3.13-5.80)	<10 ⁻⁶	20	48,320	188,673	Significant	96%	No/no	Yes
B	Heterosexual	Suicide attempts (past year)	OR=4.81 (3.71-6.23)	<10 ⁻⁶	13	46,403	189,950	Significant	94%	No/no	Yes
B	Heterosexual	Suicide attempts (lifetime)	OR=4.79 (3.77-6.08)	<10 ⁻⁶	11	23,812	131,763	Significant	75%	No/no	Yes
GB men	Non-GB men	Suicide attempts (lifetime)	RR=4.21 (2.39-7.40)	<10 ⁻⁶	5	1,518	32,756	Not significant	84%	Yes/yes	Yes
LGB	Non-LGB	Suicide attempts (lifetime)	RR=2.49 (1.84-3.36)	<10 ⁻⁶	4	2,216	35,872	Not significant	61%	No/no	Yes
B	Non-LGBTQI+	Suicide attempts	OR=6.71 (5.33-8.44)	<10 ⁻⁶	7	11,393	161,686	Significant	83%	No/no	Yes
LG	Non-LGBTQI+	Suicide attempts	OR=6.05 (3.50-10.48)	<10 ⁻⁶	8	23,126	240,226	Not significant	99%	Yes/no	Yes
LGBTQI+	Non-LGBTQI+	Suicide attempts	OR=4.38 (3.59-5.34)	<10 ⁻⁶	35	156,416	795,718	Significant	99%	Yes/no	Yes
Gender diverse	Cisgender	Suicide attempts	OR=4.00 (3.18-5.04)	<10 ⁻⁶	34	80,464	3,795,306	Significant	97%	No/no	Yes
TIQ	Non-LGBTQI+	Suicide attempts	OR=3.46 (2.56-4.69)	<10 ⁻⁶	8	31,122	156,106	Significant	93%	No/no	Yes
B	Heterosexual	Suicidal ideation (past year)	OR=3.97 (3.22-4.90)	<10 ⁻⁶	15	85,284	253,433	Significant	89%	No/no	Yes
B	Heterosexual	Suicidal ideation (lifetime)	OR=4.38 (3.10-6.20)	<10 ⁻⁶	7	62,405	230,261	Significant	94%	No/no	Yes
Non-binary	Cisgender	Suicidal ideation (lifetime)	OR=2.13 (1.67-2.72)	<10 ⁻⁶	3	1,884	672	Not significant	29%	No/no	Yes
LGB	Non-LGB	Suicidal ideation (lifetime)	RR=2.04 (1.57-2.64)	<10 ⁻⁶	2	5,688	30,801	Not significant	73%	No/no	Yes
GB men	Non-GB men	Suicidal ideation (lifetime)	RR=2.01 (1.56-2.59)	<10 ⁻⁶	2	4,613	28,085	Not significant	71%	No/no	Yes
B	Non-LGBTQI+	Suicidal ideation	OR=5.03 (4.13-6.13)	<10 ⁻⁶	10	67,656	208,631	Significant	88%	No/no	Yes
LGBTQI+	Non-LGBTQI+	Suicidal ideation	OR=3.80 (3.13-4.61)	<10 ⁻⁶	34	534,548	3,152,180	Significant	99%	No/no	Yes
TIQ	Non-LGBTQI+	Suicidal ideation	OR=3.48 (2.64-4.58)	<10 ⁻⁶	9	329,134	470,227	Significant	97%	No/no	Yes
LG	Non-LGBTQI+	Suicidal ideation	OR=2.59 (1.95-3.44)	<10 ⁻⁶	11	153,148	211,222	Not significant	97%	Yes/yes	Yes
B	Heterosexual	Suicidal ideation or suicide attempts	OR=5.73 (3.51-9.35)	<10 ⁻⁶	5	36,870	99,799	Not significant	91%	No/no	Yes
<i>Within LGBTQIA+ populations, mixed age groups (adolescents and adults)</i>											
B	LG	Depressive symptoms (current)	OR=1.47 (1.29-1.68)	<10 ⁻⁶	20	9,988	12,494	Not significant	49%	No/no	Yes

G – gay, B – bisexual, L – lesbian, T – transgender, Q – questioning, I – intersex, A – asexual, PTSD – post-traumatic stress disorder, OR – odds ratio, RR – risk ratio, SMD – standardized mean difference, PI – prediction interval, SSE – small study effect, ESB – excess significant bias, LS – largest study with significant effects

body image disturbance among gay compared with lesbian populations, lesbian women reported lower body image disturbance compared with heterosexual women (SMD=−0.14, 95% CI: −0.20 to −0.08), and gay men reported higher body image disturbance compared with heterosexual men (SMD=0.35, 95% CI: 0.22–0.47) (see Table 2).

By removing the criterion of more than 1,000 cases, 16 associations changed from class IV to higher classes. Specifically, six associations (37.5%) were reclassified to class I, six (37.5%) to class II, and four (25%) to class III (see supplementary information). Among the associations that reached convincing evidence (class I), three compared LGBTQIA+ populations with cisgender heterosexual populations in mixed adolescent/adult samples. GB men had higher risk of past-year depressive disorders compared with non-GB men (RR=2.41, 95% CI: 1.79–3.22). Regarding suicidality and self-harm, GB men had a higher risk of past-year suicidal ideation compared with non-GB men (RR=1.64, 95% CI: 1.37–1.97), and LB women had higher risk of lifetime suicide attempts compared with non-LB women (RR=1.82, 95% CI: 1.59–2.10). Three additional class I associations involved comparisons between subgroups of LGBTQIA+ populations, all related to self-harm. Bisexual populations had higher odds of non-suicidal self-injury compared with asexual populations (OR=6.01, 95% CI: 3.94–9.16) and with gay populations (OR=2.96, 95% CI: 2.02–4.35). LG populations also had higher odds of non-suicidal self-injury compared with asexual populations (OR=3.72, 95% CI: 2.73–5.08).

The results of the sensitivity analyses restricting the evidence to individual studies conducted within the same continent are reported in the supplementary information. Six class I associations were identified for North America. Among comparisons between LGBTQIA+ and heterosexual populations, two associations from the main analysis remained class I: among adolescents, gay populations continued to show higher odds of purging behaviors compared with heterosexual peers (OR=6.09, 95% CI: 4.61–8.05); in mixed adolescent/adult samples, LGB populations continued to show higher risk of past-year suicide attempts compared with non-LGB populations (RR=2.51, 95% CI: 2.14–2.94). One additional association reached class I under this restriction: in mixed samples, bisexual populations showed higher odds of suicide attempts compared with heterosexual populations (OR=4.59, 95% CI: 3.90–5.40).

In within-LGBTQIA+ comparisons, three associations remained class I in North American studies: gay populations reported lower body image disturbance compared with lesbian populations (SMD=−0.23, 95% CI: −0.31 to −0.15); and bisexual populations showed higher odds of both non-suicidal self-injury (OR=2.23, 95% CI: 1.89–2.63) and suicidal ideation (OR=1.89, 95% CI: 1.61–2.22) compared with LG populations.

DISCUSSION

This umbrella review provides the most comprehensive synthesis to date of mental health disparities affecting LGBTQIA+ populations. Across 162 associations derived from 22 SRMAs and

398 individual studies, eight (4.9%) reached convincing evidence (class I) and 46 (28.4%) highly suggestive evidence (class II). The most robust evidence emerged for disparities in depressive disorders, suicidal behaviors, and eating disorder-related symptoms when comparing LGBTQIA+ populations with cisgender heterosexual populations. Within LGBTQIA+ populations, bisexual populations showed higher odds of anxiety and depressive symptoms, as well as non-suicidal self-injury, compared with LG populations, suggesting a broader mental health burden in this group. Body image disturbance showed a consistent gradient across sexual orientation, with higher levels among heterosexual women, followed by lesbian women, gay men, and heterosexual men.

Among the associations reaching the highest credibility (class I), LGB populations were about twice as likely to experience a depressive disorder compared with heterosexual populations. Both the prevalence and severity of depressive symptoms were already elevated among sexual minority adolescents (class II), indicating that this disparity emerges early in life, in line with previous umbrella review evidence¹³. Our findings extend this observation to adulthood, in line with meta-regression analyses reporting a positive association between mean age and the prevalence of depressive disorders within LGBTQ+ samples⁴¹. This pattern may reflect cumulative lifetime risk⁴², since older LGBTQ+ individuals are more likely to have been exposed to less affirming social and health care environments^{43–45}, as well as generational differences in identity disclosure⁴⁶.

Class II evidence for specific sexual minority populations versus heterosexual counterparts consistently confirmed these disparities concerning depressive symptoms/disorders, indicating that they are observed across different sexual minority subgroups rather than being confined to a single orientation category. This evidence may be interpreted in light of the minority stress models, which posit shared stress-related exposures linked to minority status^{47–49}. Several well-established risk factors for depression – including parental rejection, bullying and trauma exposure, reduced social support, housing instability, and maladaptive coping – have been reported at higher rates among sexual minority populations⁵⁰. Differential exposure to these determinants may contribute to the elevated depressive burden observed across subgroups.

Evidence for non-binary populations remains more limited, but suggestive. In the present umbrella review, one association – greater depressive symptom severity among non-binary compared with cisgender populations – reached class II credibility, providing the first graded quantitative signal linking non-binary identities to depressive burden. This disparity may reflect the combined impact of limited legal recognition, lower societal understanding of non-binary identities, and barriers within health care systems that remain largely structured around binary gender models^{51,52}.

Increased risk of suicidal ideation and suicide attempts in LGB compared with non-LGB populations reached convincing evidence (class I) across mixed-age samples including both adolescents and adults. Notably, more than half of the associations supported by highly suggestive evidence (27 of 46 class II associations) concerned suicidal outcomes, making suicidality the

most represented domain at this level of credibility. Of these, four referred to suicide attempts in adolescent samples, aligning with previous umbrella evidence documenting elevated suicidality among LGBTQIA+ youth¹³. Other associations were derived from mixed-age populations, indicating that disparities in suicidal outcomes are observable across developmental stages. Consistent across comparisons, suicidal outcomes were higher in all sexual minority groups than in cisgender heterosexual populations, suggesting that this disparity is widespread among sexual minorities, and parallels the pattern observed for depressive disorders.

Indeed, suicidal behaviors frequently co-occur with depressive disorders⁵³, and several psychosocial risk factors associated with depression in sexual minority populations – including parental rejection, discrimination, identity-based victimization, and housing instability – have also been linked to suicidal risk, with a cumulative effect when multiple stressors co-occur^{54,55}. Recent qualitative evidence further suggests that suicidal behaviors are often described in the context of chronic stigma, perceived burdensomeness, and social disconnection, offering an experiential perspective that complements the observed epidemiological gradients⁵⁶.

Gay adolescents showed significantly higher odds of disordered eating symptoms (i.e., dieting and purging) than their heterosexual peers, supported by convincing evidence (class I). Class II associations broadened this pattern, showing higher odds of eating-related symptoms (i.e., diet pill use and purging) also among LB adolescent girls compared with heterosexual peers. Our results provide the first graded quantitative confirmation of this disparity. Converging clinical evidence further suggests that sexual and gender minority individuals may present with greater eating disorder symptom severity⁵⁷. Among adults, gay men reported significantly greater body image disturbance than heterosexual men, whereas heterosexual women showed higher global body image disturbance than lesbian women. Moreover, lesbian women showed greater body image disturbance than gay men. This gradient (heterosexual women > lesbian women > gay men > heterosexual men) may be interpreted in light of sociocultural models emphasizing gendered objectification and differential exposure to appearance norms, which exert strong body-related pressures on women and gay men, while lesbian women may experience partial buffering from heteronormative beauty ideals²¹.

Beyond sociocultural objectification processes, prior research suggests that vulnerability to disordered eating in sexual minority populations may also be influenced by minority-specific body ideals⁵⁸, internalized stigma⁵⁹, and exposure to weight- or appearance-based discrimination^{60,61}, factors that can intersect with broader gendered pressures. No graded meta-analytic evidence was identified for non-binary and transgender populations in this domain, pointing to an important gap in quantitative synthesis. However, individual studies have reported markedly elevated rates of eating disorder diagnoses among transgender individuals^{62,63}.

Taken together, depressive disorders, suicidality, and disordered eating symptoms emerge as the most robustly and consistently documented mental health disparities affecting LGBTQIA+ populations, with high-credibility evidence supporting their presence across developmental stages and sexual minority subgroups.

Several class II findings further delineate the mental health burden affecting LGBTQIA+ populations. Anxiety disorders were more prevalent among LGB populations than in heterosexual counterparts, and PTSD risk was elevated across LGBTQIA+ groups, particularly among transgender populations. Sexual minority women also reported greater PTSD symptom severity. The elevation of anxiety and PTSD outcomes is consistent with disproportionate exposure to trauma, discrimination, and chronic stressors documented in sexual and gender minority populations^{64–66}. Among adults, LGB populations showed higher rates of psychotic experiences compared with heterosexual peers, extending the pattern of elevated affective and stress-related symptoms to the psychosis spectrum. In several studies, bullying victimization, discrimination, and childhood trauma were reported as significant contributors to the association between sexual minority status and psychosis-related outcomes, whereas substance use appeared to play a comparatively smaller role^{67,68}.

Within LGBTQIA+ populations, evidence indicates marked heterogeneity in mental health outcomes. Class I associations showed higher anxiety symptoms and non-suicidal self-injury among bisexual than lesbian or gay populations, while class II evidence revealed more frequent depressive symptoms, suggesting a broader affective burden in the former group. These disparities may be interpreted in light of evidence that bisexual individuals are exposed to stigma and identity invalidation in both heterosexual and sexual minority contexts, alongside lower levels of perceived belonging and social support⁶⁹. Such “double marginalization” may contribute to the broader affective and self-harm burden observed in this subgroup⁶⁹.

Notably, this umbrella review highlights major evidence gaps. No quantitative synthesis was available for access to mental health care services, preventing any assessment of disparities in access or quality of mental health care. However, recent population-based evidence may be considered in this respect. In a representative sample of young adults, sexual minority individuals were more likely than heterosexuals to report having used mental health services in the previous year, but also more likely to report unmet mental health care needs, defined as perceiving a need for care without receiving professional treatment⁷⁰. Complementary health system data further indicate that LGBTQ individuals, in addition to higher outpatient mental health use, are also disproportionately represented in emergency department visits for mental health crises⁷¹. Together, these findings suggest that increased service contact does not necessarily translate into adequately met mental health needs. Elevated mental health burden may therefore coexist with persistent gaps in care continuity and adequacy, which is concerning given the established association between untreated mental disorders, symptom persistence, functional impairment, and suicidal risk⁷². Potential contributors to these gaps include limited LGBTQ-specific clinical competence, prior negative health care experiences, concerns about stigma or discrimination within health care settings, and structural constraints within systems that are not fully equipped to address sexual and gender diversity^{73–76}.

Likewise, evidence remains scarce for severe psychiatric disorders. Only one meta-analysis evaluated psychosis as a broad out-

come³⁷, while no data were available for specific diagnoses such as schizophrenia or bipolar disorder. The absence of high-quality meta-analytic evidence for the most severe and disabling psychiatric conditions is striking, given their public health relevance and the well-documented social stressors affecting LGBTQIA+ populations.

This umbrella review has several notable strengths. It adopts the broadest scope to date, encompassing the full spectrum of sexual orientations, gender identities, and age groups within LGBTQIA+ populations. By systematically organizing outcomes across diagnostic categories, symptom dimensions, suicidality, and access to mental health care, it allows a comprehensive mapping of mental health disparities. The use of validated credibility criteria to grade the strength of evidence represents a major methodological advance and provides a transparent, quantitative framework for interpreting the robustness of findings. Importantly, the review not only consolidates existing knowledge, but also identifies key evidence gaps, particularly regarding access to mental health care and severe psychiatric disorders. All methodological procedures followed established standards for umbrella evidence synthesis, ensuring transparency and reproducibility.

This study also has some limitations. As with any umbrella review, the findings depend on the quantity and quality of the available meta-analyses. Overall, the methodological quality of the included SRMAs, as assessed by AMSTAR-2, was low or critically low, mainly due to recurrent shortcomings in a limited number of critical domains. The most frequent issue was the absence of a list of excluded studies with reasons for exclusion, followed by inadequacies in the search strategy – largely attributable to English-language restrictions – and insufficient consideration of risk of bias when interpreting results. Language restrictions may also have contributed to the geographic concentration of the evidence, as sensitivity analyses showed that most primary studies originated from North America, limiting the generalizability of findings beyond Western high-income contexts. Together, these methodological and structural limitations highlight the need for future SRMAs to prioritize pre-registered protocols, transparent study selection, unrestricted or explicitly justified language criteria, and explicit integration of study-level bias, in order to improve the reliability and clinical applicability of evidence in this field. Furthermore, most of the underlying studies were cross-sectional, limiting causal inference and the understanding of temporal relationships between minority stress and mental health outcomes⁷⁷.

Beyond clinical implications, our findings align with global policy efforts aimed at reducing health inequities for sexual and gender minorities. The World Health Organization has recently articulated a broad framework for improving LGBTQIA+ health, emphasizing the integration of inclusive practices across health systems⁷⁸. The European Commission's LGBTQIA+ Equality Strategy similarly calls for national action plans to address violence, discrimination, and health inequalities⁷⁹. However, mental health remains insufficiently represented within these initiatives. By identifying which disparities are supported by the most credible evidence, our review provides a data-driven foundation for strengthening these policy frameworks and for prioritizing prevention,

early detection, and tailored mental health care within LGBTQIA+ populations⁸⁰.

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Consensus-based clinical and research recommendations for use of glucagon-like peptide-1 receptor agonists in the context of eating disorders: a modified Delphi study

Aaron Keshen¹, Elena Koning¹, Kelly C. Allison², Anastassia Amaro³, Sara Bartel⁴, Pauline Belliveau⁵, Lisa Boniferno⁶, Simran Brar⁷, Sonia Butalia⁸, Cynthia M. Bulik^{9,11}, Ariana M. Chao^{12,13}, Jennifer Couturier¹⁴, Kimberly Dennis^{15,16}, Laura Dixon⁴, Deena El-Ziftawi¹⁷, Chloe Gao¹⁸, Susan Gamberg¹, Anthony P. Goldstone¹⁹, Riccardo Dalle Grave²⁰, Anna I. Guerdjikova^{21,22}, Tanya M. Halliday²³, Margaret Hahn^{24,28}, Anastasia Harris¹, Hubertus Himmerich²⁹, William B. Horton³⁰, Monique Jericho³¹, Brooke Langman¹⁷, Amanda Lightbody³², Diane A. Klein³³, Laurel E.S. Mayer³⁴, Susan L. McElroy³⁵, Michael Mindrum²², Nicholas C. Peiper³⁶⁻³⁸, Colby Price¹, Amanda Raffoul³⁹, Jesse Richards⁴⁰, Lauren M. Schaefer⁴¹, Joanna Steinglass³⁴, Valerie H. Taylor³¹, Beverly G. Tchang⁴², Nami Trappenberg¹, B. Timothy Walsh³⁴, Michael A. Weintraub⁴³, Ashley White⁴⁴, Susan Wnuk^{27,45}

¹Department of Psychiatry, Dalhousie University, Halifax, NS, Canada; ²Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; ³Division of Endocrinology, Diabetes and Metabolism, University of Pennsylvania, Philadelphia, PA, USA; ⁴Nova Scotia Provincial Eating Disorder Service, Nova Scotia Health, Halifax, NS, Canada; ⁵McGill University Health Center, Montreal, QC, Canada; ⁶Independent Social Work Practitioner, London, ON, Canada; ⁷Department of Psychology, McGill University, Montreal, QC, Canada; ⁸Division of Endocrinology, Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, AB, Canada; ⁹Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; ¹⁰Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ¹¹Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; ¹²Johns Hopkins University School of Nursing, Baltimore, MD, USA; ¹³Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; ¹⁴Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada; ¹⁵Department of Psychiatry, University of Illinois Chicago College of Medicine, Chicago, IL, USA; ¹⁶SunCloud Health, Northbrook, IL, USA; ¹⁷Toronto, ON, Canada; ¹⁸Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada; ¹⁹PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, Faculty of Medicine, Imperial College London, Hammersmith Hospital, London, UK; ²⁰Department of Eating and Weight Disorders, Villa Garda Hospital, Garda, Verona, Italy; ²¹Lindner Center of Hope, Mason, OH, USA; ²²Department of Psychiatry and Behavioral Neuroscience, College of Medicine, University of Cincinnati, Cincinnati, OH, USA; ²³Department of Health and Kinesiology, University of Utah, Salt Lake City, UT, USA; ²⁴Schizophrenia Department, Centre for Addiction and Mental Health, Toronto, ON, Canada; ²⁵Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada; ²⁶Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada; ²⁷Department of Psychiatry, University of Toronto, Toronto, ON, Canada; ²⁸Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ²⁹Centre for Research in Eating and Weight Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; ³⁰Division of Endocrinology and Metabolism, Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA, USA; ³¹Department of Psychiatry, University of Calgary, Calgary, AB, Canada; ³²New Brunswick, Canada; ³³Department of Psychiatry, New York University School of Medicine, New York, NY, USA; ³⁴Department of Psychiatry, Columbia University Irving Medical Center and New York State Psychiatric Institute, New York, NY, USA; ³⁵Department of Internal Medicine, Dalhousie University, Halifax, NS, Canada; ³⁶Department of Epidemiology and Population Health, University of Louisville, Louisville, KY, USA; ³⁷Department of Psychological and Brain Sciences, University of Louisville, Louisville, KY, USA; ³⁸Cancer Care and Delivery Program, Brown Cancer Center, University of Louisville, Louisville, KY, USA; ³⁹Department of Nutritional Sciences, University of Toronto, Toronto, ON, Canada; ⁴⁰Department of Internal Medicine, School of Community Medicine, University of Oklahoma, Tulsa, OK, USA; ⁴¹Center for Biobehavioral Research, Sanford Research, Fargo, ND, USA; ⁴²Comprehensive Weight Control Center, Division of Endocrinology, Diabetes and Metabolism, Weill Cornell Medicine, New York, NY, USA; ⁴³Department of Endocrinology, New York University School of Medicine, New York, NY, USA; ⁴⁴Community Obesity Medicine Practice, Hamilton, ON, Canada; ⁴⁵Bariatric Surgery Program, University Health Network, Toronto, ON, Canada

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), initially developed for type 2 diabetes management and later expanded to obesity treatment, have shown preliminary efficacy in reducing binge eating episodes. However, the appetite-suppressing and weight-loss effects of GLP-1RAs raise concerns about misuse and potential exacerbation or emergence of eating disorders (EDs). Evidence remains limited and inconsistent, requiring structured, expert-informed guidance. Using a modified three-round Delphi method, a multidisciplinary panel of experts in diabetes, obesity and/or EDs, and individuals with lived experience of an ED and/or GLP-1RA use (N=45) achieved ≥70% consensus on recommendations (average consensus: 91.7%). Clinical recommendations include: a) the implementation of screening for current and historical ED before initiating GLP-1RAs, using a brief psychometrically validated instrument; b) routine monitoring of ED symptoms with intensity stratified by risk level; c) the development of standardized educational materials for patients and providers; and d) offering concurrent evidence-based psychotherapy to individuals with EDs prescribed GLP-1RAs. These medications should generally be avoided in individuals with active EDs, particularly anorexia nervosa, atypical anorexia nervosa, and bulimia nervosa with marked dietary restraint and/or significant weight suppression. Clinicians should also proceed cautiously in patients with a past history of these EDs. Research recommendations include: a) longitudinal epidemiological studies to assess the incidence, risk factors, and outcomes of EDs in individuals using GLP-1RAs compared to non-users; b) regulatory studies and policies to enhance patient safety in GLP-1RA prescribing practices; and c) clinical trials to investigate the safety, efficacy and psychological outcomes of GLP-1RAs in individuals with binge eating disorder. Overall, these consensus-based recommendations support evidence-informed practice and future research aimed at weighing potential benefits against risks of use of GLP-1RAs in ED populations.

Key words: Glucagon-like peptide-1 receptor agonists (GLP-1RAs), eating disorders, binge eating episodes, appetite-suppressing effects, patient safety, consensus-based recommendations

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Glucagon-like peptide-1 receptor agonists (GLP-1RAs) were first approved for type 2 diabetes and later expanded to obesity treatment, beginning with liraglutide (daily injection), approved by the US Food and Drug Administration (FDA) in 2014 and the European Medicines Agency in 2015¹. GLP-1RAs now carry multiple additional indications, including cardiometabolic risk reduction, chronic weight management, and other obesity-related conditions²⁻⁴.

Tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, was approved by the FDA in 2024 for obesity and subsequently for obstructive sleep apnea⁵.

GLP-1RAs function by activating GLP-1 hormone receptors that regulate several metabolic pathways¹, resulting in reduced appetite, lower blood glucose and blood pressure, slowed gastric emptying, and clinically meaningful weight loss⁶. The impressive

clinical efficacy of some of these agents, such as semaglutide and tirzepatide, has accelerated their clinical adoption and prompted interest in broader therapeutic applications.

One emerging area of interest is the potential role of GLP-1RAs in treating eating disorders (EDs), which are mental disorders defined by maladaptive eating behaviors and excessive concerns about body weight^{7,8}. Prominent EDs include anorexia nervosa (AN), “atypical” AN, bulimia nervosa (BN), and binge eating disorder (BED), which differ in patterns of restriction, binge eating, and compensatory behaviors. All EDs carry substantial morbidity (e.g., cardiovascular complications, electrolyte imbalances, bone density loss, infertility), and high mortality (e.g., AN all-cause relative mortality risk is 5.52⁹) driven by medical complications and an elevated risk of suicide⁹⁻¹¹. Disordered eating refers to distressing and/or maladaptive concerns about body weight/shape and engagement in two or more unhealthy behaviors that occur at a frequency or intensity below the diagnostic threshold for EDs.

Preliminary studies of GLP-1RAs for obesity management have reported reduced binge-eating episodes and decrease in general ED psychopathology¹²⁻¹⁴. These early findings suggest that these medications may act on neural pathways relevant to ED pathology that include potential GLP-1 signaling deficits described in BN^{15,16}, mitigating receptor resistance associated with emotional eating¹⁷, and exerting broader effects on appetite regulation and food reward processing¹⁸.

Despite the therapeutic potential of GLP-1RAs, the relevant evidence base remains limited, as few empirical studies have examined their effects among individuals with EDs¹⁹. The majority of studies have focused on BED, and consist of case reports, pilot trials, or retrospective studies with small sample sizes. Several case and pilot studies, including one placebo-controlled study, reported reductions in body weight, body mass index, or waist circumference in individuals with BED treated with liraglutide, semaglutide or dulaglutide²⁰⁻²⁴. Research has also found reductions in binge eating in individuals with BED treated with liraglutide^{23,24}, semaglutide^{22,25}, and dulaglutide^{21,26}.

Other studies showed mixed results. For instance, the most rigorously controlled trial to date for BED did not demonstrate significantly greater decreases in binge frequency, despite producing greater weight loss, compared to placebo²⁰. Even less is known about GLP-1RA effects in BN: only one case report has been published to date, describing a patient who achieved sustained remission of binge-purge behaviors over a five-year course of liraglutide²⁷. Furthermore, there are no published observational or placebo-controlled studies in BED using the dual GLP-1/GIP receptor agonist tirzepatide, though a phase 2, randomized, placebo-controlled clinical trial is underway (NCT06847399).

Overall, while there is some suggestion of the potential therapeutic benefit of GLP-1RA use for EDs, existing studies are largely non-placebo-controlled, underpowered, heterogeneous, and/or lack long-term follow-up.

Alongside growing interest for the therapeutic promise of GLP-1RAs in ED populations, there is also mounting concern regarding their potential harms²⁸. Since GLP-1RAs act on appetite-regulatory pathways and can produce substantial weight loss, they may be as-

sociated with the development or relapse of EDs, particularly in individuals with prior histories of or an elevated risk for disordered eating.

Case reports described two individuals with a history of AN who relapsed into disordered eating behaviors following GLP-1RA treatment for obesity^{29,30}. The first case involved a patient with a history of AN in whom tirzepatide treatment was associated with a return of restrictive eating behaviors and a rate of weight loss that exceeded expectations²⁹. In the second case, semaglutide misuse precipitated relapse of atypical AN, with severe gastrointestinal complications³⁰. These reports highlight the potential for relapse in individuals with prior or concurrent AN, and the difficulty of detecting ED-related symptoms in individuals who may conceal them to avoid discontinuation of GLP-1RA therapy.

Population-level data also raise concerns. A retrospective cohort study found that individuals with obesity and a history of prior mental health diagnoses were twice as likely to develop an ED within two years of starting a GLP-1RA compared to those without such a history, with the highest incidence observed for AN³¹. Although preliminary, these findings align with clinical anecdotes of rising ED cases linked to GLP-1RA use. In addition, common side effects of GLP-1RAs – such as nausea, constipation and vomiting – may complicate ED management, particularly for individuals vulnerable to purging behaviors and/or laxative misuse.

Currently, no guidelines or clear recommendations exist to help clinicians and researchers navigate the complex use of GLP-1RAs in an ED context. Given the rapid expansion of GLP-1RA use in the general population, individuals with or at risk for EDs will likely encounter these medications in routine care. Clinicians deserve guidance on how to weigh potential benefits against risks, and monitor for adverse effects. Moreover, researchers require coordinated priorities to design studies that address key questions, such as different responses across ED diagnoses, long-term outcomes, and mechanisms of action through which these medications may improve ED symptoms.

When empirical evidence is limited but clinical decisions are required, structured consensus approaches such as the Delphi method provide a systematic way to synthesize expert opinion. The Delphi method, widely used in medicine to develop recommendations and research priorities, relies on iterative feedback and pre-defined agreement thresholds to effectively build collective agreement³².

The aim of this project was to develop recommendations for clinical care and research regarding use of GLP-1RAs in ED contexts. Using a modified Delphi method, we sought to synthesize expert perspectives to address the urgent need for guidance in this evolving area, provide a foundation for evidence-informed practice, and identify priorities for future research.

METHODS

This study used an adapted three-round Delphi method in which a panel of experts attended working group meetings and provided iterative feedback to develop consensus on clinical and

research recommendations. Consensus was defined as 70% or greater agreement among panelists, consistent with commonly recommended thresholds in the Delphi literature³². The Nova Scotia Health research ethics board reviewed the project and granted exemption from a full ethics review.

Core research team and panel selection

The selected panel of experts included clinicians and/or researchers with expertise in diabetes, obesity and/or EDs, and individuals with lived experience of an ED and/or GLP-1RA use. Purposive sampling was used to select an initial core research team (N=12), which was expanded to the full panel (N=45) via snowball sampling of participants' professional networks. Lived experience representatives were recruited via social media. Overall, 16 diabetes/obesity/endocrinology clinicians and researchers, 22 ED clinicians and researchers, and seven lived experience representatives agreed to participate.

Evidence review and consensus process

A structured, Delphi-informed consensus process was undertaken to develop clinical and research recommendations regarding GLP-1RA use in the context of EDs. Prior to panel recruitment, a core research team (N=12) was convened by the first author (AK) based on expertise and reputation in the fields of obesity and EDs. This group participated in two virtual sessions (January-February 2025) to identify and refine preliminary themes for clinical and research recommendations, informed by recent literature on GLP-1RA medications and EDs²⁸. The team collated and organized the emerging themes into an initial framework consisting of the following topics in the context of use of GLP-1RA medications: a) screening for an ED; b) educational materials for patients and clinicians; c) monitoring ED symptoms; d) concurrent non-pharmacological treatment; e) epidemiological research; f) regulation and patient safety; and g) clinical trials for BED.

Members of the core research team recommended additional experts and individuals with lived experience to join a larger expert/lived experience panel. This panel attended one or more of three virtual meetings (June 2025) to provide verbal feedback on the draft framework. Detailed notes were recorded, and participants were subsequently invited to complete an anonymous, open-ended written feedback survey.

Recommendations and sub-recommendations were generated based on this feedback and circulated to all panelists via another anonymous online survey (August 2025). Participants rated their agreement with each statement using a 4-point Likert scale (strongly disagree, disagree, agree, strongly agree), and could provide written comments. Percent agreement and qualitative feedback were analyzed to refine the recommendations. The core research team synthesized these data into an advanced draft, which was recirculated to all panelists for final review and approval, resulting in the consensus recommendations presented below and in Tables 1-2.

RESULTS

Clinical recommendations (see Table 1)

Screening for EDs before GLP-1RA treatment

Consensus was reached (94.7%) for the following recommendation: *Prior to initiating GLP-1RAs, clinicians should assess all individuals for a current ED or history of an ED.*

In those who disagreed with this recommendation (5.3%), the main reasons for disagreement were concerns about the lack of equitable access to follow-up interventions for positive screens, and the time burden of screening in non-specialty settings such as primary care.

Sub-recommendations included the following:

- *Use a brief screening tool (3-5 questions) to assess full-threshold EDs, history of EDs, and risk factors for EDs (e.g., body weight/shape concerns, restrictive behaviors)* (consensus: 89.5%). While some experts advocated for more comprehensive validated measures such as the Eating Disorder Examination³³, and others worried that even short tools may be impractical in busy clinical settings, most supported using concise, validated options such as the Eating Disorder Screen for Primary Care (ESP)³⁴.
- *Screening should be implemented in clinical settings where GLP-1RAs are prescribed, including primary care settings* (consensus: 94.7%). Concerns were raised about feasibility and time burden, with suggestions that screening at the same time as medication eligibility is assessed would be most practical.
- *Positive screens should lead to referral to an ED specialist, increased monitoring, patient education and/or treatment modification, based on symptom severity* (consensus: 92.1%). In high-risk cases, experts suggested delaying initiation of GLP-1RA treatment pending a comprehensive ED risk assessment and/or avoiding GLP-1RA initiation.
- *GLP-1RAs should generally be avoided in individuals with active EDs, particularly AN, atypical AN, and BN with marked dietary restraint and/or significant weight suppression. Clinicians should also proceed cautiously in patients with a past history of these EDs* (consensus: 100%). Experts emphasized that this recommendation should not be interpreted as an absolute contraindication across all ED presentations, given the current limitations of the evidence base regarding differential risk by diagnosis and clinical context. Rather, it is intended to support risk-aware prescribing and should be applied with clinical judgment, including an individualized assessment of symptom profile, illness severity, nutritional status, and treatment context. Experts also highlighted that, although individuals with BED are generally at lower theoretical risk of harm from GLP-1RAs (and in some cases may be more likely to derive benefit), caution remains warranted in this population. In particular, some individuals with BED also exhibit clinically significant dietary restraint and/or weight suppression. Finally, experts noted that obesity does not preclude an ED diagnosis. Individuals with obesity may have co-occurring EDs (e.g., atypical AN, BED or BN) and, in such cases, may not be appropriate candidates for

Table 1 Clinical recommendations for use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the context of eating disorders (EDs), with percent agreement

Prior to initiating GRP-1RAs, clinicians should assess all individuals for a current ED or history of an ED (94.7%).

Use a brief screening tool (3-5 questions) to assess full-threshold EDs, history of EDs, and risk factors for EDs (e.g., body weight/shape concerns, restrictive behaviors) (89.5%).

Screening should be implemented in clinical settings where GLP-1RAs are prescribed, including primary care settings (94.7%).

Positive screens should lead to referral to an ED specialist, increased monitoring, patient education and/or treatment modification, based on symptom severity (92.1%).

GLP-1RAs should generally be avoided in individuals with active EDs, particularly anorexia nervosa (AN), atypical AN, and bulimia nervosa (BN) with marked dietary restraint and/or significant weight suppression. Clinicians should also proceed cautiously in patients with a past history of these EDs (100%).

All individuals receiving GLP-1RAs should be monitored for physical and psychological signs of an ED during treatment and following treatment, should medication discontinuation occur (84.2%).

Tailor monitoring intensity based on baseline screening results, with adjustments for emerging risks, such as extreme appetite loss (97.4%).

Monitor variables such as ED psychopathology, weight loss rate, nutrition, hunger/satiety, vital signs, mood, and quality of life (86.8%).

If ED symptoms are identified, provide psychoeducation, refer to an ED specialist, or consider discontinuing the GLP-1RA, based on symptom type and severity (92.1%).

Standardized educational materials on GLP-1RA treatment and EDs should be developed and disseminated for prescribers and patients (92.1%).

Base materials on peer-reviewed literature, treatment manuals, and professional association guidelines (92.1%).

Disseminate provider materials via quick guides, webinars, electronic medical record (EMR) integration, and training, such as continuing education credits (89.2%).

Provide patient materials through accessible formats such as videos, handouts, apps, and moderated support forums (89.5%).

Use social media to increase public awareness and counter predatory marketing (83.7%).

Provide psychoeducation on best practice dietary guidelines to prevent maladaptive restrictive behaviors, and on expected GLP-1RA effects that could increase risk of disordered eating, such as appetite suppression (86.8%).

Develop harm reduction strategies for remote prescribing, including ED screening and monitoring protocols (91.9%).

Individuals with diagnosed EDs who take GLP-1RAs should receive concurrent evidence-based psychotherapeutic interventions (81.6%).

Recommend evidence-based psychotherapy consistent with best practice guidelines (e.g., cognitive behavior therapy, dialectical behavior therapy) for those with full-threshold EDs (86.8%).

For at-risk patients, or sub-threshold EDs, offer interventions such as guided self-help, group therapy, telehealth, or dietitian counselling, in a stepped care approach (81.1%).

Encourage patient-driven intervention selection to enhance engagement and empowerment (86.5%).

GLP-1RA treatment.

Routine monitoring for EDs after GLP-1RA initiation

Consensus was reached (84.2%) for the following recommendation: *All individuals receiving GLP-1RAs should be monitored for physical and psychological signs of an ED during treatment and following treatment, should medication discontinuation occur.*

In those who disagreed with this recommendation (15.8%), the main reason for disagreement was concern that there is insufficient research on the prevalence of new-onset EDs following GLP-1RA initiation to justify monitoring of all individuals for disordered eating behaviors. There were also concerns regarding the increased burden on prescribers if all individuals taking GLP-1RAs have to be monitored.

Sub-recommendations included the following:

- *Tailor monitoring intensity based on baseline screening results, with adjustments for emerging risks, such as extreme appetite loss* (consensus: 97.4%). Specific monitoring practices, including the frequency of follow-up and parameters assessed, should be

determined on the basis of each individual's baseline screening results, with heightened vigilance for those who screen positive for EDs or have a prior ED history. Monitoring should be adjusted in response to emerging concerns, such as rapid weight loss beyond what is expected for a particular agent (typically more than 1-2 pounds per week, though this varies by patient context³⁵), which may signal developing ED symptoms. This individualized approach supports flexible yet consistent oversight, while facilitating early identification of new or recurrent ED presentations.

- *Monitor variables such as ED psychopathology, weight loss rate, nutrition, hunger/satiety, vital signs, mood, and quality of life* (consensus: 86.8%). Key variables to monitor include ED psychopathology through brief validated tools, rate of weight loss to distinguish therapeutic from potentially pathological weight changes, nutritional intake and hunger/satiety cues (accounting for expected therapeutic medication effects such as adaptive appetite reduction), and signs of physical health stability. Simplifying this list may be necessary in primary care settings to enhance feasibility, focusing on core indicators before escalating to specialists.

Table 2 Research recommendations for use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the context of eating disorders (EDs), with percent agreement

Research should investigate the incidence, risk factors and outcomes of EDs in individuals using GLP-1RAs compared to non-users (100%).

Conduct longitudinal cohort studies, case-control studies, and electronic medical record (EMR) reviews to assess ED incidence and risk factors, such as psychiatric history and sociodemographic factors (100%).

Validate brief screening tools for detecting disordered eating in GLP-1RA users (97.4%).

Incorporate neuroimaging and genetic studies to explore GLP-1RA's neurobiological effects on ED psychopathology (89.5%).

Compare GLP-1RA outcomes to other medications influencing eating behaviors to assess relative risk (92.1%).

Regulatory studies and policies should be developed to enhance patient safety in GLP-1RA prescribing practices (91.9%).

Create a national register to track GLP-1RA prescriptions and ED outcomes (73.7%).

Conduct case-control and cross-sectional studies to evaluate risks from telehealth or compounded GLP-1RA prescriptions (86.1%).

Analyze Internet searches and social media for off-label use and predatory marketing trends (94.7%).

Establish guidelines for referring patients to obesity or ED specialists based on screening and monitoring outcomes (94.6%).

Clinical trials should be conducted to investigate the safety, efficacy, and psychological outcomes of GLP-1RAs in individuals with binge eating disorder (BED) (100%).

Incorporate monitoring in trial designs to assess BED-specific outcomes, including frequency of binge episodes, "food noise", and maladaptive dietary restriction (100%).

Include physiological measures (e.g., weight loss rate, liver function, loss of menses) and laboratory parameters to evaluate safety and adverse events (97.4%).

Investigate psychological mechanisms, such as the drive behind binge-eating behaviors and their relationship to GLP-1RA treatment outcomes, using validated tools (100%).

Examine neurobiological (e.g., neuroimaging, genetics) and behavioral effects of GLP-1RAs on BED psychopathology (94.7%).

Compare GLP-1RA effects to other medications impacting BED (e.g., topiramate, lisdexamfetamine) to assess relative efficacy and durability post-discontinuation (94.7%).

Investigate combining GLP-1RAs as an adjunct to evidence-based psychotherapies for BED (94.7%).

- *If ED symptoms are identified, provide psychoeducation, refer to an ED specialist, or consider discontinuing the GLP-1RA, based on symptom type and severity* (consensus: 92.1%). Consideration of discontinuing GLP-1RAs should be balanced against the potential medical benefits of continued use. Some experts noted that decisions about discontinuation should be collaborative and individualized, recognizing the challenges of distinguishing between therapeutic medication effects (e.g., adaptive restrained eating and controlled weight loss) and emergent ED symptoms.

Development of educational materials

Consensus was reached (92.1%) for the following recommendation: *Standardized educational materials on GLP-1RA treatment and EDs should be developed and disseminated for prescribers and patients.*

In those who disagreed with this recommendation (7.9%), the main reason for disagreement was concern that there may not be sufficient research to support educational materials at this time. It was suggested by a small minority that the creation of materials should be delayed until there are additional data available. There was also an expressed concern that education may not be effective.

Sub-recommendations included the following:

- *Base materials on peer-reviewed literature, treatment manuals, and professional association guidelines* (consensus: 92.1%).

Some experts noted that these resources remain limited and require ongoing updates as new evidence emerges. Suggestions were made to include psychosocial contributors to EDs, such as weight-based discrimination, that may influence GLP-1RA use.

- *Disseminate provider materials via quick guides, webinars, electronic medical record (EMR) integration, and training, such as continuing education credits* (consensus: 89.2%). Some experts cautioned against widespread dissemination until stronger evidence links GLP-1RAs with ED risk.
- *Provide patient materials through accessible formats such as videos, handouts, apps, and moderated support forums* (consensus: 89.5%). Some experts re-emphasized concerns that creating patient materials may be premature.
- *Use social media to increase public awareness and counter predatory marketing* (consensus: 83.7%). While there was some concern about creating an unduly negative view of GLP-1RAs, the importance of counterbalancing pharmaceutical marketing with evidence-informed perspectives was highlighted, supported by data showing social media's effectiveness for health information sharing³⁶.
- *Provide psychoeducation on best practice dietary guidelines to prevent maladaptive restrictive behaviors, and on expected GLP-1RA effects that could increase risk of disordered eating, such as appetite suppression* (consensus: 86.8%). Some experts emphasized that these guidelines should be individualized and trialed before broader dissemination.
- *Develop harm reduction strategies for remote prescribing, includ-*

ing ED screening and monitoring protocols (consensus: 91.9%). Although concerns were raised about feasibility in settings where objective measures such as body weight cannot always be verified, this recommendation was viewed as particularly important for rural populations where remote prescribing is routine.

Psychotherapeutic interventions for individuals with EDs receiving GLP-1RAs

Consensus was reached (81.6%) for the following recommendation: *Individuals with diagnosed EDs who take GLP-1RAs should receive concurrent evidence-based psychotherapeutic interventions.*

Those who disagreed with this recommendation (18.4%) noted that it should be considered good practice, but not serve as a barrier to accessing GLP-1RAs, given the extended wait-times for psychotherapies in some public ED services and cost of private therapy. Individuals would also need to consent to engage in such interventions. It was also argued that the research literature available to date may not be sufficient to support the recommendation.

Sub-recommendations included the following:

- *Recommend evidence-based psychotherapy consistent with best practice guidelines (e.g., cognitive behavior therapy, dialectical behavior therapy) for those with full-threshold EDs* (consensus: 86.8%). Guidelines from the American Psychological Association (APA)³⁷ and the UK National Institute for Health and Care Excellence (NICE)³⁸ should be consulted. As previously mentioned, GLP-1RAs should generally be avoided in individuals with active EDs, particularly AN, atypical AN, and BN with marked dietary restraint and/or significant weight suppression.
- *For at-risk patients, or sub-threshold EDs, offer interventions such as guided self-help, group therapy, telehealth, or dietitian counselling, in a stepped care approach* (consensus: 81.1%). For those considered at-risk or with sub-threshold or mild ED symptoms, a stepped care model was suggested (as per international ED guidelines), offering lower-intensity interventions^{37,38}.
- *Encourage patient-driven intervention selection to enhance engagement and empowerment* (consensus: 86.5%). The recommended psychotherapeutic interventions should be pursued collaboratively with the patient, to foster engagement, and be tailored flexibly according to available evidence-based options and individual needs.

Research recommendations (see Table 2)

Epidemiological research on GLP-1RAs and EDs

Consensus was reached (100%) for the following recommendation: *Research should investigate the incidence, risk factors, and outcomes of EDs in individuals using GLP-1RAs compared to non-users.*

Sub-recommendations included the following:

- *Conduct longitudinal cohort studies, case-control studies, and EMR reviews to assess ED incidence and risk factors, such as*

psychiatric history and sociodemographic factors (consensus: 100%). Comments highlighted EMR under-reporting, inclusion of disordered eating and sub-threshold ED symptoms (i.e., conditions not meeting the full diagnostic criteria threshold), and long-term youth safety. The importance of matched samples and of establishing real-world comparator groups was emphasized.

- *Validate brief screening tools for detecting disordered eating in GLP-1RA users* (consensus: 97.4%). Some experts disagreed with the need for new instruments when existing ones might work. Supporters stressed tool adaptation for GLP-1RA-specific effects, drawing parallels to tools validated in other high-risk groups (e.g., the development of the Athletic Disordered Eating Screening Tool).
- *Incorporate neuroimaging and genetic studies to explore GLP-1RA's neurobiological effects on ED psychopathology* (consensus: 89.5%). Some experts expressed concerns over cost, feasibility, and limited clinical utility of this line of research.
- *Compare GLP-1RA outcomes to other medications influencing eating behaviors to assess relative risk* (consensus: 92.1%). Such comparative investigations were endorsed to gauge relative risks, such as an ongoing trial comparing tirzepatide to lisdexamfetamine (NCT06847399). Some experts expressed concerns that such research could unintentionally rationalize or justify the potential harms of these medications.

Regulatory studies for patient safety

Consensus was reached (91.9%) for the following recommendation: *Regulatory studies and policies should be developed to enhance patient safety in GLP-1RA prescribing practices.*

In those who disagreed with this recommendation (8.1%), the main reasons for disagreement were concerns related to insufficient evidence to justify new regulations at this time, and the risk of creating additional stigma or invasive monitoring for individuals taking GLP-1RAs.

Sub-recommendations included the following:

- *Create a national register to track GLP-1RA prescriptions and ED outcomes* (consensus: 73.7%). A national register was proposed to generate systematic data, though concerns were raised about feasibility, privacy, and data quality.
- *Conduct case-control and cross-sectional studies to evaluate risks from telehealth or compounded GLP-1RA prescriptions* (consensus: 86.1%). Such investigations were recommended to better understand risks associated with "low-threshold tele-prescribing services", which may prioritize profit over proper assessment and distribute compounded products from questionable sources. Some experts questioned the feasibility of these study designs and data reliability.
- *Analyze Internet searches and social media for off-label use and predatory marketing trends* (consensus: 94.7%). Experts emphasized the potential of artificial intelligence tools for identifying patterns in online GLP-1RA discussions. Some noted challenges with this line of research due to ambiguity of language

and intent, demographic and cultural biases, and algorithmic misclassification.

- *Establish guidelines for referring patients to obesity or ED specialists based on screening and monitoring outcomes* (consensus: 94.6%). Referral guidelines were endorsed due to risk of GLP-1RAs triggering or worsening ED symptoms, although some experts raised concerns about the utility of such guidelines given current evidence gaps.

Clinical trials of GLP-1RA treatment in BED

Consensus was reached (100%) for the following recommendation: *Clinical trials should be conducted to investigate the safety, efficacy, and psychological outcomes of GLP-1RAs in individuals with BED.*

Sub-recommendations included the following:

- *Incorporate monitoring in trial designs to assess BED-specific outcomes, including frequency of binge episodes, “food noise”, and maladaptive dietary restriction* (consensus: 100%). In addition to measuring binge-eating frequency, clinical trials should incorporate secondary BED-specific outcomes such as “food noise” (i.e., constant preoccupation with food-related decisions) and cognitive features, such as overvaluation of body shape and weight, using validated questionnaires tailored for this population (e.g., the Binge Eating Scale³⁹ or the Eating Disorder Examination-Questionnaire³³). Some experts suggested specific study design considerations, such as stratifying individuals by the presence or absence of body shape/weight overvaluation as a potential mediating/moderating factor.
- *Include physiological measures (e.g., weight loss rate, liver function, loss of menses) and laboratory parameters to evaluate safety and adverse events* (consensus: 97.4%). These measures were recommended as part of safety and tolerability assessments.
- *Investigate psychological mechanisms, such as the drive behind binge-eating behaviors and their relationship to GLP-1RA treatment outcomes, using validated tools* (consensus: 100%). Some panelists recommended instruments such as the Binge Eating Scale and phenomenological approaches.
- *Examine neurobiological (e.g., neuroimaging, genetics) and behavioral effects of GLP-1RAs on BED psychopathology* (consensus: 94.7%). Some experts cautioned about feasibility, cost, and limited past translational benefit of these lines of research.
- *Compare GLP-1RA effects to other medications impacting BED (e.g., topiramate, lisdexamfetamine) to assess relative efficacy and durability post-discontinuation* (consensus: 94.7%). Some experts suggested building augmentation protocols and evaluating efficacy for BED symptoms alongside metabolic comorbidities.
- *Investigate combining GLP-1RAs as an adjunct to evidence-based psychotherapies for BED* (consensus: 94.7%). Although this was highlighted as a promising avenue for investigation, some experts urged for initial studies of GLP-1RA monotherapy and highlighted challenges with psychotherapy access.

DISCUSSION

This Delphi consensus study convened multidisciplinary experts to develop a series of clinical and research recommendations regarding the intersection of GLP-1RA treatment and EDs (consensus: $\geq 70\%$ agreement). Given the widespread emergence of GLP-1RA use in clinical settings and the scant empirical evidence on risks to ED populations, these recommendations offer a framework to inform clinicians on expert perspectives and guide researchers to address the identified and prioritized knowledge gaps.

The recommendations focused on two distinct issues: a) the risk that GLP-1RAs may trigger new EDs or relapse in individuals receiving these medications for obesity or other metabolic conditions; and b) their potential therapeutic role in treating EDs, particularly BED and BN. The following sections expand on this consensus and propose the next logical steps for advancing GLP-1RA research and clinical care in ED populations.

Clinical implications

Screening

Despite logistical concerns regarding accessibility of follow-up interventions and provider burden, the consensus group strongly supported the implementation of screening for a current or prior ED before initiating GLP-1RA treatment. Overall, the consensus suggested the use of a brief screening instrument in all settings where a GLP-1RA is prescribed.

There have been several systematic reviews conducted on ED screening tools^{40–43}, and potential candidates include the Eating Disorder Screen for Primary Care (ESP)³⁴, the Eating Disorders in Obesity (EDO)⁴⁴, the Sick, Control, One stone, Fat, and Food (SCOFF) questionnaire⁴⁵, the Eating Disorder-15 (ED-15)⁴⁶, and the Short Evaluation of Eating Disorders (SEED)⁴⁷. However, validation studies are needed to determine the utility of these instruments in the context of GLP-1RAs and ED populations, and/or to develop new instruments specific to this context.

To further improve the precision of ED screening, operationalizing ED risk criteria was recommended by experts, as there is currently no established categorical classification for level of ED risk or the recommended course of clinical action for each risk level. A risk-stratification approach could categorize individuals by the presence and severity of ED concerns, guiding actions from routine monitoring and education in low-risk cases, to specialist referral and closer follow-up for moderate risk, and potential delay of GLP-1RA initiation pending urgent assessment in high-risk situations. This framework requires further development and validation before routine clinical use.

Monitoring

A small minority of experts critiqued the recommendation to

implement monitoring of ED risk after GLP-1RA initiation, due to the perceived burden, which may be disproportionate when considering the lack of empirical evidence on the topic. The current literature on GLP-1RA-mediated ED risk is largely based on case reports, though consensus was achieved for this recommendation due to the clear theoretical risk to ED populations^{28-30,48}.

Similar to screening, exploring stratification by risk is suggested, in which intensity of monitoring should be adjusted based on clinical factors (e.g., baseline ED risk, emergent psychopathology, rate of weight loss, ED type), and the clinical setting (e.g., essential core monitoring in general practice vs. more comprehensive monitoring in specialist clinics). Future work is needed to operationalize ED risk criteria (e.g., maladaptive dietary restriction and weight loss), validate tools to identify ED risk, and develop treatment protocols for each monitoring outcome.

Educational materials

The concern for insufficient evidence of risk related to GLP-1RAs and EDs extended to the development of educational materials for prescribers and individuals taking these medications. However, the consensus suggests that standardized educational materials should be disseminated to provide balance for pervasive pharmaceutical marketing and the proliferation of misinformation on social media amid rising off-label use⁴⁹⁻⁵¹.

Evidence for the effectiveness of educational materials in health care remains mixed, and efforts are needed to develop effective resources to promote comprehensive care, health literacy, and reduced risks to GLP-1RA users⁵²⁻⁵⁵. Several recent recommendations on nutritional strategies for GLP-1RA treatment offer valuable insights to lead the development of dietary guidelines and related educational materials in ED contexts (e.g., nutritional monitoring and support to mitigate malnutrition/dehydration⁵⁶⁻⁵⁹).

Psychotherapy

Experts recommended evidence-based psychotherapies such as cognitive behavior therapy, per established clinical guidelines^{60,61}, for individuals with diagnosed EDs receiving GLP-1RAs, with the key exception that GLP-1RAs should be generally avoided in individuals with AN, atypical AN, and BN with marked dietary restraint and/or significant weight suppression.

However, some experts noted limitations related to access to psychotherapy in the context of GLP-1RA treatment. As per international guidelines, a stepped care model may offer accessible options to treat mild-moderate EDs (e.g., self-help, group psychotherapy, brief or focused psychotherapies)^{62,63}, addressing some access barriers noted by experts in disagreement^{64,65}.

Further, there is evidence to suggest that patient-centered treatment selection may enhance therapeutic outcomes. Research across diagnostic categories suggests that, when individuals select their own treatment from evidence-based options, drop-out is lowered, therapeutic alliance is strengthened, and some symptom-level

outcomes are improved^{66,67}. However, studies on this topic within ED populations are limited to date, and have mixed results^{68,69}.

Research directions

Epidemiological research on GLP-1RAs and EDs

To advance clinical care and fill the aforementioned gaps in clinical recommendations, several research areas were recommended by experts. First, epidemiological investigations on the relationships between GLP-1RA treatment and EDs are needed to clarify incidence, risk factors, and outcomes, including sub-clinical symptoms and population-level factors. Moreover, psychometric development and validation studies are needed for screening and monitoring ED symptoms/diagnoses in the context of GLP-1RA treatment.

Drug regulation

While a minority of experts considered regulatory investigations premature, the majority agreed that such studies are important, particularly in contexts with potential risks, such as “low-threshold tele-prescribing services”. National registers for outcome tracking, such as the US National Cardiovascular Data Registry, are suggested to inform regulatory initiatives and contribute to large-scale predictive analyses⁷⁰.

Further, online analyses of predatory marketing (e.g., artificial intelligence-driven social media scans) may contribute to risk awareness, although there are concerns regarding data biases and causality gaps⁷¹.

BED clinical trials

The majority of empirical evidence for GLP-1RA treatment in EDs is the result of preliminary studies in BED, with one phase 2 placebo-controlled trial currently underway comparing tirzepatide to placebo and lisdexamfetamine (NCT06847399). We recommend conducting clinical trials with long-term follow-ups and, beyond binge-eating episodes frequency, to measure psychological outcomes relevant to EDs (e.g., maladaptive dietary restraint and internalized weight stigma)^{28,48}. The incorporation of physiological assessments, neurobiological measures, and genetic risk scores is also suggested.

With inconsistent GLP-1RA pilot data currently available in EDs, such clinical trials may help bridge empirical gaps for refining clinical guidelines.

Limitations

The Delphi consensus panel members were not representative of all experts, and participants had varying levels of involvement across different stages of recommendation development. Al-

though the 70% consensus threshold was selected based on commonly cited Delphi methodologies, no standardized threshold exists⁷². A higher threshold may have strengthened consensus by prompting additional rounds of rating and discussion.

In addition, these recommendations may not be applicable to every clinical scenario, due to individual variability, provider burden, and practice constraints. Health care professionals should exercise clinical judgment. Importantly, the recommendations focus on GLP-1-based medications. Novel non-GLP-1 weight-loss compounds are in development, and future research will need to examine their mechanisms of action and potential roles in ED onset or relapse.

The recommendations presented herein may change as new evidence emerges regarding relationships between weight-loss pharmacotherapies and EDs. Therefore, as emphasized by the consensus panel, ongoing work is needed to validate and update these recommendations and the corresponding clinical and research practices.

CONCLUSION

The current Delphi consensus provides a series of expert-informed clinical and research recommendations for the use of GLP-1RAs in ED contexts. The recommendations focus on screening, monitoring, education, and psychotherapy, as well as epidemiological and regulatory research, and advanced clinical trial design in BED.

These recommendations are expected to evolve alongside emerging evidence, aiming to promote the weighing of potential benefits against risks in the use of GLP-1RAs in ED populations.

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The effect of nature on mental health

There is currently great interest in using interactions with nature as a possible ancillary intervention for several mental disorders, including depression, anxiety, post-traumatic stress disorder (PTSD), Alzheimer's disease, and attention-deficit/hyperactivity disorder (ADHD). In fact, health care providers in certain countries are already prescribing these interactions – such as walks in parks, greenspaces, blue spaces, and beaches – as supplemental interventions for depression and anxiety¹. While it is far too early to conclude that interactions with nature could be used as a therapy on par with clinically validated pharmacological or psychotherapeutic interventions, the research evidence in this area is growing.

How we define what a nature exposure represents is of great importance to clarify the benefits that interactions with nature may confer². Does being out in a park have the same effects as looking at nature from a window? Can filling a space with artificial plants have a similar impact as hiking on a trail? These are questions that need to be answered. Most studies that explore the effects of nature on mental health involve having participants interact with real natural environments, such as walking in parks, arboreta, and other real outdoor natural spaces.

Early research has shown that interacting with natural environments can make people feel better, as emerging from subjective reporting. These interactions have been shown to increase positive affect, decrease negative affect, and increase feelings of energy and restoration³. In addition to an effect on subjective feelings, changes in objective cognitive performance have also been reported⁴, and, importantly, these cognitive effects were not driven by changes in mood⁴. In other words, participants did not need to enjoy the nature interaction to get these cognitive benefits. Other work has shown that walking in a nature arboretum can improve attention and working-memory performance¹, and can induce people to think less about themselves and more about others compared to walking in an indoor shopping mall⁵.

Why might nature have these effects on cognition and affect? Attention restoration theory (ART)^{1,4} posits that these positive psychological effects occur because of nature's ability to improve attention. According to ART, humans have two main kinds of attention. One is directed attention, also known as top-down or endogenous attention, which is the kind of attention used at work and school, where an individual chooses what to attend to, even if it is not the most fascinating or interesting stimulation. It is thought that directed attention is finite and can be depleted, i.e., individuals can only direct attention for a limited time before they become mentally fatigued^{1,4}. The second kind is involuntary attention, also known as bottom-up or exogenous attention, which is the kind of attention that is automatically captured by interesting stimulation in the environment. It is hypothesized that this kind of attention is less susceptible to fatigue or depletion^{1,4}. The idea behind ART is that, if individuals can interact with environments that do not place demands on directed attention, while simultaneously having interesting stimulation to activate their involuntary attention, they could restore or replenish the precious directed-attention re-

source.

Many natural environments tend to meet these criteria of not placing a lot of demands on directed attention, while simultaneously having interesting stimulation that softly captures involuntary attention. It is also thought that directed attention, while important for work or school performance, can be thought of as a kind of mental energy that underlies many psychological functions such as self-control, goal-directed behavior, and executive functioning¹. Therefore, improving directed attention abilities can have many downstream consequences on a broad range of behaviors¹, and may be able to alleviate cognitive deficits that accompany several mental disorders.

Building off of this theory, there is research showing that interactions with nature can improve cognitive performance and affect in clinical samples. For example, we conducted a study⁶ in persons diagnosed with clinical depression as ascertained via the Structured Clinical Interview for DSM-IV. Participants first had their mood assessed by the Positive and Negative Affect Schedule (PANAS), and their attention and short-term memory performance evaluated by a backwards digit span (BDS) task. They were then asked to recall a negative thought or memory that was bothering them and to write about it. They were subsequently given a map of a 2.6 mile walk in a natural arboretum or a 2.6 mile walk in an urban environment. Both walks took them about 50 min to complete. Participants wore a global positioning system (GPS) watch, so that we could track them to ensure compliance. We also kept their mobile phones in the lab, so that they would not be distracted during their walks. Upon returning, participants were administered the PANAS and the BDS task again. Finally, they returned to the lab a week later, and repeated the whole procedure again, but walked in the other environment (i.e., if nature the first week, urban the second week, or vice versa). A significant improvement on the BDS task was found after the walk in nature, but not after the walk in the urban environment⁶. These results suggest that brief interactions with nature could be cognitively beneficial for those suffering from clinical depression.

Using a similar within-subject design, a preliminary study reported that a 20-min walk in nature significantly improved attention and short-term memory performance, as measured by the BDS task, in children with ADHD, compared to when they walked in an urban environment⁷ (although the complex nature of this neurodevelopmental disorder clearly requires replication of the results). Using a between-subjects design, researchers have also found that the mental distress and the attention problems which accompany breast cancer and its treatment can be alleviated by interactions with nature, such as walks in parks or gardening, compared to other leisure activities (e.g., doing crossword puzzles)⁸. In a cross-sectional study, researchers also reported that children living in neighborhoods with more greenspace had lowered risk for developing psychiatric disorders in adulthood, even when controlling for sociodemographic factors⁹.

These studies suggest that different interactions with nature may

be beneficial for mental health. In addition to the obvious need for replication, there are still limitations to this work. One limitation is that it is unknown whether increasing attention and working-memory span actually implies a therapeutic efficacy. In other words, it is unclear how these cognitive effects translate to symptom reductions in depression and ADHD. A second limitation is that most experimental work only tests brief, single-dose exposures to nature. It would be important to know how long-lasting these effects are, and what cumulative benefits can be obtained with repeated nature exposure. Finally, to determine clear evidence of clinical efficacy, interventions that expose participants to nature need to be compared to other treatments with known clinical efficacy. Only then could strong conclusions be drawn.

While not clinically validated, this body of research suggests that interactions with nature may be effective ancillary or supplemental therapies for conditions such as depression and ADHD. Clinicians may consider having patients interact with nature to boost mood, improve attention and increase positive thoughts. Interestingly, some work is also showing that just viewing nature pictures,

listening to nature sounds, or watching nature videos can lead to psychological benefits¹, though these effects are weaker than interacting with real nature. In all, this is an exciting area of research that deserves further investigation.

Marc G. Berman

University of Chicago, Chicago, IL, USA

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The new science of sensation and the long-term management of mood disorders

Two decades ago, the science of sensation was re-invigorated by the discovery of a neuroanatomical pathway for interoception, the representation of the body's internal state¹. Interoception has a special role with regard to mental health, not only for the ongoing regulation of physiology, but also as the basis for feeling states that inform our sense of well-being. How we interpret or appraise interoceptive signals varies. Adaptive interoceptive appraisal habits (IAHs) orient us to attend and learn from evocative events, providing greater choice for regulatory responding². Yet, maladaptive IAHs are also common, in which discomfort with interoceptive signals leads to avoidance and counterproductive coping strategies that can exacerbate clinical conditions.

Given their importance for mental health, the cultivation of adaptive IAHs has been a focus of psychological therapies that predates the neuroscientific discovery of an interoceptive brain network. Mindfulness meditation, in which participants are trained to tune attention to physical sensations, is one of the most utilized approaches. A recent meta-analysis³ indicated a small to medium effect size ($g=0.31$) for the relationship between mindfulness meditation and self-reported adaptive IAHs. By attending to interoceptive signals with attitudes of curiosity and non-judgment, a participant may restructure IAHs to better reflect and respond to emotionally evocative events.

In the clinical realm, there is increasing support for the idea that improving IAHs can be especially helpful in the long-term management of depressive and anxiety disorders. Interventions with a focus on restructuring IAHs such as mindfulness based cognitive therapy (MBCT) have a strong evidence base for depressive relapse prophylaxis following symptom remission⁴. Changes in

IAHs may underlie treatment response: compared to a treatment-as-usual control group, patients receiving MBCT showed greater increases in adaptive IAHs, an effect that mediated MBCT's reduction of residual depressive symptoms⁵.

Given the multifaceted nature of depression, why should interoceptive training exert such a powerful prophylactic function? Our neuroimaging work suggests a surprising mechanism of action, casting depression vulnerability as a disorder of interoception. In our functional magnetic resonance imaging (fMRI) research, dysphoric emotions such as sadness were consistently associated with the inhibition of sensory brain regions⁶, letting networks for rumination and negative self-evaluation run unchecked. Sensory inhibition was evident in a sample of remitted depressed patients ($N=85$) who were scanned before and after relapse prevention therapy and were then followed for two years. Patients who showed the greatest sensory inhibition also demonstrated an eightfold increase in the risk of episode recurrence over the clinical follow-up. These findings aligned with our previous community-based research⁷, in which sadness-related sensory inhibition was associated with higher levels of depressive symptoms.

If dysphoria-evoked sensory inhibition is a biomarker of depression vulnerability, how can we generalize the benefits of MBCT and other interoceptive training programs to help patients keep sensation in mind as a mental health resource? We suggest "sense foraging"⁸, which can be defined as "purposely shifting attention from thinking to sensing with receptivity to the sensory world", as a general framework.

Sense foraging helps people become receptive and curious to momentary experiences, in contrast to being preoccupied with the

outcomes of their actions. In our study of depressive relapse, participants who responded to relapse prevention therapies that included elements of sense foraging learned to stop blocking sensation when low mood was present, as did participants in our community study who learned mindfulness meditation.

Our data suggest that depressed patients in recovery have difficulty recognizing when they are stuck in a pattern of stress-related sensory inhibition. Fostering such recognition, along with an understanding of the importance of preserving sensory processing for emotion regulation, may encourage patients to seek out their own sense foraging activities, in much the same way that we appreciate the importance of integrating physical exercise into one's daily routine.

Sense foraging provides a transdiagnostic framework for understanding the growing number of clinical interventions that leverage sensory engagement to achieve symptom reduction⁹. Grounding techniques, which encourage patients to attend to each of their senses in turn, appear efficacious against anxiety, and somatosensory stimulation interventions have shown promise in autism spectrum disorders. Increasingly, the treatment of trauma has expanded to include consideration of somatic expressions of trauma as targets of intervention, with improvement of IAHs seen as a core mediator of change.

An advantage of understanding the importance of sensory processing for mental health is that sense foraging techniques can also be flexibly introduced in clinical practice. These techniques are particularly suited for patients who find themselves stuck in ruminative or worry cycles. Engaging with the sensory world can create a wider attentional field in which there may be a measure of relief along with the potential for new insights.

For example, one could suggest that a patient go on a walk to clear his/her head and benefit from the exercise. Yet, a person could easily go on that walk while lost in rumination and judgment, scarcely attending to sensory experience, and ultimately receiving minimal benefit. By contrast, the same activity could be recommended with a sense foraging agenda, emphasizing the benefits of leveraging the walk to activate sensory parts of the brain.

In time, success with sense foraging may afford a growing sense of agency in how one allocates attention, even in the presence of repetitive negative thinking. Taking advantage of the ubiquity of sensory information can thereby help to reduce the dominance of habitual thought patterns by broadening the scope of experience,

simultaneously providing the basis for novel adaptive IAHs.

To introduce sense foraging, we would recommend four major steps. First, *assess*: ask the patient to describe his/her current balance of attention: how much of his/her mental energy is being split between thinking and sensing? Second, *commit*: invite the patient to set a clear intention to shift attention towards momentary sensation, either internal to the body or a canvassing of external sensory stimuli. Third, *engage*: pick a brief sense foraging activity. If taking a walk in nature, the patient may be asked to identify five objects he/she can see, or listen for the sounds of at least three different birdsongs. He/she could explore the feeling of the ground against his/her feet, the change of weight with each step, or feelings of heat or coolness in different parts of the body. Finally, *reflect*: re-assess the balance of attention, to determine whether there is a growing sense of comfort, familiarity or stability in the sensory world. Such feelings can become a marker of adaptive IAHs that motivate further sense foraging.

The emerging neuroscience of interoception affirms the often overlooked importance of spending time strengthening our relationship to our senses. The example above was intended to illustrate how easily sense foraging can transform any number of daily activities, such as washing dishes, engaging in exercise, or listening to music. Precisely because it is so adaptable, sense foraging affords clinicians the flexibility to choose activities that have the highest likelihood of patient engagement.

As evidence supporting the use of sense foraging practices continues to accumulate, patients may discover that shifting attention to sensation in everyday activities can build resilience in the long-term project of managing their mood disorder.

Zindel Segal¹, Norman Farb^{1,2}

¹Graduate Department of Psychological Clinical Science, University of Toronto Scarborough, Toronto, ON, Canada; ²Department of Psychology, University of Toronto Mississauga, Mississauga, ON, Canada

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Risks from self-medicating with psychedelic drugs

There is a global resurgence in psychedelic drug use¹. Late-phase clinical trials, in which a psychedelic drug is often used alongside cognitive therapy, suggest that these drugs may effectively treat mental disorders such as severe depression, post-traumatic stress disorder (PTSD), certain anxiety disorders, and substance use disorders. Earlier-phase trials are further studying efficacy to treat pain,

eating disorders, obsessive-compulsive disorder, and other mental health conditions.

Psychedelic drugs induce pharmacological, neurological and psychological changes, and these different levels of action may integrate and/or parallel each other into a unified theory describing the mechanism through which mental health improves². Though

each psychedelic drug induces neurological changes unique from others, it is clear that all induce multi-level changes and, when used in the right context and with the right support, can produce meaningful improvements in mental health.

Alongside trials, certain jurisdictions have made it easier to access psychedelic drugs. Australia authorized psilocybin prescriptions for PTSD and treatment-resistant depression in 2023. Canada in 2022 and Germany in 2025 instituted special access programs. Two US states (Oregon in 2020 and Colorado in 2022) created legal avenues for licensed facilitators to administer psychedelic drugs in controlled settings. Jurisdictions worldwide have decriminalized possession and use. Attention from popular media, intense clinical research focus, and rapidly changing legal landscapes will almost certainly lead individuals to seek psychedelic drugs to self-treat their mental health problems.

Self-medication with psychedelic drugs may emerge from a need to treat the same mental health problems as those currently studied in trials. While trials and studies in licensed settings show that psychedelic treatment is generally safe, with few adverse events, their conditions are rigorously controlled and monitored. Substantial oversight (both from trial investigators and regulatory bodies) helps ensure that risk factors for adverse events are minimized or excluded entirely from trials. People with comorbid health disorders are often excluded, as are those using multiple drugs. Doses are manufactured and delivered with precision. While these controls help test the efficacy of drugs under a pre-defined protocol, adverse events may occur less frequently than in other settings where conditions are not so rigorously controlled. Self-medication with psychedelic drugs is likely to occur in uncontrolled settings with uncertain source and potency of the drug. There are at least three areas of potential concern.

First, poorly managed mental disorder symptoms may disrupt a person's life enough for them to seek self-medication. However, this is itself a primary risk factor for adverse experiences. Pre-existing mental disorders elevate individuals' risks of acute and delayed adverse events compared to healthy control subjects in clinical settings, as observed in a recent meta-analysis³. Acute events – such as mania, psychosis and seizures – more frequently occurred in people with a history of mental disorders, primarily when using lysergic acid diethylamide (LSD). Delayed events – such as worsening depression, persistent mania, suicidal thoughts and behaviors, and adjustment disorder – were observed for both LSD and psilocybin. Overall, approximately 4% of patients with mental disorders experienced a severe event across the studies examined, while no events occurred in healthy controls.

In a study of individuals using psychedelics outside a clinical setting, 4.2% reported persistent hallucinations requiring hospital care⁴. Poison centers in the US have additionally noted agitation and tachycardia requiring emergency care, more so with LSD than psilocybin, though observed for both⁵. In a trial setting with regular follow-up and controlled doses, these events can be professionally managed, greatly improving patient outcomes and shortening recovery time. In self-medication settings, there is likely much less support for people when events occur.

Second, people self-medicating with psychedelic drugs risk toxic drug-drug interactions with approved medications. Fatal overdose is extremely rare⁶. However, serotonergic toxicity is possible when serotonin-releasing agents or reuptake inhibitors are combined with drugs that prevent serotonin metabolism. Mild reactions involve insomnia, nausea and anxiety, while more severe reactions lead to neuroexcitation, agitation, delirium, and cardiovascular events⁷. Most popular psychedelics increase intrasynaptic serotonin concentrations. The greatest risk of toxicity occurs when monoamine oxidase inhibitors (MAOIs) are combined with a drug that increases serotonin⁷. High doses of multiple drugs increasing serotonin confer lower, though not negligible, risk of toxicity. Particularly in situations where people who self-medicate do not know the potency of the psychedelic drug, they risk toxic effects if they do not wash-out from a prescribed serotonin-increasing pharmacotherapy.

Third, individuals are more open and receive suggestions more easily while under the influence of psychedelic drugs⁸. Physical and sexual abuse has occurred even in trial settings⁹, suggesting that the likelihood of abuse occurring in self-medication settings would be at least similar, if not worse. Processing and managing common experiences such as confusion, paranoia, delusions and agitation is more difficult when using the drug alone. In the rare cases of death involving psychedelics, physical trauma (not toxicity) is the common cause⁶. In all these situations, using alone is very risky, because seeking help while under the influence of the drug is much more challenging. Using the drug with a sober, trusted person, even someone untrained, means that this person can at least call for help. In the future, wearable health technology may be adapted to alert trusted people if a problem occurs, closing gaps in support.

Jurisdictions that enable access to psychedelics should support community resources that reduce harms. Peer-support helplines can guide people through challenging experiences, and support specialists should be educated on the additional complications that accompany self-medication. Public health information campaigns should present risks alongside benefits, with particular attention given to helping people identify harmful drug-drug interactions, giving them the opportunity to wash-out if needed. Drug checking services reduce harm by empowering the individual with information about drug composition and potency, which has proven effective for people using opioids. Services testing the potency of psychedelic drugs would similarly reduce harm by giving people the information they need to make well-informed choices.

While harm reduction is an essential component of public health, preventing risk in the first place is better. Preventing harms from self-medication means that patients should have the best health care options to begin with. Available health care should guide patients to the best evidence-based therapies, which may involve psychedelic drugs in appropriate cases. Psychedelic drugs are not for every patient nor every condition, and research into why some individuals do not respond will better equip providers with information to help their patients. If people do choose to self-medicate for mental disorder symptoms, other trusted people

should be present or rapidly available.

Joshua C. Black

Rocky Mountain Poison and Drug Safety, Denver Health and Hospital Authority, Denver, CO, USA

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Using the Hierarchical Taxonomy of Psychopathology (HiTOP) for precision psychiatry

Progress in developing effective psychiatric interventions has been slow, in part because of the heterogeneity of diagnostic categories¹⁻³. Within a single diagnosis, specific treatments are often helpful for some patients but not others. This has led psychiatry to an interest in individual differences and to the rise of precision psychiatry⁴.

Drawing on the more general concept of precision medicine, a central premise of precision psychiatry is that knowing the specifics of an individual's biological makeup will facilitate intervention more effectively than knowing only a diagnosis. However, identifying robust links between neurobiological variables and psychiatric problems has proved difficult, partly due to the limitations of diagnostic categories.

A large body of evidence indicates that mental disorders are not discrete categorical biological entities but instead exist on continuous spectra across the general population³. Physical medicine explicitly recognizes that the designation of a threshold for diagnosis (e.g., hypertension) often does not indicate a qualitative boundary, because many biological variables (e.g., blood pressure) are fundamentally dimensional. Here, we argue that precision psychiatry can benefit from adopting a similar dimensional approach, and that the Hierarchical Taxonomy of Psychopathology (HiTOP) offers an excellent framework for doing so, addressing several key limitations of official nosologies.

HiTOP is a dimensional model developed by a large consortium of researchers on the basis of statistical analysis of the covariation among symptoms and diagnoses^{3,5,6}. This quantitative approach is helpful, because patterns of covariance among symptoms often do not match diagnostic criterion sets. In other words, symptoms do not actually tend to cluster in the patterns indicated by official nosologies^{2,3}. This means that problems with existing diagnoses cannot be remedied simply by transforming them directly from categorical to dimensional, maintaining the same symptom criteria and aggregating those to indicate a spectrum for each disorder.

Instead, to match actual covariance patterns, HiTOP reorganizes symptoms into multiple dimensions across hierarchical levels, with the core level containing six broad spectra: internalizing, antagonistic externalizing, disinhibited externalizing, thought disorder, detachment, and somatoform. Above the spectra are superspectra,

including the general factor of psychopathology (or p factor), which represents the shared likelihood of all mental disorders, and below the spectra are various subfactors; below those are many specific symptom dimensions³.

HiTOP provides a degree of precision in characterizing clinical phenomena similar to what the Research Domain Criteria (RDoC) aims to provide at the neurobiological level, thereby rendering the two systems complementary^{5,6}. HiTOP offers assessments that are effective targets of neuroscientific research⁵. Both HiTOP and RDoC are not only dimensional and transdiagnostic, but also hierarchical, encompassing broad constructs representing extensive patterns of covariation and narrower constructs nested within them. A thorough understanding of the neurobiology of psychopathology will require identifying neural correlates of broad spectra (e.g., internalizing) to explain symptom coherence, as well as distinct correlates of specific symptoms (e.g., anhedonia) that account for their differentiation at lower levels of the hierarchy⁷.

Precision psychiatry can and should work on both sides of the equation, delivering precision in clinical description by using a system such as HiTOP, while at the same time delivering precision in neurobiological characterization⁶. One of the core tenets of precision psychiatry is to use data-driven classifications⁴. Such work is already being conducted on the neurobiological side, and this is exactly what HiTOP provides for clinical description, classifying symptoms into broader spectra based on analysis of covariance. Precision psychiatry will be most likely to identify effective treatments based on characterizing individual patients in terms of their full symptom profile, in conjunction with various biological assessments.

In research aiming at precision psychiatry, an increasingly common approach to dealing with heterogeneity is to identify subtypes within existing diagnoses based on neurobiological variables^{1,8}. Despite the potential value of employing cutting-edge neuroscientific methods to identify distinctions within diagnoses, this subtyping approach has two important limitations.

First, it starts from categories that are not scientifically valid. If a diagnosis such as major depressive disorder or schizophrenia is already known to include people with very different symptoms and to exclude people with meaningfully similar symptoms, searching

for precision within that diagnosis will yield incomplete information. Studying a broader treatment-seeking population would be more effective.

Second, the subtyping approach generates putative categories (i.e., subtypes) where the available evidence suggests that categories are unlikely to exist in nature. Like symptoms, variables derived from human neuroimaging are typically distributed dimensionally without clear demarcations that would indicate categorical entities. This fact may explain why neurobiological subtyping has often failed to replicate and why its division of individuals within a given sample depends heavily on the neurobiological variables analyzed⁸.

A solution to both of these challenges is to relate neurobiological variables to transdiagnostic symptom dimensions in more inclusive samples, such that precision comes from linking a reasonably comprehensive hierarchy of symptom dimensions to a broad array of neurobiological variables.

HiTOP is a good framework for symptom assessment in part because its dimensions have been found to explain more variance in neural correlates than diagnoses do, even in the same sample⁹. A recent systematic review shows both the increasing use of dimensional approaches in clinical neuroscience and the promise of HiTOP for the field⁵. This review of 164 neuroimaging studies with sample sizes ≥ 194 identified ten replicated findings (though with additional failures to replicate in three cases) at five different levels of the dimensional hierarchy. These levels ranged from associations of the *p* factor with reduced brain volume, to associations of the thought disorder spectrum with reduced frontotemporal functional connectivity, to associations of depressed affect (a specific symptom dimension) with reduced amplitude of brain responses to reward. As more such associations are identified, they will provide a key ingredient to the biological side of precision psychiatry, complementing symptom assessments with insights into potential neural mechanisms.

The dimensional approach is a crucial advance for clinical neuroscience and precision psychiatry. However, within this approach, challenges arise when researchers measure only one or a small range of symptom dimensions. Without a sufficiently comprehen-

sive set of dimensions, it is difficult to determine whether a finding of association between a neural variable and a particular symptom dimension is truly specific to that dimension, or is instead more strongly associated with a different dimension that shares some variance with the first dimension or with a broader construct that subsumes that dimension.

HiTOP offers a solution. With an assessment covering all of the HiTOP spectra, one can identify not only what symptoms a given neural variable predicts, but also what symptoms it does not predict. In other words, one can establish discriminant validity. This means identifying not only the relevant dimension, but also the level of the hierarchy to which a variable relates.

Once an evidence base has accumulated in which we know with confidence what level and dimension many neurobiological variables are linked to, precision psychiatry will be better positioned to achieve its full potential. Accurate clinical phenotyping is necessary for effectively identifying the biological basis of individual differences, and HiTOP can provide it, offering an accelerator for precision psychiatry.

Colin G. DeYoung¹, Elizabeth A. Martin², and the HiTOP Neurobiological Foundations Workgroup

¹Department of Psychology, University of Minnesota, Minneapolis, MN, USA; ²Department of Psychology, University of California, Irvine, CA, USA

For a complete list of members of the HiTOP Neurobiological Foundations Workgroup, please see <https://www.hitop-system.org/neurobiological-foundations-workgroup>.

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Clinical high-risk vs. population-level prevention of mental disorders: a false dichotomy

An ongoing scientific debate focuses on the relative usefulness of two different types of preventive interventions for psychosis. On the one hand, the clinical high-risk for psychosis (CHR-P) paradigm, an “indicated” preventive approach, focuses on a subgroup seeking help because of mild symptoms that are distressing and impacting their lives and functioning¹. On the other hand, population-level prevention, a “universal” preventive approach, targets the whole population regardless of symptomatology or impairment. Some clinicians and researchers have questioned the value of indicated prevention for psychosis, suggesting that resources would be better invested in universal strategies. Here we discuss these criticisms and argue for advancing both targeted and population-level approaches in tandem.

First, it has been argued that, since CHR-P individuals have “only” about a 20% chance of developing a first episode of psychosis in the subsequent two years, preventive efforts in this group are worthless. However, endocrinologists are implementing indicated prevention for pre-diabetes, a clinical high-risk state, based on a probability of transitioning to diabetes of “only” 2.5% within two years². Furthermore, the two-year risk of psychosis in CHR-P samples is 47 times higher than the risk in socio-demographically matched healthy controls (i.e., 0.43% at 2 years)¹. Notably, we recently demonstrated that, in real-world CHR-P samples, the long-term probability of transitioning to psychosis peaks at 46% after 14–18 years³. Finally, most of the CHR-P individuals who do not transition to psychosis (who are technically termed “false positives”) continue displaying mental health burden at follow-up, most frequently non-psychotic comorbidities that are already present at baseline, with non-remission from the CHR-P state being common: not transitioning cannot be conceptualized as healthy recovery.

Second, it has been pointed out that, among CHR-P individuals who develop psychosis, only about one-third develop schizophrenia⁴. However, meta-analyses showed that 73% of CHR-P people transitioning to psychosis develop schizophrenia-spectrum psychosis⁵. It has also been suggested that the CHR-P condition is a pluripotent risk state for mental health problems in general⁴. However, empirical studies indicate that, while most CHR-P individuals have comorbidities at baseline (and thus the CHR-P state is cross-sectionally transdiagnostic), the CHR-P paradigm is not a pluripotent transdiagnostic state for outcome prediction. For example, to predict the emergence of new cases of bipolar disorder, different psychometric assessment instruments are required, such as the Semistructured Interview for Bipolar At Risk States (SIBARS).

Third, it has been argued that, given the lack of approved interventions for CHR-P individuals¹, CHR-P research should be dismissed. However, in somatic medicine, there are no effective preventive interventions for dementia, but preventive research in this area still remains a hot topic. Furthermore, the interpretation of the current evidence for preventive interventions in CHR-P individuals is more nuanced: because of large meta-analytic confidence

intervals, we do not know how effective the available preventive interventions are (i.e., the absence of evidence is not evidence of absence)¹. This is likely amplified by the large heterogeneity of the CHR-P group, the significant effect of needs-based interventions that are also offered in the placebo arms of preventive trials, and the one-size-fits-all approach of current preventive interventions. This uncertainty underscores the need for continued research, not its discontinuation. Furthermore, there is ongoing research on interventions for CHR-P populations (e.g., cannabidiol). Without detecting CHR-P individuals, we will be unable to assess the effectiveness of such interventions. As the incidence of psychosis in the general population is low, and the latency period between exposure and onset is long, directly identifying effective universal preventive interventions is much more challenging.

Fourth, it has been reported that only a tiny proportion of patients with a first onset of psychosis have ever presented with a CHR-P to the local clinic⁴. However, more recent evidence suggests that about 80% cases of first episode psychosis are preceded by a CHR-P state⁶, and that this is detectable. Innovative digital screening methods to improve the detection of CHR-P individuals are under development. Moreover, inefficient detection is not specific to the CHR-P paradigm: early intervention or first episode services only detect less than half (i.e., 46%) of the local cases of incident psychosis⁷. Therefore, we should focus on improving and optimizing detection strategies in preventive and early intervention services, which are currently suboptimal.

Fifth, it has been argued that there is no economic argument for investing additional resources in specific CHR-P services⁴. On the contrary, several cost-effectiveness studies and even meta-analyses have been published and have already impacted clinical guidelines and national health care policies¹.

Sixth, it has been pointed out that the CHR-P approach only targets a few people. The CHR-P is a “targeted” preventive approach by definition, precisely because it focuses on supporting young people with subtle symptoms who have an imminent risk of developing psychosis. Targeted prevention is common in somatic medicine (e.g., pre-diabetes and mild cognitive impairment). Furthermore, available meta-analyses estimating the global population attributable fraction indicate that a theoretical reduction of CHR-P features or cannabis abuse would translate into a comparable 12% global reduction in the incidence of new cases of psychosis⁸.

Seventh, building on these premises, it has been argued that cardiologists are now “moving upstream” and restricting to universal prevention of established and asymptomatic cardiovascular risk factors to prevent coronary artery disease. However, they are not dismissing the importance of concurrently implementing targeted prevention in clinical high-risk states such as angina and pre-diabetes², despite the availability of effective universal interventions for these conditions. Their work is teaching us that the dichotomy between targeted and universal prevention is false, because

these approaches are not mutually exclusive: they are complementary and therefore should be pursued together⁶. Moreover, given that no universal interventions for psychosis have yet proven effective, the most pragmatic starting point for preventive efforts lies in the earliest identifiable high-risk (i.e., targeted) population. Importantly, CHR-P services already implement numerous universal preventive approaches, beyond their targeted prevention (e.g., raising awareness on risk factors for mental health, mental health promotion campaigns, anti-stigma interventions)⁹.

In conclusion, rather than throwing out the baby with the bathwater, the universal preventive capacity of CHR-P services should be enhanced and integrated with population-level initiatives that leverage extensive epidemiological knowledge on risk factors for psychosis. For example, the existing CHR-P outreach campaigns could be enriched by specific population-level programs focusing on cannabis and substance use prevention. The integration of targeted and universal preventive approaches would better align psychiatry with somatic medicine, maximize the efficiency of existing preventive clinical research infrastructure, and enhance preventive education and training capacity for health care workers. It would also cross-fertilize clinical and epidemiological expertise and consolidate the much-needed critical mass of clinicians, researchers, persons with lived experience, policy makers, and institutional representatives necessary to address global population-

level preventive challenges.

Amplifying the artificial schism between targeted and universal preventive approaches risks fragmenting the limited available resources, delaying translational research, and weakening the clinical impact of preventive psychiatry, with a detrimental effect on the lives of many young people.

Paolo Fusar-Poli¹⁻³, Dominic Oliver^{1,4-6}

¹Early Psychosis: Interventions and Clinical-Detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; ²Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy; ³South London and Maudsley NHS Foundation Trust, London, UK; ⁴Department of Psychiatry, University of Oxford, Oxford, UK; ⁵NIHR Oxford Health Biomedical Research Centre, Oxford, UK; ⁶OPEN Early Detection Service, Oxford Health NHS Foundation Trust, Oxford, UK

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Brain-enriched extracellular vesicle microRNAs could help to predict onset of psychosis in people at clinical high risk

A key challenge in the clinical management of people at clinical high risk (CHR) for psychosis is the absence of a reliable method to distinguish the minority of individuals who will subsequently transition to illness from the majority who will not¹. Several candidate interventions for the prevention of psychosis in people at CHR are currently under evaluation^{2,3}. The clinical utility of such treatments could be enhanced by biomarkers that help to identify the CHR individuals most likely to progress to psychosis⁴: preventive interventions could then be offered to those at greatest risk.

A well-established pathophysiological model⁵ proposes that psychosis results from alterations in central redox-hub function, with bidirectional interactions between redox, mitochondrial, N-methyl-D-aspartate receptor (NMDAR), blood-brain barrier and immune-inflammatory processes driving sustained oxidative stress. These processes are regulated, in part, by microRNAs (miRNAs), small non-coding RNAs that modulate gene expression. miRNAs from brain can cross the blood-brain barrier within extracellular vesicles, meaning that their concentration can be measured in samples of peripheral blood⁶. Circulating extracellular vesicles thus provide a peripherally accessible window on brain molecular regulation.

We examined the relationship between circulating, brain-enriched miRNAs that regulate redox-hub function and the onset of psychosis in CHR individuals. Employing a hypothesis-led ap-

proach, we selected five miRNAs for analysis (miR-9, miR-34a, miR-132, miR-137 and miR-941), based on evidence that these miRNAs normally regulate redox-related pathways and have also been implicated in previous studies of psychosis (see supplementary information).

Plasma samples were collected at presentation from two independent cohorts of CHR individuals. Participants were then followed clinically for at least two years to determine which individuals subsequently developed psychosis. We first examined samples from 251 CHR individuals recruited from centres in Europe, South America and Australia, as part of the European Union Gene-Environment Interactions (EU-GEI) study. Forty-eight individuals from this cohort developed psychosis during follow-up (CHR-T) and 203 did not (CHR-NT).

We then examined plasma samples from CHR individuals recruited at sites in North America as part of the North American Prodrome Longitudinal Study (NAPLS-3). Forty-eight CHR individuals from this cohort developed psychosis (CHR-T) and were compared with 55 CHR-NT participants matched on socio-demographic variables.

Extracellular vesicles enriched for canonical neural markers were isolated from plasma using a standardized, precipitation-based protocol suitable for multicentre studies, and authenticated through a double-validation workflow combining canonical extra-

cellular vesicle and tissue-relevant markers. Samples that did not meet pre-specified thresholds for total extracellular vesicle signal or brain-marker enrichment were excluded. The five pre-specified miRNAs were then quantified in these brain-enriched extracellular vesicle preparations. The analyses were conducted under blinded conditions, with researchers unaware of participant group allocation (CHR-T vs. CHR-NT).

We next evaluated whether the five selected miRNAs could predict transition to psychosis, employing a regularized logistic regression model developed according to gold standard methodological guidelines⁷. The model used the concentrations of these miRNAs, and controlled for site and batch effects using mean offset correction and the ComBat harmonization method (neuro-ComBat), respectively, within a repeated nested cross-validation framework (5 outer folds, 5 inner folds, 10 repeats) to mitigate data leakage.

In the EU-GEI dataset, this model discriminated between CHR-T and CHR-NT individuals with a high level of performance (C-index = 0.977, 95% CI: 0.954-0.995). Calibration showed evidence of under-estimation of risk at higher observed probabilities (intercept = 0.29, slope = 2.40).

A high level of discrimination performance was again evident when the model was applied to the independent NAPLS-3 dataset (C-index = 0.725, 95% CI: 0.619-0.818), despite substantial differences in case-mix, study design, and geography. Miscalibration was, however, more pronounced in this external validation (intercept = 7.25, slope = 0.14) than in the EU-GEI cohort, though this was largely resolved by logistic recalibration (intercept = -0.01, slope = 1.04).

The two CHR datasets that we studied were large enough to provide adequate power for the analyses, with 95% CIs all above C=0.60, and high performance retained in external validation, indicating statistical robustness.

Univariate analyses using Mann-Whitney U tests to assess pairwise significance, and Wilcoxon effect size (*r*) to assess effect sizes, revealed a pattern of group differences in the levels of (batch- and site-corrected) individual miRNAs that was strikingly similar across the two datasets. In both cohorts, the levels of miR-34a were higher in the CHR-T than the CHR-NT group (*r*=0.52, 95% CI: 0.42-0.61 in the EU-GEI dataset; *r*=0.17, 95% CI: 0.01-0.36 in the NAPLS-3 dataset).

Conversely, the group differences in the concentrations of miR-9, miR-132, miR-137 and miR-941 reflected higher levels in the CHR-NT than the CHR-T group (miR-9: *r*=0.12, 95% CI: 0.01-0.23 in the EU-GEI dataset, and *r*=0.01, 95% CI: 0.002-0.24 in the NAPLS-3 dataset; miR-132: *r*=0.08, 95% CI: 0.01-0.22 in the EU-GEI dataset, and *r*=0.55, 95% CI: 0.39-0.68 in the NAPLS-3 dataset; miR-137: *r*=0.07, 95% CI: 0.004-0.18 in the EU-GEI dataset, and *r*=0.02, 95% CIs: 0.004-0.22 in the NAPLS-3 dataset; miR-941: *r*=0.19, 95% CIs: 0.07-0.31 in the EU-GEI dataset, and *r*=0.14, 95% CI: 0.01-0.34 in the NAPLS-3 dataset).

These data indicate that transition to psychosis is associated with higher concentrations of some miRNAs, but lower levels of others, implicating the down-regulation of some redox-hub pathways, but the up-regulation of other pathways.

Overall, our findings indicate that the plasma levels of brain-enriched miRNAs that regulate redox-hub function are associated with psychosis onset in CHR individuals. The results were externally validated in an independent dataset, and are biologically plausible: the miRNAs we examined are regulators of redox activity, mitochondrial bioenergetics, immune function/neuroinflammation, and NMDAR pathways (see supplementary information), all of which have been implicated in the pathophysiology of psychosis⁵. One of the miRNAs that we found to be associated with non-progression to psychosis (miR-941) was among the miRNAs previously linked to non-transition in a data-driven analysis in peripheral leukocytes from CHR participants⁸.

If alterations in redox-hub miRNAs play a role in the onset of psychosis, this pathway may represent a novel target for preventive interventions. Interestingly, two candidate preventive treatments for psychosis (cannabidiol² and N-acetyl cysteine³) have significant antioxidant effects and could therefore act through modulation of redox-related mechanisms. Another potential therapeutic approach that is being evaluated in physical health disorders is to directly modify the function of specific miRNAs: the effects of a miRNA can be suppressed by administering an oligonucleotide that binds to it, or enhanced through administration of a synthetic copy⁹.

Several caveats warrant emphasis. First, the prediction model described here is not yet ready for clinical use. The present findings need to be confirmed in further CHR datasets, and the model should be recalibrated in cohorts recruited from the settings intended for clinical implementation, to reduce miscalibration. Second, the extracellular vesicles studied were enriched for, but not exclusive to, brain origin. Dedicated methods to isolate and validate brain-specific extracellular vesicles can further strengthen causal inference about brain involvement. Third, the external validation cohort was recruited using a case-control rather than a representative cohort design, which may have influenced model performance metrics. Finally, clinical implementation will require prospective evaluation studies in line with local regulatory frameworks.

Nevertheless, these findings suggest that plasma levels of brain-enriched miRNAs are promising, biologically plausible biomarkers that could be used, along with clinical variables, for the stratification of psychosis risk in CHR populations, and have the potential to guide the provision of preventive care and the development of novel, mechanism-based interventions.

Ines Khadimallah¹, Dominic Oliver^{2,3}, Kim Q. Do¹, William Pettersson-Yeo^{2,3}, Matthew J. Kempton⁴, Lucia Valmaggia^{4,7}, EU-GEI High Risk Study Group, NAPLS-3 Study Group, Clark D. Jeffries⁸, Diana O. Perkins⁹, Philip McGuire^{2,3}

¹Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland; ²Department of Psychiatry, University of Oxford, Oxford, UK; ³NIHR Oxford Health Biomedical Research Centre, Oxford, UK; ⁴Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; ⁵Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; ⁶Centre for Youth Mental Health, University of Melbourne, Parkville, VIC, Australia; ⁷Orygen, Parkville, VIC, Australia; ⁸Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA; ⁹Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA

The EU-GEI High Risk Study Group also includes: T. Pollak, M. Calem, S. Tognin, G. Modinos (UK); M. van der Gaag, L. de Haan, B. Rutten, J. van Os, E. Velthorst, T.C. Kraan, D.S. van Dam, N. Burger, P.A. Delespaul (The Netherlands); B. Nelson, P. McGorry, G.P. Amminger, C. Pantelis, A. Politis, J. Goodall (Australia); A. Riecher-Rössler, E. Studerus, S. Borgwardt (Switzerland); R. Bressan, A. Gadelha, E. Brietzke, G. Asevedo, E. Asevedo, A. Zugman (Brazil); N. Barrantes-Vidal, A. Racioppi, M. Monsonet, L. Hinojosa (Spain); M.-O. Krebs, M. Kazes, C. Daban, J. Bourgin, O. Gay, C. Mam-Lam-Fook (France); M. Nordentoft, D. Nordholm, L. Randers, K. Krakauer, L. Glenthøj, B. Glenthøj (Denmark); S. Ruhrmann, D. Gebhard, J. Arnhold, J. Klosterkötter (Germany); G. Sachs, I. Lasser, B. Winklbaur (Austria); T. Domínguez-Martínez (Mexico); T.R. Kwapil (USA). The NAPLS-3 Study Group also includes: J. Addington (Canada); C.E. Bearden, K.S. Cadenhead, R.E. Carrión, M. Keshavan, D.H. Mathalon, T.H. McGlashan, W.S. Stone, E.F. Walker, S.W. Woods, T.D. Cannon (USA). The EU-GEI Project was funded within the European Community's Seventh Framework Programme (grant agreement HEALTH-F2-2010-241909). Additional support was provided by a UK Medical Research Council Fellowship (MR/J008915/1). The NAPLS-3 project was supported by the US National Institute of Mental Health (grants nos. U01MH082004, U01MH081984, U01MH081928, U01MH081944, U01MH081902, U01MH081988, U01MH082022, U01MH076989 and U01MH081857). I. Khadimallah is supported by Alamaya Foundation. D. Oliver, W. Pettersson-Yeo and P. McGuire are

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What happens after tapering off antipsychotics? Clinical trajectories of 267 first-episode patients who discontinued antipsychotic medication

Patients with first-episode psychosis (FEP) often wish to discontinue their antipsychotic medication shortly after remission. While maintenance treatment effectively prevents relapse, two randomized controlled trials (RCTs) showed long-term functional benefits after early dose reduction or discontinuation^{1,2}.

Information on clinical courses after early discontinuation is crucial for shared decision-making regarding an early tapering attempt, but data are scarce. The few studies investigating outcomes following discontinuation^{1,3-6} indicated that only a minority of patients remain medication-free in the long term. More detailed knowledge is needed to make a well-balanced shared decision, including information on personal characteristics allowing to better predict the risk for hospitalization or long-term successful discontinuation in individual cases.

We identified the clinical trajectories of 267 patients who discontinued antipsychotic medication after remission of FEP. All participants were closely monitored and had a gradual tapering trajectory with up to 4-year follow-up. We assessed the interval until patients needed to restart antipsychotics or were hospitalized for a psychosis relapse, and identified predicting factors for the different trajectories a person may go through after discontinuation.

Patients in early remission (3-6 months) from a FEP still using medication were recruited in 26 Dutch psychosis centres⁷. They had a DSM-5 diagnosis of schizophrenia (41.9%), schizoaffective disorder (23.2%), schizophreniform disorder (30.3%), brief psychotic disorder (4.1%), or unspecified schizophrenia spectrum and other psychotic disorder (0.4%). Those with dangerous behavior during FEP or coercive treatment were excluded.

Only patients with full discontinuation (until dose zero) and sufficient post-discontinuation data were included. Participants provided written informed consent. The trial was approved by the University Medical Center Groningen (NL62202.042.17). Medi-

cation use was assessed between September 2017 and June 2025 using self-report and pharmacy dispensation records, converting antipsychotic doses to olanzapine equivalents.

We quantified maximum duration of medication-free periods and timing of hospitalization over 4 years after discontinuation. Using k-prototype clustering, we identified four distinct clusters of clinical trajectories after discontinuation and the patient characteristics associated with each, defined by antipsychotic restart, hospitalization, and proportion of follow-up off antipsychotics (see also supplementary information).

Two hundred sixty-seven FEP patients (30.7% female) fully discontinued antipsychotics following a closely monitored tapering trajectory. Prior to tapering, they had a mean age of 27.7±8.8 years, used an average of 8.9±5.3 mg/day olanzapine equivalents, and showed moderately impaired daily functioning (mean score of 65.4±11.8 on Global Assessment of Functioning, GAF).

One year after discontinuation, approximately half of these patients had resumed antipsychotic treatment. Medication restart increased gradually over time, with 10.5% resuming after one month, 36.3% after six months, 52.8% after 12 months, 64.4% after 24 months, 68.9% after 36 months, and 71.2% after 48 months (see also supplementary information). Discontinuation was sustained by 46.4% of patients at one year, 28.5% at two years, 16.9% at three years, and 10.1% at four years. For some patients, no information was available due to loss to follow-up or pending assessments. These results are in line with those reported by Wunderink et al¹, who found that 40% of patients remained medication-free without relapse for on average 13 months after discontinuation, and with the findings in the Danish registry cohort⁶, showing that 6.5% of FEP patients remained medication-free for at least five years after discontinuation.

After 4-year follow-up, only 23 patients (8.6%) had required hos-

pitalization for psychosis relapse, predominantly within the first six months after discontinuation. Cumulative hospitalization incidence was 8.7% within one month, 34.8% by three months, and 78.3% by six months. Incidence plateaued thereafter, reaching 91.3% by 12 months and 100% by 24 months, with no further hospitalizations until 48 months. These findings are consistent with those reported by Gitlin et al⁵, showing a hospitalization rate of 13% within two years after cessation in recent-onset schizophrenia patients who underwent guided tapering, and by Wilson et al⁴, who also found that most hospitalizations occurred soon (average of four months) after discontinuation in a slightly higher portion of FEP patients (22%). For clinical practice, these results imply that close clinical monitoring is critical in the initial six months after discontinuation, with potentially less intensive follow-up thereafter in the first year.

K-prototype cluster analysis identified four different trajectories after discontinuation: cluster 1 with early restart of medication and without need for hospitalization; cluster 2 with early restart of medication and need for hospitalization; cluster 3 with later need to restart medication without hospitalization; and cluster 4 with sustained discontinuation without hospitalization.

Cluster 1 patients (N=76, 28.5%) restarted antipsychotics without hospitalization after a median of 3.9 months. They had the lowest baseline global functioning (mean GAF score: 60.9), the greatest difficulties in daily life (mean score on WHO Disability Assessment Schedule, WHODAS 2.0: 55.9), the highest baseline symptom severity (total mean score on Positive and Negative Syndrome Scale, PANSS: 46.4), the longest mean duration of FEP (215.4 days), and the highest mean dose before tapering (9.7 mg/day olanzapine equivalents), indicative of a severely affected subgroup.

Cluster 2 patients (N=23, 8.6%) had a medication-free period of five months and no need of hospitalization. They were predominantly male (87.0%), of relatively old age (mean: 29.1 years), with low education, and high smoking prevalence (47.8%). They also had approximately double the health care use compared to other clusters (4.6 contacts/month), and the lowest score on Patient Activation Measure, PAM (11.6). The combination of the low PAM score with high care needs may reflect a reduced illness awareness, which has been associated with increased risk of hospitalization⁸.

Cluster 3 patients (N=92, 34.4%) had a delayed antipsychotic restart without hospitalizations (median 8.8 months medication-free) and showed the highest global functioning (mean GAF score: 68.6), fewest difficulties in daily life (WHODAS 2.0 mean score: 52.7), the lowest symptom severity (PANSS mean score: 42.4), the highest proportion living with family (52.2%), and the largest proportion of women (38.0%), indicative of a less severely affected subgroup.

Cluster 4 patients (N=76, 28.5%) remained successfully medication-free in the long term (median follow-up: 36.2 months) without hospitalizations. This cluster was associated with the youngest age at FEP onset (average 25.1 years), the largest proportion of higher education (48.7%), the lowest body mass index (24.3), and the highest rates of employment (77.6%), partnered status (21.0%)

and financial independence (75.0%). Substance use was prominent, with the highest drug use (23.7%; 7.3 units/month) and high alcohol use (64.5%; 11.4 glasses/month). This subgroup may be characterized as young, high-functioning individuals with relatively low genetic vulnerability for schizophrenia, among whom drug use may have contributed to FEP onset in some cases⁹.

It is important to consider that the remitted FEP patients in the present study were RCT participants, representing a selected sample with potentially more favorable outcomes, as many patients may not have been invited by their clinicians or have declined participation. Yet our findings aligned with the unselected Danish registry cohort⁶. In addition, our data only apply to clinically monitored remitted FEP patients during their first discontinuation attempt.

In conclusion, we showed that about half of FEP patients who discontinued antipsychotics resumed medication within the first year. Hospitalization was needed in 8.6% of them and mainly occurred within the first six months, indicating that close clinical monitoring is critical in these initial six months, with potentially less intensive follow-up thereafter. Remaining medication-free in the long term was more common in young, high-educated patients with high drug use, whereas it was less common in patients who had lower education and greater functional impairments. These findings can inform shared decision-making on antipsychotic tapering early after remission, and monitoring needs in those who have discontinued their medication, by clarifying hospitalization risk and medication-free periods.

Franciska de Beer¹, Ben Wijnen², Sanne Koops¹, Marieke J.H. Begemann¹, Nico van Beveren^{3,4}, Nynke Boonstra⁵⁻⁷, Sinan Gulokuz^{8,9}, Lieuwe de Haan¹⁰, Martijn Kikkert¹¹, Wim Veling¹², HAMLETT-OPHELIA Consortium, Shiral S. Gangadin¹, Iris E. Sommer^{1,12}

¹Center for Clinical Neuroscience and Cognition, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands; ²Centre of Economic Evaluations & Machine Learning, Trimbos Institute, Netherlands Institute of Mental Health and Addiction, Utrecht, The Netherlands; ³Parnassia Group for Mental Health Care, The Hague, The Netherlands; ⁴Department of Neuroscience, Erasmus Medical Centre, Rotterdam, The Netherlands; ⁵Department of Healthcare, NHL Stenden University of Applied Sciences, Leeuwarden, The Netherlands; ⁶KieN VIP Mental Health Care Services, Leeuwarden, The Netherlands; ⁷Department of Psychiatry, UMC Utrecht Brain Center, Utrecht, The Netherlands; ⁸Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands; ⁹Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; ¹⁰Department of Psychiatry, Amsterdam UMC, Amsterdam, The Netherlands; ¹¹Arkin, Institute for Mental Health, Amsterdam, The Netherlands; ¹²Department of Psychiatry, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

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Neighborhood socioeconomic disadvantage and mental health among US veterans

Major depressive disorder (MDD), post-traumatic stress disorder (PTSD) and suicidal ideation (SI) are profound challenges for global mental health¹. MDD affects approximately 300 million people and is the leading cause of disability worldwide. PTSD and SI often co-occur with MDD and contribute to substantial functional impairment, reduced quality of life, and premature mortality. Among military personnel in particular, MDD and PTSD are associated with considerable suffering and elevated risk for suicidal behavior, underscoring the need to identify contextual factors that may account for risk beyond individual vulnerabilities.

While decades of research have elucidated individual-level risk factors for MDD, PTSD and SI, comparatively less attention has focused on how structural social contexts – including economic deprivation, environmental stressors, and community resources – may contribute to their etiology². Neighborhood environment represents a promising yet under-examined social determinant of mental health. Publicly available geospatial data, derived from sources such as the US Census and the American Community Survey (ACS), provide objective indicators of neighborhood conditions.

One widely used composite measure, the national area deprivation index (ADI), assesses multiple dimensions of neighborhood socioeconomic disadvantage – including education, employment, income, and housing quality – within a given catchment area³. The ADI provides an objective standardized national metric of neighborhood context, enabling researchers to quantify the socioeconomic environment at fine spatial scales, and to link these contextual factors with individual-level health outcomes.

In the present study, we tested whether neighborhood disadvantage, indexed by the national ADI, was independently associated with current MDD, PTSD and SI in a large, nationally representative sample of US military veterans, after accounting for individual-level risk factors. Veterans represent an ideal population for examining these associations, given their high rates of trauma exposure, elevated prevalence of mental disorders, and diversity in socioeconomic backgrounds and living conditions. This heterogeneity allows for the examination of how neighborhood-level disadvantage may be linked to mental health beyond individual characteristics. Because mechanisms linking socioeconomic disadvantage and mental health may operate similarly across populations, identifying these associations in veterans is likely to have global relevance for informing interventions that address structural determinants of mental health.

Data were analyzed from the National Health and Resilience in Veterans Study (NHRVS), which surveyed a nationally representative sample of 4,069 US veterans between November 18, 2019 and March 8, 2020. Post-stratification weights were used to generate estimates representative of the US veteran population.

The national ADI is a nationally standardized, rank-based measure of neighborhood socioeconomic disadvantage (range: 1 = least disadvantaged to 100 = most disadvantaged). The index integrates

17 variables from the ACS 5-year estimates, encompassing key domains of education (e.g., percentage of adults without a high-school diploma), employment (e.g., unemployment rate), income (e.g., median family income, percentage below the federal poverty line), and housing quality (e.g., households lacking complete plumbing or experiencing overcrowding)³. The ADI is calculated at the census block group level, providing a fine-grained representation of local neighborhood conditions.

For this study, we used the 2020 national ADI dataset, the most contemporaneous with the NHRVS data collection period. Each veteran's ADI score was determined by geocoding his/her residential address to the corresponding census block group, yielding an objective, contextual measure of neighborhood disadvantage.

Current MDD was defined as a score ≥ 3 on the Patient Health Questionnaire-2; current PTSD as a score ≥ 33 on the PTSD Checklist for DSM-5; and current SI as a score ≥ 1 on item 9 of the Patient Health Questionnaire-9.

Three multivariable logistic regression models were used to examine the independent effects of ADI on current MDD, PTSD and SI after adjusting for age, sex, race/ethnicity, education, marital/partner status, household income, years of military service, combat exposure, adverse childhood experiences, cumulative lifetime trauma, military sexual trauma, lifetime psychiatric and substance use disorders, and number of medical conditions.

After adjustment for these individual-level factors, each decile increase in ADI was associated with an 8%, 7% and 5% greater likelihood of current MDD, PTSD and SI, respectively. Compared with veterans in the least disadvantaged decile, those in the most disadvantaged decile exhibited a nearly 3-fold higher prevalence of MDD (13.3% vs. 4.7%) and PTSD (9.5% vs. 3.3%), and a more than two-fold higher prevalence of SI (12.5% vs. 5.3%).

These findings indicate that objectively-assessed neighborhood socioeconomic disadvantage is independently and meaningfully associated with current MDD, PTSD and SI, even after extensive adjustment for individual-level demographic, trauma-related, and clinical variables. Indeed, moving from the least to the most disadvantaged neighborhoods was associated with two- to three-fold higher prevalence of these outcomes.

These results suggest that objective measures of “where people live” may be a significant determinant of mental health, with community-level conditions shaping risk and recovery alongside individual vulnerabilities. They align with prior evidence showing that socioeconomically disadvantaged areas are characterized by higher levels of chronic stress and social disconnection, and reduced access to health-promoting resources⁴⁻⁷. Each of these contextual factors has been linked to increased vulnerability to mood and trauma-related disorders across diverse populations. Among veterans, these factors may amplify the psychological impact of trauma, heighten physiologic dysregulation, and reduce opportunities for social connection and engagement with care.

Although the present study focused on a population-based sample of US military veterans, its implications extend to people and societies worldwide. The pathways through which neighborhood socioeconomic disadvantage may influence mental health – such as chronic stress, social disconnection, limited access to care – are universal and observed across high-, middle- and low-income countries⁸. Identifying and addressing these contextual factors could help inform global strategies aimed at reducing the population-based burden of common mental disorders.

Incorporating neighborhood-level metrics such as the ADI into epidemiological research and clinical risk assessment represents a critical step toward advancing equitable, context-informed models of health care worldwide. Because neighborhood disadvantage is at least partly modifiable⁹, strategic investments in affordable housing, community safety, accessible evidence-based health care, and robust social support systems have potential to reduce mental health disparities and improve outcomes for individuals

living in highly disadvantaged communities.

Ian C. Fischer^{1,2}, Peter J. Na¹, Dilip V. Jeste³, Benson S. Ku⁴, Robert H. Pietrzak^{1,2}

¹Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; ²National Center for PTSD, VA Connecticut Healthcare System, West Haven, CT, USA; ³Global Research Network on Social Determinants of Mental Health and Exposomics, La Jolla, CA, USA; ⁴Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

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A European platform trial for major depressive disorder

Robust and relevant evidence from clinical trials is needed to guide treatment decisions by health care professionals and their patients. However, in mental health, there is often a lack of informative trials¹. Many randomized controlled trials (RCTs) are underpowered², and even large multicenter trials rarely make it into clinical guidelines³, indicating that they are often considered non-informative. Moreover, the rate of transition from phase 2 to approval in psychiatry continues to be low⁴, and licensing of new medicines is scanty⁵. New ways of generating clinically informative evidence faster and more efficiently are therefore needed.

Platform trials are highly adaptive trial designs that simultaneously evaluate different treatments under a common master protocol, using a shared trial infrastructure and shared control groups, and allowing seamless addition of new treatments over time and dropping of treatments that turn out to be ineffective. These trials may help to overcome some of the limitations of traditional trials, because they have built-in statistical and operational efficiencies, which can increase statistical power and decrease burden, time and cost^{6,7}.

The EU-PEARL consortium (<https://eu-pearl.eu>) built the conceptual framework for such trials in different indications, including major depressive disorder⁸, by bringing together persons with lived experience, clinicians, and trial methodologists from academia and industry, as well as regulators and members of ethics commissions. The consortium has recently received funding from the Wellcome Trust to implement its reusable trial infrastructure for depression, with enrolment expected to start in 2026.

The integrated platform trial (IPT) consists of three components: a trial site network, a longitudinal observational cohort, and the platform trial itself, called European Platform trial for the Evaluation of Augmentation strategies and Relevant Long-term outcomes in Depression – an Infrastructure for treatment deVeloPment and Repurposing (EU-PEARLDIVER). Details about the trial's design and infrastructure are available in the supplementary information

and at www.eu-pearldiver.eu.

The site network is the backbone of the IPT and serves as recruitment infrastructure for both the longitudinal observational cohort and the platform trial itself. We will start with a site network of approximately 30 sites, distributed across six European countries (Denmark, Germany, Italy, The Netherlands, Spain, and the UK) (see also supplementary information). Each national site network is led by a coordinating site, and includes academic hospitals that are members of the European University Hospital Alliance.

The longitudinal observational cohort serves as a readiness cohort and a tool for collecting long-term outcome data, including post-trial outcomes for participants who have completed the trial, and observational data for those not entering the trial (see also supplementary information).

The platform trial is designed for participants who have not benefitted sufficiently from previous treatments. In the trial, new (or repurposed) treatments are added to current antidepressant medication (a selective serotonin reuptake inhibitor, SSRI, or a serotonin-norepinephrine reuptake inhibitor, SNRI) and compared to adding a matching control (e.g., placebo). The primary endpoint is change in depression severity from baseline to six weeks after randomization, measured by the Montgomery-Åsberg Depression Rating Scale (MADRS), with secondary outcomes covering a range of symptoms (such as anhedonia, anxiety, sleep, cognition) and other patient reported outcomes (such as quality of life and functioning) as well as novel exploratory outcome measures such as digital phenotyping.

EU-PEARLDIVER can include several experimental drugs that have the same route of administration and share a control group, together making up a “domain” of the platform trial (see supplementary information). Moreover, the trial can simultaneously host several different “domains”. Each domain has its own shared control group, and blinding is maintained within that domain (but not across domains). The trial can also accommodate different sample

sizes per experimental treatment (it is modeled in the trial simulations for sample sizes ranging from N=40 to N=120, but can also be much larger)⁹.

The trial can address superiority as well as non-inferiority questions (including seamless superiority/non-inferiority designs). For the initial phase, we will focus on the pharmacological domain (with oral drugs). However, in later stages, we plan to gradually expand the trial to include other domains, which may also include non-pharmacological, digital or combined treatments (such as enhanced psychotherapy).

People with lived experience are central partners of the project, involved in every aspect of the trial design, and continue to shape the trial, e.g. as voting members in the trial management group. Moreover, the trial's design was discussed with regulators, such as the European Medicines Agency and national competent authorities, and we are currently continuing this engagement. Additional stakeholder events included industry representatives, members of ethics commissions, and patient advocacy groups.

The described IPT is a major infrastructure investment, and our vision is that such an investment should benefit the field and not just individual investigators or organizations. This means that all decisions within the consortium will be jointly made by all its members. It also means that the consortium will be open for additional members, new sites (via the national leads), additional countries and regions, new interventions to be tested, and new treatment modalities. This will ensure that EU-PEARLDIVER remains adaptable to a fast-changing research environment.

We are launching the trial with two arms of oral drugs. The consortium has conducted a systematic process of drug prioritization, and screened 59 candidate drugs with sufficient rationale for evaluating them as add-on to SSRI/SNRI in treatment-resistant depression (TRD) (see supplementary information). After evidence synthesis, voting, and guidance from the consortium members, including our lived experience team, we have produced a ranked short list of six drugs, with trazodone and pramipexole identified as the top candidates.

Trazodone was chosen as an on-label candidate because it is often used in combination with other antidepressants, but the systematic search did not identify a properly powered trial evaluating its use as add-on in TRD. Adding to this rationale, its pharmacology as a presynaptic alpha2 autoreceptor antagonist, coupled with the lack of weight gain, would make it a better adjuvant treatment for TRD compared with, for example, mirtazapine, if found to be effective.

The third ranked drug, oral semaglutide, will replace either of the two starting drugs in case they meet criteria for early termination at interim analysis (see supplementary information). Funding for these arms and their shared placebo control group is already included in our current budget.

For any further additions of treatment arms or domains in the trial, we are open to discussing opportunities for joint grant applications with any individuals or organizations, or direct suggestions and funding concepts from compound owners or other entities. Investigators submitting successful funding proposals for inclusion

in the EU-PEARLDIVER platform trial will be offered membership in the collaborative group, including authorship on subsequent publications of the consortium (as determined by our authorship policy, available on our website).

Selected and approved sites will receive case payments for recruitment and, if applicable, set-up fees. We are also open for enquiries and discussions with sites (including in other countries and regions) to explore the possibility of future expansion of the trial network, and joint funding applications to support such extensions.

Criteria to formally join the consortium, the publication and authorship policy, and other trial materials – as well as eventually progress reports and results – of EU-PEARLDIVER are publicly available and kept updated on our website.

We hope that EU-PEARLDIVER will help to transform the evidence landscape of depression treatment, for the benefit of those accessing mental health care and those administering it.

Stefan M. Gold^{1,4}, Jelena Brasanac¹, Francesco Benedetti^{5,6}, Nina Grootendorst⁷, Witte Hoogendijk⁷, Ole Köhler-Forsberg⁸, Franz König⁹, Fanni-Laura Mäntylä¹⁰, Amelie Michon¹¹, Carmine M. Pariante^{12,13}, Martin Posch⁹, J. Antoni Ramos-Quiroga¹⁴⁻¹⁷, Christian Otte^{1,3}, for the EU-PEARLDIVER Collaborative Group

¹Department of Psychiatry, Charité - Universitätsmedizin Berlin, Berlin, Germany; ²Medical Department, Psychosomatic Medicine Section, Charité - Universitätsmedizin Berlin, Berlin, Germany; ³German Center for Mental Health (DZPG), partner site Berlin-Potsdam, Germany; ⁴Institute of Neuroimmunology and Multiple Sclerosis, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; ⁵Vita-Salute San Raffaele University, Milan, Italy; ⁶Psychiatry and Clinical Psychobiology, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy; ⁷Department of Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands; ⁸Psychosis Research Unit, Aarhus University Hospital Psychiatry and Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; ⁹Institute of Medical Statistics, Medical University of Vienna, Vienna, Austria; ¹⁰Lived Experience Expert, Helsinki, Finland; ¹¹European Clinical Research Infrastructure Network, Paris, France; ¹²National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, London, UK; ¹³Institute of Psychiatry, Psychology & Neuroscience, Department of Psychological Medicine, King's College London, London, UK; ¹⁴Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute, Barcelona, Spain; ¹⁵Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Instituto de Salud Carlos III, Barcelona, Spain; ¹⁶Department of Mental Health, Hospital Universitari Vall d'Hebron, Barcelona, Spain; ¹⁷Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

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Caring for the world's youngest and loneliest population requires a change in approach

While loneliness affects people across all ages and regions, it is particularly common in low- and middle-income countries (LMICs) and among young people. Prevalence in Africa (24.3%) is more than double that in Europe (10.1%), and rate of loneliness among adolescents (20.9%) is considerably higher than in adults (15.1%) worldwide¹.

Beyond emotional pain, loneliness is linked to an increased risk of depression, anxiety, self-harm, suicide, paranoia, dementia, cardiovascular disease, stroke, reduced quality of life, and premature mortality¹⁻³. Globally, loneliness is associated with an estimated 100 deaths every hour, imposes billions in health care and educational costs, and makes teenagers 22% more likely to struggle academically¹.

Research and policy initiatives addressing loneliness have progressed most visibly in high-income countries (HICs), with the UK and Japan appointing ministers for loneliness^{1,2}. In contrast, comparable efforts in LMICs are only beginning to emerge^{4,5}. The urgency is acute for young people in Africa, a region overlooked in loneliness research, but home to the world's youngest population (three-quarters under 35) and projected to exceed one billion people aged 15 to 35 by 2063. These figures underscore not only demographic trends, but the scale of lived experience at stake.

Young people are vulnerable to loneliness during key neurodevelopmental stages marked by changing interpersonal relationships, evolving identity, and heightened sensitivity to stressors. This vulnerability may be aggravated by cyberbullying, social media comparisons, and exposure to violence^{1,6}. While many of these factors are universal, the experience of loneliness among young people is different among regions.

Loneliness in African youth is often rooted in cultural identity and shaped by the implicit expectations within families and communities. Social taboos, limited access to mental health services, and low digital literacy leave many young people feeling unheard. In contexts where meeting basic needs such as food and housing takes priority, expressions of emotional distress are frequently regarded as a luxury. Adolescents who speak of loneliness may be perceived as demanding or ungrateful, which discourages disclosure, while others may not recognize loneliness at all, reducing the likelihood of seeking help. These realities underscore the need for approaches to loneliness in Africa that are attuned to its cultural, social and structural contexts.

The Africa Research, Implementation Science, and Education (ARISE) Network, together with its adolescent and youth advisory board, is advancing adolescent and youth health research and education across seven countries: Burkina Faso, Ethiopia, Ghana, Nigeria, South Africa, Tanzania and Uganda. This work encompasses evidence synthesis, observational studies, behavioral and policy interventions, implementation research, and capacity building. ARISE is the first research network to prioritize addressing loneliness among young people in Africa.

Addressing loneliness in Africa requires solutions that resonate with the continent's unique context and the lived experiences of young people. Loneliness in this region often stems from identity-based exclusion on the basis of religion, tribe or community. This stands in contrast to Africa's long-standing philosophy of Ubuntu ("I am because we are"), emphasizing collective identity and shared humanity. Similarly, in Senegal, "Teranga" reflects communal hospitality and inclusion, while, in Zimbabwe, "Ubukhosi" embodies community cohesion and shared responsibility. A theoretical framework is needed that can effectively address the complexity of loneliness within the African context, while reflecting these cultural ideals.

Empirical research in the African context must move beyond borrowed concepts and tools from HICs. Many African languages lack a direct term for loneliness. While the Western concept of loneliness may exist in African cultures, it can rarely be encapsulated by a single word, underscoring the need for a more nuanced approach to describing this experience. Existing loneliness scales, largely developed by Western researchers in the 1980s, may fail to capture salient African experiences, such as feeling unheard, disrespected, or unable to contribute meaningfully to family or community life.

Calls for "common measures" across studies and sites risk overlooking these dimensions. Reliance on self-reporting also introduces bias, as adolescents may underreport distress due to social desirability. Innovative approaches, such as the use of smartphone behavioral and sensor data (i.e., to track physical activity and social media use) could indirectly be used to trace loneliness⁷. Yet, the feasibility of these approaches may be limited by disparities in access to technology, electricity and connectivity in rural and remote regions. Effective measurement requires not just translation of words or surveys, but translation of lived experiences into appropriate metrics.

In addition, intervention strategies in Africa must prioritize cost-effective, community-based models. Given the shortage of mental health professionals, task-shifting approaches are essential. Programs such as Zimbabwe's Friendship Bench, where trained lay health workers deliver psychological support, offer a model for scalable impact⁸. Creative formats, such as storytelling, comic books or edutainment videos, co-created with youth who bring lived experience, may promote learning and behavior change⁹. Interventions embedded in schools, families and communities are likely to maximize both reach and sustainability.

Policy responses must also be tailored to the African context. Unlike in HICs, where national loneliness strategies are emerging, most African countries lack formal policies. Progress requires strengthening local research networks, elevating youth voices, mobilizing community champions, and establishing a shared agenda. Supportive environments must extend beyond digital spaces to physical ones, through investment in youth centres, public spaces

designed for spontaneous interaction, intergenerational activities, volunteerism, and inclusive education. After-school programs, cultural and religious leadership, and inclusive education can further nurture connection. Governments should recognize youth loneliness as a health and societal issue, not just a personal struggle.

Future research should explore loneliness across cognitive (expectations), behavioral (withdrawal) and affective (distress) dimensions, while considering shifting cultural attachments and rising rates of intercommunity marriage. Studies should examine collective loneliness, such as shared disappointment or isolation felt by families or communities displaced by war, disease, climate change, or poverty. Research should trace loneliness pathways from causes to long-term impacts, and distinguish between within-person and between-person effects, including state and trait loneliness.

Priority underserved groups include people who are displaced, homeless, living with chronic diseases, incarcerated, or otherwise marginalized. Socioeconomic consequences (e.g., suicide, incarceration and crime, school dropout, absenteeism, unproductivity, and health care costs) should be carefully investigated. Intervention and implementation research should be human-centered, culturally embedded, and theory-driven^{8,9}.

Tackling loneliness among young people in LMICs will require more than adapting HIC models. The marked diversity across regions such as Africa calls for dedicated data, context-specific definitions and pathways, and tailored, culturally sensitive solutions, supported by collaborative partnerships spanning research, policy, and community practice. Recognizing loneliness as real, connection as healing, and care for the world's youngest and loneliest

population as a collective responsibility is imperative.

Shuyan Liu^{1,2}, Hiwot Daniel Sime³, Amani Masaule⁴, Maya Adam^{5,6}, Dixon Chibanda⁷, Palmira Fortunato dos Santos^{8,9}, Julianne Holt-Lunstad^{9,10}, Pamela Qualter^{9,11}, Mary Mwanjika Sando⁴, Dan J. Stein¹², on behalf of the ARISE collaborators

¹Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, Berlin, Germany; ²German Centre for Mental Health (DZPG), Berlin, Germany; ³Addis Continental Institute of Public Health, Addis Ababa, Ethiopia; ⁴Africa Academy for Public Health, Dar es Salaam, Tanzania; ⁵Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA; ⁶Heidelberg Institute of Global Health, Faculty of Medicine, Heidelberg University, Heidelberg, Germany; ⁷Friendship Bench, Harare, Zimbabwe; ⁸Mental Health, Trauma and Violence Program, National Institute of Health, Ministry of Health, Maputo, Mozambique; ⁹Technical Advisory Group on Social Connection, World Health Organization, Geneva, Switzerland; ¹⁰Social Connection and Health Laboratory, Department of Psychology, Brigham Young University, Provo, UT, USA; ¹¹Institute of Education, University of Manchester, Manchester, UK; ¹²Department of Psychiatry and Mental Health, and South African Medical Council Research Unit on Risk and Resilience in Mental Disorders, University of Cape Town, Cape Town, South Africa

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DISCOURSE in Psychosis: introducing an international consortium for research on thought, language and communication

Language is the thread that weaves our thoughts with society. It is the primary medium for patients to share experiences and for clinicians to provide interventions. When this thread is untied, the essence of the self and its social presence is threatened. Nowhere is this more acutely observed than in psychotic disorders such as schizophrenia, where thought, language, speech and communication disturbances (TLSC) have been defining, yet persistently enigmatic, core phenomena¹.

From Wernicke's hypothesis that aphasia may be the starting point for understanding mental illnesses to Bleuler's influential description of "loosening of associations", TLSC have consistently been identified as crucial predictors of illness onset, persistent disability, poor treatment response, and significantly reduced quality of life². Despite this, our understanding, measurement and treatment of these disruptions have lagged behind other aspects of psychopathology. For the past 50 years, psychiatry has primarily focused on the more obvious symptoms of delusions and hallucinations, leaving the profound complexities of thought and language to recede to the background.

We are now witnessing a historic confluence of opportunities

to overcome this impasse. A revolution in computational linguistics, a move towards collaborative open data science, and advances in digital measurement-based care have created an unprecedented moment³.

DISCOURSE in Psychosis is a coordinated, global response that began as a consortium in 2021 with three primary goals: a) to provide a global platform for researchers from mental health, linguistics, neuroscience, data science, and sociology to meet, collaborate and set shared priorities to reduce the burden of TLSC; b) to address foundational conceptual issues, phenomenology and measurement of TLSC in psychosis, and overcome barriers to understanding their cognitive/computational and neural implementational basis; c) to promote opportunities ensuring that knowledge growth translates into tangible clinical benefits for patients. Identifying strategies for methodological and transdiagnostic integration beyond psychosis has been integral to these goals. The consortium's work is organized around key thematic priorities, which are outlined below.

Reliably evaluating TLSC during routine clinical encounters is a challenge. Patients do not actively complain about being thought

disordered. The subtle nature of disorganized speech, poverty of thought, and pragmatic failures often evade clinician's notice, even with standardized scales, creating a collective blind spot. These measurement challenges also hinder our understanding of the developmental and epidemiological aspects of TLSC in psychosis. Our current understanding is biased, as it is almost exclusively based on patients with long-term illness assessed cross-sectionally in clinical settings. Yet, the most devastating functional deficits – social isolation, unemployment, relational breakdown – often unfold early in the illness course. The consortium's priority is to harmonize clinical measurements and collaboratively implement new quantitative methods (e.g., corpus-based speech tagging, distributional semantics, graph-theoretical analysis) to derive automated and scalable readouts of TLSC. These approaches show early promise as accessible markers for prediction and monitoring⁴, and they also offer a means to refine psychiatric semiology, enriching clinical training and practice.

Antipsychotic medications, while effective for positive symptoms, have a minimal impact on persistent TLSC. Moreover, clinical trials often circularly focus on measuring only what current treatments can change, systematically excluding patients with significant thought disorder. This creates a vicious cycle in which the very symptoms most predictive of poor outcome are the least likely to be investigated as treatment targets. The success of cognitive remediation ushers a path for interventions targeting TLSC to be designed and evaluated in psychosis. However, the difficulties in recruiting people with thought disorder for interventional trials diminishes the probability of successful empirical evaluation of treatment effects on this core feature of psychosis. Therapeutic progress requires concerted efforts to select and validate linguistic treatment targets, facilitate inclusion of patients with language deficits in ongoing trials, and develop focused remediation approaches against key linguistic deficits with the most functional relevance for patients.

Without a mechanistic understanding of TLSC, we will continue to shoot in the dark for treatments to reverse them. Large-scale initiatives – from neuroimaging to molecular biology – are generating unprecedented data⁵. To bring this approach to study TLSC, we need deep phenotyping that cuts across levels of analysis, from genes to circuits to behavior. *In-silico* models already suggest specific neural computational failures underlying language deficits, offering testable parameters for imaging and electrophysiology. Integrating these detailed cognitive models from psycholinguistics with clinical measurements and experimental approaches (e.g., perturb-and-measure designs) can provide mechanistic understanding. The goal is to bridge the gap between microcircuit aberrations and the lived experience of disrupted thought. To this end, DISCOURSE aims to collate repeated measurements of bio-behavioral data using multiple modalities in various contexts among transdiagnostic samples with a lifespan perspective.

Language is not merely a biomarker of intrinsic physiological disturbances; it is a biosocial marker. Early-life economic conditions, social class, ethnicity, and migration status indelibly shape our language use. Large-scale, cross-cultural linguistic analysis offers an unprecedented opportunity to investigate the social path-

ogenesis of psychosis. For instance, why does immigration increase psychosis risk 2-3 fold? Preliminary evidence suggests that the “linguistic distance” between one's native and host language may be a critical, and previously unappreciated, factor⁶. Testing such sociolinguistic theories will become feasible with ecological momentary assessment of spontaneous face-to-face conversations, data-pooling and collaboration among epidemiologists, anthropologists and comparative linguists with a shared interest in psychosis.

DISCOURSE has grown to a 360-member open network with five workgroups, including a Lived Experience panel. Several members have successfully raised grants to contribute to and/or utilize the collective effort of the network (totaling US\$ 44.45M from a variety of funders, including the European Union, the US National Institutes of Health, and the Wellcome Trust). The appeal of speech assessment includes its relative inexpensiveness and non-invasiveness, and the high participant acceptability, enabling the expansion of efforts by forming several national chapters (e.g., India, Brazil, Italy).

We have developed a harmonized protocol (available in 16 languages) with a minimal set of contextual variables to collect speech data as a by-product of routine clinical care, and created an accessible psychosis speech bank (<https://talkbank.org/psychosis>) in conjunction with the TalkBank repository system⁷. This expanding resource currently contains 890 speech samples in four languages, filling the void in harmonized, culturally and linguistically diverse shared data for clinical computational linguistics, measurement science and sociological applications in psychosis.

The study of communication in psychosis is, by its nature, interdisciplinary. DISCOURSE acts as a hub for knowledge exchange and training. We host a regular webinar series (six times annually, with 26 global events completed to date) and annual in-person consortium meetings. With philanthropic support, we have established the DISCOURSE Early Career Awards, which have supported over 50 awardees to attend the annual events. The consortium also develops and disseminates teaching materials for clinicians interested in language science and researchers interested in psychosis and thought disorder.

Language and speech analysis stands as one of the most promising and accessible objective tools in the history of psychosis research and care. Its large-scale use has the power to transform our field by enriching phenomenology, improving cultural and economic inclusivity in big-data studies, and leveraging state-of-the-art informatics to map the lifetime trajectory of a core feature of severe mental illnesses.

Lena Palaniyappan¹, Maria F. Alonso-Sanchez², Valentina Bambini³, Emre Bora⁴, Wolfram Hinzen^{5,6}, Gina Kuperberg⁷, Brian MacWhinney⁸, Natalia Mota⁹, Julianna Olah¹⁰, Susan Rossell¹¹, Iris E. Sommer¹², Frederike Stein¹³, Sunny X. Tang^{14,15}, Alban Voppel¹⁶

¹Department of Psychiatry, Douglas University Mental Health Institute, McGill University, Montreal, QC, Canada; ²Escuela de Fonoaudiología, Universidad de Valparaíso, Valparaíso, Chile; ³University School for Advanced Studies, Pavia, Italy; ⁴Department of Psychiatry, Dokuz Eylül University, İzmir, Turkey; ⁵Institut Català de Recerca i Estudis Avançats, Barcelona, Spain; ⁶Universitat Pompeu Fabra, Barcelona, Spain; ⁷Tufts University, Medford, MA, USA; ⁸Carnegie Mellon University, Pittsburgh, PA, USA; ⁹Instituto de Psiquiatria, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; ¹⁰Psyris Inc., San Francisco, CA, USA; ¹¹Swinburne University of Technology, Melbourne, VIC, Australia; ¹²University Medical Center, Groningen, The Netherlands; ¹³Philipps-Universität Marburg, Marburg, Germany;

¹⁴Zucker School of Medicine at Hofstra/Northwell, New York, NY, USA; ¹⁵Feinstein Institutes, Manhasset, NY, USA; ¹⁶Douglas University Mental Health Institute, McGill University, Montreal, QC, Canada

Further information on the DISCOURSE consortium can be found at <https://discourseinpsychosis.org>.

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Advancing mental health for all as a response to global change: WPA achievements under the Action Plan 2023-2026

The WPA Action Plan 2023-2026 drew inspiration from the 17 United Nations Sustainable Development Goals (SDGs) (<https://sdgs.un.org/goals>), a blueprint for building a sustainable, inclusive and prosperous world by 2030. As this deadline approaches, it is commonly acknowledged that we are living in turbulent times. Armed conflicts and escalating geopolitical tensions, economic instability and energy crises, mass displacements and humanitarian emergencies, climate change and natural disasters, technological acceleration and artificial intelligence (AI) safety concerns dominate the news. These global crises generate instability, uncertainty, societal divisions, and erosion of trust, all of which deeply affect daily life and mental health.

This context underscores a central truth: mental health is inseparable from the social, economic and environmental conditions in which people live. These determinants shape risk, resilience, and access to care, and they can reinforce intergenerational cycles of disadvantage and poor health¹.

Mental health indicators (i.e., reducing suicide mortality and harmful alcohol use) are explicitly included in SDG 3 - Good health and well-being. Yet, progress in mental health also depends on advances in many other SDGs: reducing inequalities and discrimination (Goals 5 and 10), ending wars (Goal 16), strengthening economic security (Goals 1 and 8), improving education (Goal 4), and protecting the environment (Goal 13). Addressing mental health at a systemic level, therefore, requires strong partnerships that mobilize expertise, resources and influence across sectors (Goal 17).

Against this framework, the WPA Action Plan 2023-2026 proposed a scientifically grounded, multi-level strategy to advance mental health for all through four key pillars: improved clinical practice and comprehensive care; early prevention and early intervention; equity and inclusivity; and strengthened collaborations.

Evidence-based treatments for mental disorders exist, yet their overall impact is often constrained by limited real-world clinical effectiveness, substantial variability in individual treatment response, and inadequate access to care². While research to develop more effective treatments must continue, the WPA is committed to fostering better implementation of existing evidence-based treatments and improving the translation of research into practice.

A major achievement has been the development of the Specialist Corner: Advances of science and their application in clinical practice (www.wpanet.org/specialist-corner). This platform provides accessible, expert-led lectures on state-of-the-art knowledge across major classes of mental disorders, including schizophrenia and other psychoses, affective disorders, intellectual impairment, and substance use disorders. The Specialist Corner goes beyond the analysis of aetiology, symptomatology, treatment and rehabilitation. It addresses the complexity of real-world clinical practice by incorporating expert groups' perspectives on key cross-cutting themes, including comorbidity, lived and family experiences, the impact of digitalization, cultural factors, ethical and legal issues,

lifestyle and physical activity, and public mental health strategies. This initiative strengthens psychiatric professionals' ability to deliver evidence-informed, person-centred care across diverse settings.

Reducing suicide deaths is one of the main indicators of SDG 3. In response, the WPA has promoted the integration of the Brief Motivational Intervention and Long-term Regular Follow-up Contact Program (BIC) into the clinical practices of its Member Societies to help decrease suicide mortality³. The program consists of a brief motivational session before hospital discharge after a suicide attempt, and structured contact sessions for 18 months post-discharge, with more intensive follow-up initially that tapers off after three months. The WPA offers training and research resources, including videos and study protocols, for centres interested in implementing and evaluating their local BIC interventions (www.wpanet.org/bic).

Furthermore, the WPA continues to provide support through guidance, expert consultation, educational initiatives, and the dissemination of evidence-based practices to professionals working in regions affected by emergencies, such as war, conflicts, displacement, and natural disasters.

Mental disorders frequently begin early in life: the onset of a first mental disorder occurs before age 14 in one-third of individuals, and before age 18 in nearly half⁴. Early onset often coincides with the development of unhealthy behaviors that contribute to long-term physical illness and premature mortality. At the same time, robust scientific evidence shows that physical activity, healthy nutrition, and restorative sleep improve mental health outcomes across the lifespan^{5,6}.

For these reasons, the WPA has placed early prevention and lifestyle-based interventions at the centre of its strategy. The Healthy Lifestyles Hub (www.wpanet.org/healthy-lifestyle-hub) offers short psychoeducational videos on healthy lifestyle practices. These resources are designed not only for patients but also for professionals, supporting the integration of lifestyle-based interventions into routine psychiatric care. The Hub contributes to building a culture of prevention that enhances treatment outcomes and improves well-being among both service users and health care providers.

Stigma, discrimination and inequalities continue to shape mental health care and research. As a global organization, the WPA has a responsibility to address the diverse needs of populations across genders, ages, ethnicities and sociocultural contexts.

To meet this responsibility, the EDIT principles have been introduced as a framework for embedding equity and inclusivity across psychiatric research, education and clinical practice. More in particular, these principles aim to strengthen Equity across genders, ages and ethnicities; consider the Developmental stages from childhood to adulthood and beyond; promote the Inclusion of under-represented groups; and adopt Transcultural awareness and perspectives⁷. The WPA has worked to integrate these princi-

ples into its governance structures (e.g., more equal gender and geographical representation on standing and other committees and expert groups) and activities (e.g., ensuring diversity in congress sessions, fellowship winners and judges, and the medical students' essay competition). To guarantee accountability, the WPA has also begun systematically collecting and reporting data on the diversity of speakers and participants at its annual World Congress. This enables targeted initiatives, transparency, and measurable progress over time⁸.

Mental disorders account for a substantial share of the global burden of disease, representing 6.1% of all disability-adjusted life years, making them the fifth most burdensome disease category worldwide. Despite this, only about 2% of health budgets are allocated to mental health, with minimal funding directed toward community services and prevention. This imbalance fuels the global treatment gap, rising disability, and widening inequities.

Strengthening partnerships across disciplines and institutions is, therefore, essential. The WPA supported the UK Royal College of Psychiatrists' initiative to launch the Prague Agreement, a coalition of psychiatric associations and mental health charities advocating for increased global investment in mental health⁹. This initiative reframes mental health not only as a human rights imperative, but also as a foundation for economic development and societal resilience. Furthermore, the WPA strengthened collaboration with the World Health Organization, the World Federation of Neurology, and the International Alliance on Brain Health to promote integrated brain health strategies, an increasingly urgent priority given rising multimorbidity and limited resources¹⁰. These partnerships reflect the WPA's commitment to advancing mental health through coordinated, multisectoral action.

The WPA Action Plan 2023-2026 has delivered concrete prog-

ress in aligning global psychiatry with the 17 SDGs, and therefore responding to today's rapidly evolving global challenges. Through improved knowledge translation in clinical care, prevention-oriented lifestyle initiatives, systematic promotion of equity and inclusivity, and strengthened alliances across institutions, the WPA has advanced a modern vision of mental health: one that is evidence-based, person-centred, culturally informed, and grounded in partnership. In an era marked by instability and accelerating change, the WPA is determined to play a key role in shaping a more resilient and mentally healthier world.

Danuta Wasserman^{1,2}, Celso Arango^{3,4}, Andrea Fiorillo^{4,5}, G. Prasad Rao^{4,6}, Thelma S. Sanchez-Villanueva^{4,7}, Aida Sylla^{4,8}, Miriam Iosue²

¹WPA President; ²National Centre for Suicide Research and Prevention of Mental Ill-Health, Karolinska Institutet, Stockholm, Sweden; ³Hospital Universitario La Paz, School of Medicine, Universidad Autónoma de Madrid, CIBERSAM, Madrid, Spain; ⁴WPA Planning Committee; ⁵Department of Psychiatry, University of Campania "L. Vanvitelli", Naples, Italy; ⁶Schizophrenia & Psychopharmacology Division, Asha Hospital, Hyderabad, India; ⁷DEPREF and SMAG Clinic, Universidad de Guadalajara, Guadalajara, Mexico; ⁸Centre Hospitalier National Universitaire de Fann, University Cheikh Anta Diop, Dakar, Senegal

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Global investment in mental health – The Prague Agreement

The primary interest of global financiers is economic growth, and the evidence is clear that this is impacted significantly by poor mental health. This is because the majority of mental disorders start early in life and affect schooling, education and career development. Therefore, they directly impact the productivity of every nation. Thus, poor mental health is an economic issue, and any country, in order to maximize its potential to prosper, must actively focus resources on mental illness. Global financiers have the power to indicate the importance of good mental health and incentivize global change.

The Prague Agreement is an initiative aimed to do more than continue to lobby national governments which are failing to prioritize mental health care, due to lack of resources, understanding or political will. It is a collaboration between psychiatric organizations and civil society, in a cross-sector consensus that has rarely been seen before.

Globally, the economic cost of mental ill-health is estimated to be US\$ 5 trillion per year¹. Whether a nation has a high, middle or

low income, mental ill-health is impacting its prosperity. Unlike physical disorders, which primarily affect middle-aged and older adults, mental disorders arise in youth, with 34.6% starting before the age of 14 and 62.5% before the age of 24². Without a public health approach to improving health and well-being, as well as accessible mental health care that supports early intervention, these mental disorders can develop into chronic mental illness in adulthood.

Usually, when people are diagnosed with a physical non-communicable disease, they are in their middle-age; they have already been working for many years; and their disease has not impacted on their school attendance, access to higher education, career progression, and ultimately their ability to pay tax dollars to the state. The opposite is true of mental illness. Once people have survived the infectious diseases of childhood, the most likely illness they will suffer from as young persons is a mental illness, impacting their education, access to work, and ultimately their economic value. As a result of the prominence of poor mental health from a

young age, low- and middle-income countries, which tend to have younger populations, are likely to be disproportionately affected by the economic burden of mental ill-health.

A large proportion of the costs associated with mental ill-health are due to loss of workforce and reduced productivity. It is predicted that poor mental health will result in an average annual reduction in gross domestic product (GDP) of 1.7% between 2025 and 2050³. We also know that there are “intangible costs”, which can include the impacts of lost quality of life, such as the detrimental impacts of stigmatization, discrimination and social exclusion.

Many mental health conditions are preventable and treatable, especially if identified and treated early. Investing in system strengthening, community- and primary care-based prevention and treatment is crucial to ensure that children and young people do not become adults with chronic or relapsing mental illnesses that interfere with their ability to fulfil their potential and contribute meaningfully to society.

A “balanced” approach to mental health care has been proposed⁴, with majority care in the community, supplemented by inpatient resources should people need them. This model can be applied to low-, middle- and high-income countries, but requires leadership to make the shift from hospital to community for those with illness, and prevention for those yet to develop illness.

Despite this, national governments are not investing sufficient funds in mental health care. In 2018, it was proposed that high-income countries should increase their expenditure on mental health to at least 10% of their total health budget, while low- and middle-income countries should raise spending to at least 5%⁵. Data collected from 85 countries in 2020 showed that only 13 met the proposed rate of expenditure: five of these were high-income countries, six upper-middle-income and two lower-middle-income countries⁶.

Across the world, there is underinvestment in mental health. This is not necessarily because countries do not have the funding. Rather, mental health has not been prioritized. United for Global Mental Health estimates that only 2.1% of government health budgets globally are allocated to mental health, creating an annual mental health finance gap of at least US\$ 200 billion⁶. Globally, there is an average of only 0.3 psychiatrists per 100,000 people⁵.

While clinical treatment is a key element of recovery, improving mental health often is not achieved through health services alone. Well-established models suggest that clinical care accounts for 20% of health outcomes, while socioeconomic factors and physical environments make up 50%⁷.

Data from a group of lower-income African countries show that over half of mental health expenditure is on treatment, mainly hospital care⁸ – often the costliest intervention, most likely to occur when people have more severe mental illnesses and are more likely to be in crisis. Meanwhile, primary and community health care services are relatively underfunded, resulting in low access to and coverage of early treatment interventions as well as limited preventive interventions.

Evidence shows that investing in population mental health brings a good return on investment. The United Nations Develop-

ment Programme (UNDP) research in the Philippines estimates that an investment of US\$ 2.8 billion would return US\$ 4.27 billion over ten years⁹. Australia has tracked its public health investment since 2012 and noted significant gains: parenting interventions for the prevention of anxiety disorders in children saved US\$ 5.5 million, while school-based interventions to prevent depression in young people saved US\$ 24.5 million, both over a 10-year period⁹.

The impact, or return, of investing in good mental health is often felt wider than simply a reduction in demand for mental health services. Improving well-being, supporting recovery, and preventing the onset of mental ill-health reduces demand for physical health services and improves productivity. Just as there is a global emphasis on staying physically well, we should not be waiting for people to become mentally unwell to intervene. Our collective challenge is articulating that ensuring good mental health at a national level is the key to a nation's success and incentivizing governments to act.

We call for the following:

For any country to maximize its potential and prosper, it must actively focus resources to reduce population-level prevalence of mental illness, while improving care for those living with poor mental health. Population mental health planning does not exist in a silo. The bi-directional relationship with employment, education and housing is well established, yet rarely is good mental health acknowledged as the key to prosperity.

The World Bank, the International Monetary Fund and other financiers are in a unique position to incentivize this change. For a country to be successful and prosperous, it should have a robust cross-government approach to mental health – recognizing the links between good mental health and economic growth. Thus, banks and other financiers should stimulate domestic commitment to mental health care by aligning investments (health or otherwise) with the development of a national cross-government mental health strategy, with an accompanying implementation plan for improving population mental health and well-being. Each strategy would differ depending on the country, its national resources and capabilities, but would include at least one tangible commitment which could be evaluated on an annual basis to ensure accountability.

Mental ill-health must be regarded with the same concern as poor physical health. For countries that are unsure what a mental health strategy should include, global support is already available. The United Nations have recently started partnering with governments to generate country-specific investment cases for mental health which outline recommendations for improvement. The UNDP has committed to working with partners to strengthen their health system, including creating equitable access to mental health care services⁸. The World Health Organization also provides information on cost-effective and feasible mental health interventions that can be expanded to a larger scale to strengthen mental health care systems in countries⁸. The UN Children's Fund (UNICEF) global multisectoral strategy and operational framework places a focus on children, adolescents and young people, and their caregivers

in its support to nations. CCLA Investment developed the Corporate Mental Health Benchmark Global 100+ after realizing that “the stark human and economic costs associated with poor mental health represent a substantial obstacle to companies’ success”.

Psychiatric organizations and associations around the world, individually and collectively, have the expertise to support nations to develop cross-government mental health strategies and build their health care workforce; from the recruitment and retention of psychiatrists to supporting nurses, primary care workers and the voluntary sector to develop skills and capabilities to create and enhance community mental health systems and support citizens living with poor mental health⁹. Many of these organizations have a proven track record of rolling out high-quality, evidence-based training programmes – for example, the UK Royal College of Psychiatrists has supported co-produced projects in Iraq, Palestine, Uganda, Kenya, Ghana, Pakistan, Ukraine, Egypt and India. The Mental Health Action Trust in India has developed community mental health services which now cover 70 sites in South India.

We have seen a significant shift in Ukraine’s mental health agenda due in large part to the establishment of an interministerial panel under the patronage of the First Lady. This highlights how visible gestures are necessary to raise the profile of mental health. The means for improving mental health care already exist; we need global organizations to recognize their leverage for change.

Calls for sustainable funding for mental health care to match the disease burden have long been called for, yet progress has been slow. As individual nations, and a global community, we can no longer wait. A catalyst must be provided for action, and that lies in the power of international financiers. People should not be reduced to their economic value; the case for investing in good mental health should be based on human rights alone – however, this argument has not achieved the traction we all need it to. Promoting good mental health is no longer simply a human rights imperative. It makes economic sense.

Shubulade Smith^{1,2}, Jessica Rackham³, Anusha Lachman^{4,5}, Savita Malhotra^{6,7}, Ramune Mazaliauskiene^{8,9}, Theresa Miskimen^{10,11}, Taiwo Obindo^{12,13}, Thelma Sanchez-Villanueva^{14,15}, Vijayakumar Seethapathy^{16,17}, Astha Tomar^{18,19}, Danuta Wasserman^{20,21}

¹Department of Forensic and Neurodevelopmental Science, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, UK; ²President, Royal College of Psychiatrists, UK; ³Deputy Head of Policy, Royal College of Psychiatrists, UK; ⁴Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa; ⁵President, South African Society of Psychiatrists; ⁶Fortis Hospital, Mohali, India; ⁷President, Indian Psychiatric Society; ⁸Lithuanian Health Sciences University, Kaunas, Lithuania; ⁹President, Lithuanian Psychiatric Association; ¹⁰Rutgers University, New Brunswick, NJ, USA; ¹¹President, American Psychiatric Association; ¹²University of Jos, Jos, Nigeria; ¹³Association of Psychiatrists in Nigeria; ¹⁴Universidad de Guadalajara, Guadalajara, Mexico; ¹⁵Mexican Consortium of Neuropharmacology; ¹⁶Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada; ¹⁷President, Canadian Psychiatric Association; ¹⁸Monash University, Melbourne, VIC, Australia; ¹⁹President, Royal Australian and New Zealand College of Psychiatrists; ²⁰National Centre for Suicide Research and Prevention of Mental Ill-Health, Karolinska Institutet, Stockholm, Sweden; ²¹President, World Psychiatric Association

The Prague Agreement has been signed by the Royal College of Psychiatrists, UK, the World Psychiatric Association, the European Psychiatric Association, the American Psychiatric Association, the South African Society of Psychiatry, the Association of Psychiatrists in Nigeria, the Indian Psychiatric Society, the Royal Australian and New Zealand College of Psychiatry, the Canadian Psychiatric Association, and several global mental health charities. The authors are grateful for their input and support to Z. Hijazi, A. Browne, D. Chisholm, A. Kousoulis, G. Dom, M. Knapp and N. Sartorius.

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Education and publications in psychiatry: from strategy to implementation

The WPA Committee on Education and Scientific Publications coordinates and leads the WPA’s global strategy for psychiatric education, training, and scientific dissemination. The Blueprint for Advancing Psychiatric Education and Scientific Publications set out a six-year strategic framework to strengthen education and publications globally through integration, innovation and collaboration¹. During the past triennium, this strategy has been implemented with a clear focus on integrating education and publications in psychiatry and translating this into coordinated action.

An important focus has been the consolidation and expansion of publication activities. *World Psychiatry* has been further strengthened as the WPA flagship journal, with the Editor and editorial leadership continuing to maintain its position as the most prominent journal in psychiatry, and the journal with the highest impact fac-

tor in the field. *World Psychiatry* provides a global platform for research, clinical practice developments, and perspectives on policy development.

The WPA e-journal *Education and Psychiatry* was launched as a peer-reviewed, open-access platform dedicated to psychiatric education and international knowledge exchange, achieving rapid global engagement with contributions from all regions. Of special note, this platform has strong participation from early-career professionals and colleagues in low- and middle-income countries², providing confidence that they, too, have a voice in this important area.

Collaboration with journals linked to WPA Scientific Sections has been systematically reviewed, ensuring clearer alignment with WPA priorities, improved coordination, and support for joint ini-

tiatives and special issues¹. New external collaborations are also being developed, including a forthcoming special issue of *BMC Medical Education* on “Global Training in Psychiatry – Inclusion, Equity, and Shared Learning”. This will mark a strategic effort by the WPA to move beyond educating psychiatrists alone into the active engagement of the wider medical education community.

Publishing activities have further expanded through books and educational materials, including handbooks and thematic volumes, culminating in the WPA Books Triennium Forum within the 2026 World Congress of Psychiatry, which will provide a platform for advancing scholarly publishing and international collaboration.

Substantial progress has also been made in education. The WPA Global Study on Psychiatric Training addressed the core questions about what elements of psychiatry are being taught by medical schools worldwide. The study collected data from more than 100 countries represented by WPA Member Societies, providing the most comprehensive global overview of psychiatry in medical education to date³. It examined curriculum structure, clinical exposure, and training challenges, offering an evidence base for improving education and workforce development.

Extensive in-person educational opportunities have been delivered at the World Congresses of Psychiatry and other scientific meetings, all with the focus on supporting professional development and international exchange. The Committee on Education and Scientific Publications has also advanced a structured approach to continuing professional development, including accreditation of WPA educational activities, as well as co-sponsored meetings, contributing to the standardization and recognition of high-quality psychiatric education.

Significant efforts have been invested in the development of the

WPA Education Portal as a central digital infrastructure for global e-learning. The platform provides multilingual access to courses, clinical resources, and educational materials, and continues to undergo substantial technical and content development. The creation of this Portal required considerable time, energy and coordination. Its full impact will become clearer as it is fully implemented and more widely used.

The WPA Committee on Education and Scientific Publications has been very active in the past triennium. The above-mentioned initiatives demonstrate that publications and educational activities have created resources that can be integrated into mental health policy and practice worldwide, while also establishing a coherent system to support global training, knowledge dissemination, and capacity building.

Norbert Skokauskas^{1,2}, Gary Chaimowitz^{3,4}, Dina Aly El-Gabry^{4,6}, Andrea Fiorillo^{4,7}, Anusha Lachman^{4,8}, Angeles Lopez Geist^{4,9}, Paul Robertson^{4,10}, Hee Jeong Yoo^{4,11}, Bennett L. Leventhal^{4,12}

¹WPA Secretary for Education and Scientific Publications; ²Norwegian University of Science and Technology, Trondheim, Norway; ³McMaster University, Hamilton, ON, Canada; ⁴WPA Committee on Education and Scientific Publications; ⁵Ain Shams University, Cairo, Egypt; ⁶United Arab Emirates University, Al Ain, United Arab Emirates; ⁷University of Campania “Luigi Vanvitelli”, Naples, Italy; ⁸Stellenbosch University, Stellenbosch, South Africa; ⁹Association of Argentinian Psychiatrists, Argentina; ¹⁰University of Melbourne, Melbourne, VIC, Australia; ¹¹Seoul National University College of Medicine, Seoul, South Korea; ¹²University of Chicago, Chicago, IL, USA

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The WPA Neuropsychiatry Special Interest Group: charting the way forward for neuropsychiatry

As our understanding of brain structure and function continues to expand, neuropsychiatry is becoming increasingly relevant to contemporary psychiatric practice. The approval by the WPA General Assembly of a Neuropsychiatry Special Interest Group at the World Congress of Psychiatry in 2023 was, therefore, especially timely. Since then, interest in neuropsychiatry within the international psychiatric community has continued to grow.

There is, however, no universally accepted definition of neuropsychiatry. The International Neuropsychiatric Association defines it as a field of medicine that “endeavors to understand abnormal behavior and behavioral disorders on the basis of an interaction of neurobiological and psychological-social factors”¹. Others have proposed that it includes the application of neuroscientific knowledge to the understanding of disturbances in thought, behavior or emotion². A broader version of this position is adopted by neurophilosophical monists, who argue that the mind is an emergent property of the brain, and that all mental phenom-

ena arise from neural processes. From this perspective, “all psychiatry is neuropsychiatry”.

Pragmatists have taken a different view. The pioneering neuropsychiatrist W.A. Lishman described neuropsychiatry as “an amalgam of psychiatry and neurology”³. It is often regarded as lying at the borderland of the two parent disciplines – a hybrid field, or a bridge between psychopathology and neuropathology. This formulation acknowledges both the distinctiveness of psychiatry and neurology, and the existence of clinical disorders and interventions that require expertise in both. According to this view, psychiatry and neurology each occupy their own clinical territories, with an intermediate zone comprising disorders that cannot be fully claimed by either discipline, which constitutes neuropsychiatry.

Yet, defining neuropsychiatry solely by reference to its parent disciplines has limitations, because the borderland is not fixed. It shifts as neuroscientific knowledge advances. Epilepsy and neu-

rosyphilis are historical examples of disorders that moved from psychiatry to neurology with developments in electroencephalography and microbiology, respectively; autoimmune encephalitis is a more recent example. This changing frontier illustrates both the strengths and the limitations of a purely territorial definition. The British neurologist F. Walshe's memorable quip that "neuropsychiatry is like the mule, without pride of ancestry or hope of progeny" captures something of this uneasy identity.

How, then, should neuropsychiatry be defined for our Special Interest Group? Some of the above debates will inevitably re-emerge, but the hope is that the Group will take a pragmatic course rather than becoming preoccupied with definitional dispute. This will most likely involve delineating a clinical territory, while also promoting a distinctive neuropsychiatric approach and a deliberate effort to infuse general psychiatry with neuroscience.

As neuropsychiatry enters the wider psychiatric community as a sub-discipline, one of its first tasks is to establish a "secure base" of disorders that it can legitimately call its own⁴. These should not simply be conditions with which neither psychiatry nor neurology feels comfortable. Rather, they should include disorders that require the clinical and anamnestic skills, and tolerance of ambiguity, characteristic of psychiatry, together with the empiricism and objectivity associated with neurology.

Tourette syndrome is one such example. Its management requires competence in movement disorders together with expertise in the diagnosis and treatment of attention deficit disorder, obsessive-compulsive disorder, conduct disorder, mood disorders, specific developmental disabilities, autism spectrum disorder, and sleep disorders. Treatment may involve pharmacotherapy, behavioral therapy, family therapy, genetic counselling, and rehabilitation. A purely neurological or psychiatric approach is, therefore, likely to be insufficient and may overlook the most important aspects of care.

The recognition that autoimmune encephalitis may present primarily as a psychiatric disturbance has brought another group of disorders securely into the neuropsychiatric fold⁵. This is in addition to neurocognitive disorders; psychiatric symptoms occurring in the setting of established neurological conditions such as epilepsy, brain tumors, demyelination, brain injury and neurodevelopmental disorders; neurological conditions, such as movement disorders, that arise in psychiatric patients, often secondary to psychotropic drug use; and several other disorders⁶. The neuroscientific reconceptualization of conversion and dissociative disorders has similarly brought these conditions into the neuropsychiatric domain as functional neurological symptom disorders.

Another task for our Special Interest Group is to help define the neurobiological underpinnings of psychiatric disorders more clearly. Neuropsychiatrists generally regard the increasing neurobiological grounding of psychiatry as inevitable, and have been keen to develop biomarkers that may enhance diagnostic precision. In this they share common ground with so-called biological psychiatrists. There is also scope for greater recognition of the value of neuroscientific models of mental illness, even when these do not immediately translate into specific treatment pathways.

Neuroimaging, for example, is not yet diagnostic in most psychiatric settings, but it has strengthened circuit-based models of mental disorders, and an appreciation of these models is important in clinical formulations. In some cases, such understanding may also have implications for prevention or treatment.

Cerebral small vessel disease has emerged as a contributory factor, and in some cases a driver, of several psychiatric disorders. Its recognition may help identify modifiable risk factors to potentially slow progression of those disorders. Covert cerebral small vessel disease is a highly prevalent pathology in older individuals, and our Special Interest Group could usefully help to highlight its importance and encourage guidance for its management in psychiatric patients⁷.

Our Special Interest Group plans to make neuropsychiatry more visible, not as a separate enclave, but as a way of enriching general psychiatric practice. This is important, because many psychiatrists already care for patients with cognitive, neurological, developmental and other forms of brain-based complexity, and this will only increase as neuroscience advances. The Group will therefore be involved in training not simply to expand the number of neuropsychiatrists, but also to equip general psychiatrists to engage confidently with the complexity that many of their patients present.

One important initiative is the development of an interactive International e-Handbook of Neuropsychiatry, which will be regularly updated. This is being undertaken in collaboration with the International Neuropsychiatric Association. Our Group also plans to develop a teaching and training programme, as well as to foster greater inclusion of neuropsychiatric themes within WPA conferences. The broader aim is to promote a neuropsychiatric approach to the patient in which biological, psychological and social-environmental factors all receive due attention⁸. The intention is to extend this approach to neurological and general medical patients, so that psychological and social determinants and consequences of illness can be integrated with biology in patient management.

Many recent developments in psychiatric treatment also fall squarely within the neuropsychiatric domain. Brain stimulation treatments are now established interventions for selected psychiatric patients, and the field continues to expand through the development of other stimulation techniques⁹. New drugs for neurocognitive disorders such as Alzheimer's disease have generated considerable interest. Deutetrabenazine and valbenazine have been introduced for tardive dyskinesia. More broadly, therapeutics targeting mental disorders through advances in genetics, stem cell biology and immunology hold considerable promise. Neuropsychiatry is well placed to help psychiatry navigate this increasingly complex therapeutic landscape, and our Special Interest Group has an important contribution to make.

In conclusion, at a time when psychiatry is increasingly informed by neuroscience, neuropsychiatry represents both a clinical necessity and an intellectual opportunity. By promoting education, collaboration and clinical curiosity, our Group can help ensure that neuropsychiatry becomes more visible within mainstream psychiatric practice.

Perminder S. Sachdev

Centre for Healthy Brain Ageing, School of Clinical Medicine, University of New South Wales, Sydney, NSW, Australia; Neuropsychiatric Institute, Prince of Wales Hospital, Randwick, NSW, Australia

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Update on psychoneuroimmunoendocrinology

Since its emergence as a new scientific discipline, psychoneuro-immunoendocrinology (PNIE) has fostered extensive research aimed at understanding the complex relationships between psychological processes and neurobiological mechanisms, with the ultimate goal of improving therapeutic interventions in clinical psychiatry.

The most recent advances in PNIE include a broad range of studies focused on uncovering molecular mechanisms of major relevance to psychiatric research, such as signaling cascades induced by hormones and neurotransmitters, which, in turn, modulate the transcriptional regulation of specific genes. Several of these genes are known to encode cytokines, receptors, transporters, and the brain-derived neurotrophic factor (BDNF). A large body of research has focused on BDNF as a central mediator of neuroplasticity and neurogenesis, processes that play a critical role in the mechanism of action of various antidepressants.

In addition, PNIE research has expanded toward understanding how epigenetic mechanisms contribute to transcriptional regulation. These processes contribute to determine which genes may be activated or inhibited in response to environmental stressors.

Several lines of research had focused on the associations between traumatic experiences in childhood and gene $\times$ experience $\times$ development interactions¹. More recently, PNIE focused on understanding the associations between prenatal stress and epigenetic mechanisms, such as DNA methylation, implicated in the regulation of gene expression in the fetus. DNA methylation involves the addition of a methyl group to cytosine residues. Increased methylation of promoter regions is associated with decreased gene expression, while decreased methylation is associated with activation of transcriptional events.

An important body of research has focused on candidate genes involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Among these genes are *NR3C1*, which encodes the glucocorticoid receptor (GR), and *FKBP5*, which encodes a chaperone protein involved in the regulation of GR sensitivity. The association between increased methylation of these genes and prenatal stress has been recently described².

Other important candidate genes are *SLC6A4*, which encodes the serotonin transporter (SERT), and the BDNF gene. Increased methylation of these genes has been observed in depressed patients, reflecting decreased neuroplasticity and dysregulated serotonergic signaling³.

Micro RNAs (miRNAs) are small non-coding RNA strands, which may exert regulatory effects on gene expression by binding to mRNA in the cytoplasm. Multiple miRNAs have been found to be implicated in the regulation of neuroplasticity and monoamine-related genes in mood disorders. Some of them, such as miR-206, have been shown to modulate BDNF signaling and neuroplasticity⁴. Some other miRNAs have been found to participate in the post-transcriptional regulation of the serotonergic system by targeting various molecular components, such as the SERT and serotonin receptors, thereby influencing serotonin synaptic availability⁵.

Another promising area of research has been the development of novel psychopharmacological strategies for the treatment of postpartum depression (PPD). In this regard, neurosteroids are molecules synthesized within the brain, which modulate neuronal excitability through interactions with neurotransmitter receptors, particularly the GABA-A receptor. The most relevant neurosteroid is allopregnanolone, which acts as a positive allosteric modulator of the GABA-A receptor, producing widespread neuronal inhibition and exerting an inhibitory effect on corticotropin-releasing hormone (CRH) secretion. This action restores the negative feedback of the HPA axis and reduces the hypercortisolemia observed in chronic stress and depression.

Allopregnanolone has been associated with increased expression of BDNF, promoting neuroplasticity and hippocampal neurogenesis. During pregnancy, allopregnanolone levels rise substantially, but they decline sharply after childbirth, leading to a reduction in GABAergic modulation and increased neuronal excitability, associated with the anxious and depressive symptoms characteristic of PPD.

The elucidation of these neuroendocrine mechanisms led to the development of brexanolone, a synthetic formulation of allopregnanolone approved in 2019 by the US Food and Drug Administration (FDA) for the treatment of PPD via intravenous administration⁶. More recently, this led to the development of zuranolone, another synthetic analog of allopregnanolone, which was approved in 2023 for the treatment of PPD⁷ and is currently being investigated for its potential therapeutic use in treatment-resistant depression.

Recent advances in PNIE also focused on the concept of “learned helplessness”, which has been recognized as a key factor in the origin and development of depression, providing valuable insights into the neurobiological mechanisms and psychological processes

involved. More recently, the notion of “learned controllability” has been proposed as an extension and functional counterpart to that concept. This framework has enabled a more detailed characterization of the neurobiological and psychological mechanisms underlying the ability to exert control over stress, which represents the basis of resilience.

These findings may provide important resources for the development of novel approaches for the treatment of diverse clinical conditions. The “learned controllability” framework not only refines our understanding of stress vulnerability, but also establishes an integrative bridge between psychological, neural, immune and endocrine levels, guiding the development of personalized therapeutic approaches. Our WPA Section on Psychoneuroendocrinology is contributing to this research line⁸.

The Section is actively engaged with the WPA, taking part in the scientific and academic development of the Association worldwide^{9,10}. We regularly participate in World Congresses, and organize Section Symposia every year. At the World Congress held in Mexico in 2024, we delivered a lecture on “Psychoneuroendocrinology: State of the Art and State of the Science”. At the World Congress held in Prague in 2025, we presented recent advances in suicidal prevention, based on our research with strategies based on transcranial magnetic stimulation.

During the last year, our Section grew up to 125 members, from 28 different countries. In addition to the World Congress, we presented symposia at a variety of scientific meetings, such as those of the Argentine Association of Psychiatrists in October 2024 and 2025. In addition, we organized academic activities for our members, including an online course in Spanish introducing PNIE, in cooperation with the International Foundation for the Development of Neurosciences (FIDN).

We are currently organizing our activities for the next year, in-

cluding a more comprehensive course with updates on PNIE in Spanish, in cooperation with FIDN, which will include 12 speakers from different countries, all of them members of our Section. In addition, we are organizing a comprehensive course on PNIE in English, which will include prominent speakers, all of them members of our Section.

In summary, PNIE provides an integrative framework that encompasses multiple levels of human organization, from molecular and cellular mechanisms to cognitive, emotional and behavioral processes. Its transdisciplinary perspective allows a comprehensive understanding of the dynamic interactions among the nervous, endocrine and immune systems, and their continuous dialogue with subjective experience and environmental context. Looking ahead, PNIE holds the potential to guide the development of innovative diagnostic and therapeutic strategies that integrate biological and psychological dimensions in clinical psychiatry. Our Section is actively contributing to these advances.

Gustavo E. Tafet¹, Charles B. Nemeroff²

¹Department of Psychiatry, Texas A&M University, College Station, TX, USA; ²Department of Psychiatry, University of Texas at Austin, Austin, TX, USA

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