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World Psychiatry

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What is global mental health?

Looking back at 2020, historians will acknowledge the inescapable reality of global interconnectedness. Every country will have witnessed the health, social and emotional effects of the COVID-19 pandemic. For others, the outpouring of pent up anger, sadness and frustration due to generations of social inequities, exclusion, racism and discrimination – apparent both in the disparities in mortality revealed by COVID-19 and the persistent acts of structural and physical violence (highlighted among people of African descent in the US) – will be most vivid in retrospect. That these events have an emotional impact or more enduring effects on mental health will not be disputed. The appropriate responses to them – social, clinical, political, or some combination – can be debated. Such questions are ideally suited for the field of global mental health.

Global mental health is an evolving field of research and practice that aims to alleviate mental suffering through the prevention, care and treatment of mental and substance use disorders, and to promote and sustain the mental health of individuals and communities around the world[1]. It prioritizes equity, and is informed by many disciplines, including neuroscience, genomics, social sciences (especially psychology, medical anthropology and sociology), epidemiology, health services research, and implementation science. Advocacy plays a central role in the dissemination and translation of evidence into actionable policies and plans for communities, health systems and policy-makers to implement.

Global mental health activities are wide-ranging and intend to integrate a "reframed" mental health agenda into the 2030 Agenda for Sustainable Development[2]. This reframed agenda rests on four foundational pillars. The starting point is to recognize mental health as a global public good that requires action and intervention beyond the health sector. The second is adopting a dimensional approach that conceptualizes mental health as a continuum from wellness to illness, allowing equal emphasis on the prevention and treatment of mental disorders alongside the promotion and maintenance of mental health. The third pillar underscores the convergence of sociocultural experience and environmental context, genetics, neurodevelopment and psychology on brain biology to produce subjective experiences of mental health or distress. Consequently, our understanding of mental health and our ability to intervene lie at the intersection of multiple sources of knowledge. The fourth makes human rights a central tenet of global mental health action, and emphasizes the critical role that people with lived experience of mental health conditions must play in shaping prevention, care and research.

To achieve the aims of global mental health, several actions are proposed for policy-makers, funders, health system managers, advocates, and communities. Among these are the use of policies to address upstream social determinants of mental health; the scaling of mental health services and the integration of mental health into other global health priorities, from HIV/AIDS to non-communicable disease care; targeting sensitive periods of development by investing in the mental health and well-being of young people; the application of innovative approaches to extend mental health care; and the call for more financial investment in the sustained implementation of preventive measures and treatment interventions as well as in research across the relevant disciplines.

Research funding of the past decade shaped many of the current dominant themes in the field, such as task-sharing to extend human resources for mental health, and integrating mental health into global health priorities via community-based platforms both in and outside of the health care sector. The Grand Challenges in Global Mental Health, a research priority-setting exercise, distilled the insights of more than 400 participants from 60 countries around the world and specified the need for science along the translational continuum from discovery to policy research[3]. The most frequently espoused of the 40 challenges calls for primary prevention of mental disorders. Others speak to the need to enable family and community environments that support mental health, understand adaptive and resilient responses to daily life stressors, and establish cross-national evidence on factors underlying mental health disparities – all of which are relevant to the urgencies of 2020.

The authors of the Grand Challenges emphasized its global relevance, distinct from a focus on low- and middle-income countries, acknowledging the challenges that high-income countries also face when it comes to addressing mental health. Global health (and global mental health) attempts to recognize and change the power dynamics inherent in international relationships founded on colonial legacies and contemporary economic relationships. It identifies as "global" anything that concerns multiple countries, including shared determinants of health, and communicates the value of shared learning across countries and economies. "The global in global health refers to the scope of the problems, not their location"[4].

In the context of global mental health, shared determinants of health include poor investment in mental health care, inadequate attention to prevention as well as treatment of mental disorders, insufficient human resources, and consequently, limited access and quality of care. Equally important are transnational upstream determinants of mental health such as racial and other forms of discrimination, gender inequality, poverty, unplanned rapid urbanization, global economic downturns, forced migration, and complex humanitarian emergencies due to natural disasters and conflicts. Deficits in quality education, investment in early child development, safe and affordable housing, though local in their manifestations, are prevalent in many countries and ultimately affect mental health and well-being.

Global mental health recognizes a vastly interconnected world and values nurturing that interconnectedness for solving difficult problems through a diversity of perspectives. It operates on the supposition that suffering and well-being are shared

aspects of our humanity and, although distinct social, political, historical and economic drivers shape daily experience, there is promise in collective action.

Without deliberate steps toward mental health equity through multiple routes, the global mental health project falters. One route to global mental health equity is through quality mental health research. The increased investment in mental health research in low- and middle-income countries has led to an expanded evidence base on effective interventions now being implemented in diverse sociocultural settings. Greater resources for research and research capacity-building provide opportunities for more diverse ethnic and cultural populations to contribute to the evidence base, to shape research questions and the approaches to answering them, thereby increasing the likelihood that research outcomes will be of relevance to all of us.

Global diversity in mental health research participants will also permit more progress in the search for etiologies of mental illness. Our understanding of the genetic architecture of schizophrenia and bipolar disorder relies largely on Northern European data[5]. Funding flows, partnerships, and opportunities to engage new populations and pursue locally relevant research are far from equitable and this must remain a goal of global mental health.

Equity in improving population mental health outcomes will require a commitment to designing interventions to tackle social problems that limit the effectiveness of care oriented to the individual[6]. Community leadership and empowerment, alongside engagement of service users to help transform service delivery, could be hallmarks of these interventions.

Equity in the production and dissemination of global mental health knowledge requires prioritization of local cultural perspectives. Leveraging global relationships need not negate local experience. Rather, one strategy of the global mental health community should be to make known the innovation and ideas that come from communities which seldom find a global audience. In a recent initiative on suicide prevention among Arctic Indigenous people, a method was developed to build consensus across a diverse group of international stakeholders[7]. Some members of the team called for a parallel process that would use culturally acceptable methods to relay the particular experiences of specific Indigenous communities. The group applied both methods and integrated the findings in the final report[7].

Even widely experienced processes, such as deinstitutionalization, provide context-specific lessons about leveraging political opportunities into gains for mental health[8]. In many settings, deinstitutionalization and innovations in community mental health coincided with the establishment of post-colonial governments, the end of military dictatorship, or the entry of democracy. For example, the expansion of community mental health services in Jamaica after its independence developed in alignment with local cultural values, distinct from the colonial era[8]. These creative approaches to mental health care are valued, though not always widely disseminated.

Nevertheless, the influence of innovative approaches to mental health from settings with scarce resources pervades global mental health. Integrating peers, lay health workers, primary care providers, as well as technology, into mental health care adds flexibility to mental health service delivery, breaks down traditional hierarchies, and makes care more accessible[9]. Diverse ethnic and cultural groups in high-income countries that face challenges in access to and engagement in care can make use of such varied approaches.

It is possible that the global reach of the social, emotional and economic shocks of 2020 will thrust communities around the world into innovation that benefits mental health. If so, the movements, resources and networks that represent people and projects engaged in global mental health may become increasingly widely accessible. The field offers a transnational community for diverse stakeholders with distinct perspectives who value its aims.

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Optimizing personalized management of depression: the importance of real-world contexts and the need for a new convergence paradigm in mental health

In this issue of the journal, Maj et al[1] have revisited a fundamental tenet of psychiatric medicine, namely, that more precise clinical characterization of patients with depression will enhance the provision of personalized management – and the likelihood of optimal outcomes. The authors have conducted a comprehensive and balanced review of relevant domains, including clinical symptoms, severity of illness, depression subtypes, functional status, staging of illness, neurocognition, medical and psychiatric comorbidities, early life adversity, personality dysfunction, and environmental stressors. They have highlighted the importance of measurement-based assessment and care via the use of instruments both psychometrically sound and amenable to im-

plementation in practice.

Although not aiming to deal specifically with biomarkers, the authors suggest that progress in the identification and clinical use of biomarkers will be facilitated through multidimensional clinical assessment. It is indeed plausible that biomarkers will be found to correlate more closely with dimensions of psychopathology than with categorical diagnostic measures, which often hide important treatment-relevant aspects of illness. As such, biomarkers may become more useful as predictors, modifiers and mediators of response variability.

An analogy with diabetes mellitus seems appropriate: finding an abnormal blood glucose (like a positive screen for depression) mandates a clinical workup across a number of dimensions to inform appropriate clinical management, aided by the use of laboratory tests that facilitate monitoring of progress in response to treatment and in prevention of adverse sequelae.

Viewed from the perspective of someone living with depression, an optimal outcome entails both restoration of a sense of well-being and re-engagement in major social, vocational and family roles. As Maj et al note, these are among the outcomes that matter most to patients. Although reduction in symptom burden is clearly important (because residual symptoms indicate increased risk for a relapsing and chronic course), patients and their family carers hope for the return of pleasure and meaning in life, resumption of major roles, and mitigation of carer burden and its attendant demoralization.

Answering the question "How well is well?" depends, therefore, upon taking both a patient-focused and family-centered approach. Depression does not occur monadically, but more often within a family context. Nor does it occur apart from myriad social, cultural and medical issues. Optimal care involves aiming at more than relief of anguish in the pursuit of personalized management.

To say that depression does not occur "in pure culture" is thus to highlight several real-world contexts in which the more precise clinical characterization of depressed patients needs to occur. Relevant contexts for optimizing depression assessment and management include, among others, sociocultural, medical, and systems-based care-delivery issues. These contexts may be understood as a way of further grounding multidimensional clinical characterization *in vivo*.

With respect to sociocultural context, for example, persons from different racial and ethnic groups vary in their understanding of what depression is, what constitutes acceptable treatment, and even whether treatment is needed at all. For some, "depression" is both stigmatized and stigmatizing. Furthermore, engaging persons living in low-resource settings, very different from high-income countries, may be quite challenging, particularly if family members do not "buy in" to the need for treatment. Using like-ethnic community health workers, as members of a treatment team, can be useful for gaining trust and for promoting engagement in treatment, treatment adherence, and access to community resources needed by impoverished or disadvantaged depressed adults in their journey to full recovery.

Optimizing treatment outcomes, the goal of precise clinical characterization, begs the question of how best to close the world's treatment gap for depression[2]. The treatment gap arises especially from the dearth of mental-health specialty expertise in low- and middle-income countries (as well as in rural areas of high-income countries), where social determinants of ill-health, including depression, may be particularly powerful. Work-force issues further underscore the importance of early interventions to pre-empt or prevent depression in vulnerable people, as Maj et al emphasize in their discussion of staging. The implied analogy to cancer is especially compelling since, as with cancer, early preventive intervention may be curative or at least mitigate down-stream complications. In the case of depression, it may mitigate emergence of treatment resistance, chronicity, and adverse outcomes such as suicide and dementia.

How to leverage mental health expertise broadly in the service of personalized prevention and treatment, therefore, becomes the central question. The use of task-shifting strategies in order to share tasks with primary medical personnel and with community health workers has increasingly found a place in team-based systems of depression prevention and treatment (see, for example, Dias et al[3]). Sometimes called "coordinated" care, such models facilitate improvements in evidence-based assessment and guideline-based delivery of care, informed by mental health specialists in the "hub" of the system.

Models of coordinated and integrated behavioral and medical services, including the use of telemedicine and telepsychiatry, have enabled greater reach than is possible with traditional office-based treatment for depression and for reduction of suicidal behaviors. Shifts in reimbursement for telepsychiatry, where the psychiatrist does not actually have to see the patient face-to-face, is facilitating this change in practice – made even more important by the COVID-19 pandemic and its progeny of depression, anxiety, and prolonged grief disorder.

Maj et al underscore how the heterogeneity of depression (in pathogenesis, clinical presentation, and response variability) often gives rise to difficult-to-treat illness (and hence the need for multidimensional evaluation to understand the origins of treatment resistance). A particularly important aspect of optimizing depression treatment is the need for guidelines that can inform shared decision-making with respect to augmenting, switching or combining treatment modalities to help people with difficult-to-treat or even treatment-resistant depression.

In this context, since the goal of treatment is not only to avoid adverse effects and to get well, but also to stay well, understanding the long-term efficacy, effectiveness and tolerability of different strategies needs further attention. Different patient characteristics, such as neurocognitive function, the presence of suicidal ideation, and varying degrees of medical and/or psychiatric comorbidity will likely moderate, or influence, the strength of response to acute treatment and the durability of response and recovery in maintenance treatment. Personalizing management of depression depends upon identification of such variables, or moderators, as distinct from more general prognostic indicators. One can anticipate that biomarkers will be identified as response modifiers in depression treatment, as has been the case in oncology.

In conclusion, multidimensional assessment, as reviewed by Maj et al, is clearly important for personalizing the care of persons at risk for, or already living with, depression. Optimizing short- and long-term outcomes through multidimensional, patient-centered clinical assessment seems more likely when carried out within the broader sociocultural, medical, and care-delivery contexts in which depression occurs in the real world. Needed now, I would suggest, is a new transdisciplinary, convergence paradigm to inform both research and practice in mental health[4].

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The clinical characterization of the adult patient with depression aimed at personalization of management

Mario Maj[1], Dan J. Stein[2], Gordon Parker[3], Mark Zimmerman[4], Giovanni A. Fava[5], Marc De Hert[6,7], Koen Demyttenaere[8], Roger S. McIntyre[9], Thomas Widiger[10], Hans-Ulrich Wittchen[11,12]

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Depression is widely acknowledged to be a heterogeneous entity, and the need to further characterize the individual patient who has received this diagnosis in order to personalize the management plan has been repeatedly emphasized. However, the research evidence that should guide this personalization is at present fragmentary, and the selection of treatment is usually based on the clinician's and/or the patient's preference and on safety issues, in a trial-and-error fashion, paying little attention to the particular features of the specific case. This may be one of the reasons why the majority of patients with a diagnosis of depression do not achieve remission with the first treatment they receive. The predominant pessimism about the actual feasibility of the personalization of treatment of depression in routine clinical practice has recently been tempered by some secondary analyses of databases from clinical trials, using approaches such as individual patient data meta-analysis and machine learning, which indicate that some variables may indeed contribute to the identification of patients who are likely to respond differently to various antidepressant drugs or to antidepressant medication vs. specific psychotherapies. The need to develop decision support tools guiding the personalization of treatment of depression has been recently reaffirmed, and the point made that these tools should be developed through large observational studies using a comprehensive battery of self-report and clinical measures. The present paper aims to describe systematically the salient domains that should be considered in this effort to personalize depression treatment. For each domain, the available research evidence is summarized, and the relevant assessment instruments are reviewed, with special attention to their suitability for use in routine clinical practice, also in view of their possible inclusion in the above-mentioned comprehensive battery of measures. The main unmet needs that research should address in this area are emphasized. Where the available evidence allows providing the clinician with specific advice that can already be used today to make the management of depression more personalized, this advice is highlighted. Indeed, some sections of the paper, such as those on neurocognition and on physical comorbidities, indicate that the modern management of depression is becoming increasingly complex, with several components other than simply the choice of an antidepressant and/or a psychotherapy, some of which can already be reliably personalized.

Key words: Depression, personalization of treatment, symptom profile, clinical subtypes, severity, neurocognition, functioning, quality of life, clinical staging, personality traits, psychiatric antecedents, psychiatric comorbidities, physical comorbidities, family history, early environmental exposures, recent environmental exposures, protective factors, dysfunctional cognitive schemas

(World Psychiatry 2020;19:269–293)

Depression is the syndrome most frequently diagnosed in psychiatric practice. There is a wide acknowledgement that this syndrome is not a homogeneous entity, and that a further clinical characterization of the individual patient would be needed in order to personalize the management plan[1,2]. However, it is common practice to base the choice of treatment in each case solely on the syndromal diagnosis. Clinical trials have found a variety of medications and psychotherapies to be "equivalent" in the treatment of the syndrome, and these interventions are therefore commonly perceived as interchangeable.

The choice of treatment for depression is at present usually based on the clinician's and/or the patient's preference and on safety issues, in a trial-and-error fashion, paying little attention to the individual features of the specific case. This may be one of the reasons why the majority of patients with a diagnosis of depression do not achieve remission after the first treatment they receive[3], and at least 30% do not respond to two consecutive evidence-based treatments and may be classified as treatment-resistant[4].

Treatment guidelines do not help in this respect. They tend to emphasize the severity of the depressive episode as the main or only element on which to base the choice of treatment[5,6], but this emphasis is undermined in clinical practice by the lack of a reliable and widely accepted way to evaluate that severity. In fact, the definitions of the various degrees of severity of a depressive episode provided by the DSM-5[7] and ICD-11[8] (arguably, somewhat generic, without clear anchor points, not evidence based, and with poor interrater reliability) are often ignored by clinicians. Furthermore, the most recent research evidence does not seem to support the idea that response to antidepressant medications or psychotherapies depends upon the severity of the depressive syndrome[9,10].

A variety of clinical and biological predictors of response or non-response to antidepressant medication in general, or to specific antidepressants or psychotherapies, have been proposed over the decades, but the relevant evidence is fragmentary and sometimes inconsistent. So, the personalization of treatment of depression is on the one hand commonly considered essential, but on the other often perceived as unfeasible in current clinical practice.

This pessimism has recently been tempered by some secondary analyses of databases from clinical trials, using approaches

such as individual patient data meta-analysis and machine learning, which indicate that there may indeed be different symptom profiles associated with the response to different antidepressant drugs, and to antidepressant medications as opposed to specific psychotherapies[11,12]. Studies using machine learning are also suggesting that other, non-symptom variables may contribute to the identification of patients who are likely to respond to a given antidepressant drug[13,14] . The need to develop decision support tools guiding the personalization of depression management has been emphasized[15], and the point made that these tools should be developed through large observational studies using a comprehensive battery of inexpensive self-report and clinical measures.

The present paper aims to describe systematically the salient domains that should be considered in this effort to personalize the treatment of depression (Table 1). For each of these domains, the available research evidence is briefly reviewed, and the relevant assessment instruments are considered, with special attention to their suitability for use in routine clinical practice, also in view of their possible inclusion in the above-mentioned comprehensive battery of measures. The main unmet needs that research should address in this area are emphasized. Where the available evidence allows providing the clinician with specific advice that can already be used today to make the management plan for an individual patient with depression more personalized, this advice is highlighted.

We acknowledge that a significant effort is ongoing to identify biological markers that may help in the selection of treatment for depression. However, since none of these markers is currently ready for use in routine clinical practice, we do not consider them in this paper. On the other hand, we believe that biological research can benefit from a systematic clinical characterization of patients with a diagnosis of depression, since this is likely to facilitate the identification of more homogeneous subtypes of the syndrome.

Table 1 Salient domains to be considered in the clinical characterization of a patient with a diagnosis of depression

1. Symptom profile
2. Clinical subtypes
3. Severity
4. Neurocognition
5. Functioning and quality of life
6. Clinical staging
7. Personality traits
8. Antecedent and concomitant psychiatric conditions
9. Physical comorbidities
10. Family history
11. Early environmental exposures
12. Recent environmental exposures
13. Protective factors / Resilience
14. Dysfunctional cognitive schemas

This paper focuses on adult syndromal depression not secondary to another medical condition and not induced by a substance or a medication. We do not address issues relevant to subthreshold depressions or to syndromal depression in children, adolescents or the elderly. Gender- and culture-related issues are considered in some sections of the paper, when relevant, rather than being addressed in specific sections. Perinatal depression is covered elsewhere in this issue of the journal[16].

SYMPTOM PROFILE

The symptoms listed in the DSM-5 and ICD-11 for the diagnosis of depression are almost identical[7,8]. Nine symptoms (depressed mood; markedly diminished interest or pleasure in activities; reduced ability to think or concentrate, or indecisiveness; feelings of worthlessness, or excessive or inappropriate guilt; recurrent thoughts of death, or suicidal ideation, or suicide attempts or plans; insomnia or hypersomnia; significant change in appetite or weight; psychomotor agitation or retardation; and fatigue or loss of energy) are shared by the two systems, while one (hopelessness about the future) appears only in the ICD-11 list. In both systems, the presence of at least five of these symptoms is required most of the day, nearly every day, for at least two weeks, and the occurrence of either depressed mood or diminished interest or pleasure is mandatory.

There is some empirical evidence supporting the validity of these lists of symptoms. In fact, in a logistic regression analysis[17], all nine symptoms listed in the DSM-5 were found to be significant independent predictors of the diagnosis of depression, with the first two symptoms on the list having the highest positive predictive values. In a further analysis[18], hopelessness about the future, the only ICD-11 symptom not included in the DSM-5, outperformed about half of the DSM-5 symptoms in differentiating depressed from non-depressed subjects. One additional symptom, diminished drive, performed more strongly than almost all of the DSM-5 symptoms. Further items – such as lack of reactivity of mood (i.e., the individual's mood fails to brighten even temporarily in response to positive stimuli), anger, irritability, psychic anxiety, and somatic concomitants of anxiety (e.g., headaches, muscle tension) – also discriminated significantly between depressed and non-depressed subjects[18].

Indeed, a study carried out by using a network approach[19] has reported that the core symptoms of depression include "sympathetic arousal" (i.e., palpitations, tremors, sweating) and anxiety, in addition to energy loss, sadness, interest loss, pleasure loss, concentration problems, appetite problems and insomnia. Furthermore, a systematic review of qualitative studies of depression carried out worldwide[20] has found that some somatic items (i.e., general aches and pains, headaches, and "issues with the heart" such as heavy heart, heart pain and palpitations) are among the symptoms most frequently reported worldwide by depressed patients, albeit being somewhat more frequent in non-Western populations.

Overall, although the lists of depressive symptoms provided

by current diagnostic systems are supported by some empirical research, there is also some evidence that further components of the depressive syndrome are not included in those lists. Among these components, anxiety and somatic complaints are particularly prominent.

Not surprisingly, the symptoms included in the most frequently used rating scales for depression – the Hamilton Rating Scale for Depression (HAM-D)[21], the Montgomery-Åsberg Depression Rating Scale (MADRS)[22], the Beck Depression Inventory (BDI)[23], the Center for Epidemiological Studies - Depression (CES-D)[24], the Quick Inventory of Depressive Symptoms (QIDS)[25], the Inventory of Depressive Symptoms (IDS)[26], and the Zung Self-Rating Depression Scale (SDS)[27] – exceed in number those included in the DSM-5 and ICD-11 definitions[28] (see Table 2).

There are studies suggesting that the frequency of some depressive symptoms may be different in relationship to gender, with anger attacks, aggression, irritability and risk taking behaviors being more frequent in males than in females[29]. A self-report rating scale aimed to assess depression in males, the Masculine Depression Scale (MDS)[30], has indeed been developed.

Contrary to primary psychosis, in the case of depression there is no clustering of symptoms into psychopathological dimensions that is largely agreed upon by the research and clinical communities. The ICD-11 subdivides the listed depressive symptoms into three clusters (affective, cognitive-behavioral and neurovegetative), but provides no empirical support for this clustering, which is just aimed at facilitating the recollection of symptoms by clinicians[31]. However, there have been several attempts to propose and validate clusters of depressive symptoms that may be clinically useful.

Uher et al[32] proposed a model comprising three dimensions based on factor analysis: observed mood (including depressed mood and anxiety), cognitive (including pessimism and reduced interest-activity) and neurovegetative (comprising problems with sleep and appetite). Another exploratory factor analysis[33] reported a general depressive symptom factor, and four further factors reflecting vegetative symptoms, cognitive symptoms (hopelessness/suicidal ideation), weight/appetite symptoms, and symptoms of agitation and anxiety. A more recent analysis[11] reported three clusters: core emotional symptoms, sleep symptoms, and "atypical" symptoms (including psychomotor agitation, psychomotor slowing, suicidal ideation, hypochondriasis and reduced libido).

Attempts have been made to relate either individual depressive symptoms or clusters of symptoms to a preferential response to various antidepressant drugs or to antidepressant medication vs. specific psychotherapies.

Antidepressant medication in general has been found to be more effective in treating core emotional and sleep symptoms than "atypical" symptoms as defined above[11], with high-dose duloxetine being superior to escitalopram in treating both emotional and "atypical" symptoms[11]. A score of at least 7 on the HAM-D anxiety/somatization factor has been associated with a worse response to antidepressant medication in general[34], but venlafaxine has been found to be superior to fluoxetine in depressed patients with a HAM-D psychic anxiety score of at least 2[35]. An interest-activity symptom cluster including low interest, reduced activity, indecisiveness and lack of enjoyment has been associated with a decreased response to antidepressant medication, with no significant difference between response to citalopram and nortriptyline[36].

Observed mood and cognitive symptoms have been found to

Table 2 Main components of the depressive syndrome and their coverage in diagnostic systems and rating scales

	ICD-11	DSM-5	HAM-D	MADRS	BDI	SDQ	QIDS	CES-D
1. Depressed mood	+	+	+	+	+	+	+	+
2. Diminished interest or pleasure in activities	+	+	+	+	+	+	+	+
3. Reduced ability to think or concentrate, or indecisiveness	+	+	+	+	+	+	+	+
4. Feelings of worthlessness or guilt	+	+	+	+	+	+	+	+
5. Suicidal ideation, attempts or plans	+	+	+	+	+	+	+	+
6. Insomnia or hypersomnia	+	+	+	+	+	+	+	+
7. Change in appetite or weight	+	+	+	+	+	+	+	+
8. Psychomotor agitation or retardation	+	+	+	+	+	+	+	+
9. Fatigue or loss of energy	+	+	+	+	+	+	+	+
10. Hopelessness about the future	+	–	+	+	+	+	+	+
11. Anxiety	–	–	+	+	–	+	–	+
12. Irritability	–	–	+	–	+	+	–	–
13. Somatic complaints	–	–	+	–	+	+	–	–
14. Anger	–	–	–	–	–	+	–	–
15. Lack of mood reactivity	–	–	–	–	–	+	–	+

HAM-D – Hamilton Rating Scale for Depression, MADRS – Montgomery-Åsberg Depression Rating Scale, BDI – Beck Depression Inventory, SDQ – Symptoms of Depression Questionnaire, QIDS – Quick Inventory of Depressive Symptoms, CES-D – Center for Epidemiological Studies - Depression

improve more with escitalopram than with nortriptyline, while neurovegetative symptoms showed the opposite pattern[37]. Trazodone, mirtazapine and agomelatine have been reported to be particularly effective on subjective and objective measures of sleep[38]. Five HAM-D items (depressed mood, feelings of guilt, suicidal thoughts, psychic anxiety, and general somatic symptoms) have been found in an individual patient data meta-analysis to show larger improvements with antidepressant medication compared to cognitive behavioral psychotherapy[12].

Overall, some evidence seems to support the notion that the symptom profile, beyond the diagnosis of depression, may have value in predicting the response to specific antidepressants or to antidepressant medication vs. specific psychotherapies. However, this evidence is at present preliminary. Individual clinical trials have usually focused on the equivalence rather than the differences between the various treatments, and secondary analyses of databases using innovative techniques[11,12] are just starting to emerge.

Most research evidence to date has been collected using the HAM-D, but the suitability of this rating scale (originally developed to evaluate hospitalized severely depressed patients) for populations of outpatients has been questioned[32]. There is a need for a tool covering the whole range of depressive symptoms, beyond the lists provided by current diagnostic systems, and probing the presence of these symptoms using multiple questions. The identification of meaningful clusters of symptoms, once again beyond the DSM-5 and ICD-11 lists, should be encouraged. The exploration of the relationships of individual symptoms or validated clusters of symptoms to the response to different treatments for depression should be identified as a research priority, requiring large patient samples (i.e., pooling results from different studies using the same assessment instruments) and innovative approaches to data analysis[15,39,40].

Self-administered questionnaires may be more suitable than the HAM-D for use in routine clinical practice and for inclusion in decision support tools. A good example is the Symptoms of Depression Questionnaire (SDQ)[41], a 44-item validated instrument that covers anxiety, several somatic symptoms, anger attacks, irritability, and lack of reactivity of mood, in addition to the depressive symptoms listed in the DSM-5 and ICD-11. Factor analysis has led to the identification of five subscales of this tool: the first including low mood, lassitude and cognitive impairment; the second anxiety, agitation, irritability and anger; the third suicide-related items; the fourth sleep problems; and the fifth changes in appetite and weight[41].

The assessment of suicidality is an integral part of the evaluation of a patient with a diagnosis of depression, both in research and in clinical settings. A meta-analysis of 57 studies of more than 23,000 patients with depression found a lifetime rate of suicide attempt of 31%[42]. Suicidal ideation and suicide attempts are among the strongest predictors of completed suicide[43], although the positive predictive value of any risk factor or risk algorithm is not high. For the assessment of suicide risk, the Columbia-Suicide Severity Rating Scale (C-SSRS)[44] is a validated tool requiring specific training. The 7-item Concise Health Risk Tracking Self-Report (CHRT-SR)[45] is an alternative possibly more suitable for use in routine clinical practice.

All patients presenting with depression should be screened for bipolar disorder. There are two screening self-report instruments – the Mood Disorders Questionnaire (MDQ)[46] and the Mood Swings Questionnaire (MSQ)[47] – with high and comparable discriminatory capacity, that can be considered for use in clinical practice.

CLINICAL SUBTYPES

The existence of clinical subtypes of depression has been proposed and discussed for many decades. Clinicians have long endorsed the notion that there are two core subtypes: the melancholic/endogenous/vital/autonomous vs. the non-melancholic/reactive/neurotic/situational. The traditional view has been that the former depressions arise from biological perturbations, while the latter are linked to situational factors, often in the context of personality pathology. Although this view has been mostly dismissed in the post-DSM-III era, the melancholic subtype of depression has been retained by diagnostic systems.

Various definitions of melancholia have been put forward over the years[48]. Some have been based solely on the presence of particular symptoms, such as pervasive anhedonia and psychomotor slowing. Others have focused on a combination of the presence of characteristic symptoms and the absence of features thought to characterize neurotic depression, such as precipitating events and personality disorders. No definition has emerged as more reliable or valid than the others.

The DSM-5[7] defines the specifier "with melancholic features" by the presence of either loss of pleasure in all or almost all activities, or lack of reactivity to usually pleasurable stimuli, plus at least three of the following: a distinct quality of depressed mood (characterized by profound despondency, despair and/or moroseness, or by empty mood), worsening of depression in the morning, early-morning awakening, marked psychomotor agitation or retardation, significant anorexia or weight loss, and excessive or inappropriate guilt. The ICD-11 definition[8] is similar, but distinct quality of depressed mood and excessive or inappropriate guilt are not included.

The distinction between melancholic and non-melancholic depression can be assisted by the clinician-rated Sydney Melancholia Prototype Index, which has positive and negative predictive values of 0.90 and 0.88, respectively[49]. The current approach of the DSM-5 and ICD-11 to consider melancholia as a specifier to the diagnosis of depression rather than a distinct disease entity seems to be supported by the observation that, in several patients with recurrent depression, some episodes are melancholic and some others are not[50].

The evidence on the treatment validity of melancholic subtyping of depression is not robust. This subtyping has been better in predicting non-response to placebo than response to active medication[51]. Early research suggested that patients with melancholia respond less well to psychotherapy[52]. Some more recent

research, however, has failed to demonstrate that melancholic subtyping predicts or moderates the response to cognitive behavioral psychotherapy[53]. Some studies have suggested that patients with melancholia respond better to tricyclic antidepressants than to selective serotonin reuptake inhibitors (SSRIs) and are particularly responsive to electroconvulsive therapy[54,55], but the former differential response has not been consistently confirmed[56].

Among treatment guidelines, only those of the Royal Australian and New Zealand College of Psychiatrists[57] and the American Psychiatric Association[6] make qualified suggestions that biological interventions may be superior for melancholia. Overall, there is a clear disconnect between the rich history of descriptions of this subtype of depression and the modern-day empirical treatment literature based on official diagnostic criteria. Addressing this disconnect represents a clear unmet need of significant clinical relevance.

A second widely accepted subtype is psychotic depression, defined by the presence of delusions or hallucinations during the depressive episode, and the lack of persistence of psychotic symptoms outside of the period of depression. In patients with recurrent episodes of depression, the psychotic features tend to recur, but there are several patients with recurrent depression in which some episodes are psychotic and some others are not[58], again supporting the DSM-5 and ICD-11 approach of regarding psychotic features as a specifier to the diagnosis of depression rather than considering psychotic depression as a distinct disease entity.

Psychotic features in depressed patients are associated with increased suicidality, particularly during the acute episode, increased mortality from physical causes, and a poorer outcome[58]. A Cochrane Library review concluded that combination treatment with an antidepressant and an antipsychotic is superior to monotherapy with either agent alone or placebo in psychotic depression[59], and this is currently a widely shared notion.

Because of these treatment implications, it is important for clinicians to recognize psychotic symptoms in depressed patients. In research settings, these symptoms are assessed with semi-structured interviews such as the Structured Clinical Interview for DSM-5 (SCID-5)[60]. The psychosis subscale of the self-report Psychiatric Diagnostic Screening Questionnaire (PDSQ)[61] may be a reasonable alternative in clinical contexts. As emphasized in the ICD-11[8], the boundary between psychotic symptoms and persistent depressive ruminations or sustained preoccupations is not always clear.

A further subtype of depression, introduced for the first time in the DSM-5 but not included in the ICD-11, is mixed depression. This subtype has been defined in varying ways in the literature[62]. The DSM-5 requires the presence of at least three manic/hypomanic symptoms out of a list of seven (elevated, expansive mood; inflated self-esteem or grandiosity; more talkative than usual or pressure to keep talking; flight of ideas or racing thoughts; increase in energy or goal-directed activity; increased involvement in risky activities; and decreased need for sleep). This definition has been criticized because it does not include features that have been considered as typical of mixed depression, such as psychomotor agitation, irritability and distractibility[63].

The presence of manic/hypomanic symptoms during a depressive episode is associated with a higher rate of anxiety and substance use disorders, increased suicidality, greater impairment in functioning, more frequent family history of bipolar disorder, and poorer response to treatment[62]. It has been suggested that patients with mixed features who are treated with antidepressants should be monitored closely because they are at greater risk for emergence of activation, hypomania and suicidality[64]. An expert panel of mood disorder researchers, while acknowledging the limited number of prospectively designed trials for depression with mixed features, recommended atypical antipsychotic medication as the first-line treatment[65].

The most commonly used clinician-administered measure to evaluate manic/hypomanic symptoms in depressed patients is the Young Mania Rating Scale (YMRS)[66]. A self-report questionnaire, the CUDOS-M[67], has been specifically designed to assess the DSM-5 mixed features specifier to the diagnosis of depression.

The subtype of anxious depression has been introduced in the DSM-5 through the specifier "with anxious distress", and is also present in the ICD-11 ("with prominent anxiety symptoms"). The DSM-5 specifier requires the presence of at least two out of a list of five symptoms (feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry, fear that something awful may happen, feeling that the individual might lose control of himself).

Patients with anxious depression are characterized by higher levels of suicidal ideation, poorer functioning, poorer health-related quality of life, and greater chronicity[68]. Co-occurring anxiety has been reported to be a predictor of a poor response to antidepressant treatment in general[33] or to specific antidepressants[69], but these findings do not necessarily apply to anxious depression as defined in the DSM-5 and ICD-11, because alternative definitions of this depression subtype show only modest levels of concordance[70]. A self-report questionnaire, the CUDOS-A[71], has been specifically designed to assess the DSM-5 anxious distress specifier.

The concept of atypical depression gained prominence in the 1980s, when a group at Columbia University offered specific criteria focused on mood reactivity, sensitivity to rejection, extreme anergia, and the reverse vegetative features of increased appetite and increased sleep[72]. In controlled treatment trials, they found that patients meeting this subtype responded better to monoamine oxidase inhibitors (MAOIs) than to tricyclic antidepressants[72]. Based on their research, the atypical depression subtype of depression entered the DSM-IV and was retained in the DSM-5.

However, MAOIs are no longer widely used, and evidence that patients with atypical depression respond better to MAOIs than to the newer generation medications has been lacking[73]. Moreover, a recent meta-analysis found that atypical depression did not predict or moderate the response to either cognitive behavioral therapy or antidepressant medication[53]. Indeed, this specifier is not included in the ICD-11.

The subtype of seasonal depression is based on the lifetime pattern of depressive episodes. The most common pattern is

autumn/winter onset, with spring/summer resolution. Characteristic symptoms of winter depression are hypersomnia, hyperphagia, and carbohydrate craving[7]. Consistent with the hypothesis that seasonal depression is the result of a reduction in daylight hours, some epidemiological studies have found that prevalence rates are increased in Northern latitudes, though the results have been mixed[74].

Bright light therapy is an effective treatment for symptomatic seasonal depression[75]. The recurrent pattern of this subtype of depression provides a unique opportunity to examine preventive strategies. Three Cochrane Library reviews concluded that bupropion XL is effective in preventing seasonal recurrence, while the evidence is insufficient to recommend either psychotherapy or light therapy as preventive interventions[76-78]. The most frequently used screening scale for seasonal depression, the Seasonal Pattern Assessment Questionnaire[79], has been criticized for being overly inclusive. The Seasonal Health Questionnaire appears to be a more valid screening tool[80].

Overall, treatment guidelines do not identify, or are equivocal in recommending, preferred first-line treatments for most subtypes of depression, though there are some important exceptions. The American Psychiatric Association[6], the Royal Australian and New Zealand College of Psychiatrists[57], and the Canadian Network for Mood and Anxiety Treatments (CANMAT)[38] all recommend combined antidepressant and antipsychotic medication or electroconvulsive therapy as first-line treatments for psychotic depression. The UK National Institute for Health and Care Excellence (NICE) guidelines[5] explicitly state that clinicians should not vary treatment strategies by depressive subtype, though elsewhere they specify that augmentation with an antipsychotic should be considered in patients with psychotic symptoms. The Australian and New Zealand as well as the American guidelines indicate that biological interventions may be preferred for melancholia, and that light therapy is a first-line treatment for winter depression, though antidepressant medication is also effective[6,57].

Little research has examined the impact of clinical subtypes of depression on treatment decision-making in routine clinical practice. A survey of the factors influencing psychiatrists' choice of pharmacological treatment found that melancholic and atypical features were rarely the basis for selecting one medication over another, and that anxiety was the most commonly endorsed feature for selecting a particular medication[81]. This study, however, was limited to the question of how medications are selected, and did not assess other types of treatment decision-making such as referral for psychotherapy, electroconvulsive therapy, or light therapy.

In conclusion, several subtypes of depression have been identified. The most clinically relevant of these subtypes is psychotic depression, as there is consistent evidence that it requires a specific treatment approach. The melancholic subtype retains clinical appeal, but the evidence supporting its differential response to treatment is not consistent. The treatment implications of the anxious and mixed subtypes of depression remain insufficiently studied, whereas the atypical subtype seems to be less clinically relevant today than it was some decades ago. Overall, this is a research area that requires more systematic attention as part of the current effort to personalize the management of depression.

SEVERITY

While research has not been entirely consistent, the severity of depression has been associated with health-related quality of life, functional impairment, suicidality, longitudinal course, and response to treatment[82]. There are no biomarkers of depression that characterize disorder severity. Thus, researchers and clinicians base their severity ratings on the clinical features of the disorder. Almost all research on severity depends on depression symptom scales.

In the DSM-5[7], depression is classified as mild, moderate or severe based on the number of symptoms, the level of distress caused by the intensity of the symptoms, and the degree of impairment in social and occupational functioning. The definition of functional impairment is limited to social or occupational functioning and does not include other potentially important areas of functioning, such as self-care, parenting or schooling. Mild depression is specified when "few, if any, symptoms in excess of those required to make the diagnosis are present, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning". Severe depression is specified when "the number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of the symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning". The DSM-5 does not explicitly define moderate depression other than to say that the number of symptoms, their intensity, and/or functional impairment are between mild and severe.

The ICD-11 description of mild, moderate and severe depression is more detailed[8]. Mild depression requires that none of the symptoms are intense, and there is some difficulty in personal, family, social, educational, occupational or other important areas of functioning. Moderate depression is defined by a marked intensity of several symptoms or a large number of less severe symptoms, and a considerable difficulty in functioning. Severe depression requires that many or most symptoms are present to a marked degree or some symptoms to an intense degree, and there is a complete or near-complete inability to function in some domain. As with the DSM-5, there are potential problems with the logic of these definitions. For example, how should we classify a patient with symptoms of moderate intensity who is unable to work? Such a patient would meet the impairment threshold for severe depression, but not the symptom threshold.

Despite potential problems in applying the DSM-5 and ICD-11 definitions, both of them have more intuitive appeal to clinicians than severity classification based on depression symptom scales, because they consider the degree of impairment as coequal to symptom level. However, there is almost no research on the DSM and ICD definitions. It is also noteworthy that neither DSM-5 nor ICD-11 consider suicidality in their definitions of se-

verity. This contrasts with many physical illnesses, whereby severity refers to the likelihood of imminent or distal mortality, or to prognosis or future course.

The DSM and ICD definitions of depression severity have not been used in treatment studies. In almost all these studies, severity has been evaluated by the total score on a symptom rating scale, usually the HAM-D or the MADRS. Of note, adding up item scores to yield a total score as a measure of overall depression severity assumes that all symptoms are equal indicators of severity, an assumption which is not empirically supported.

According to current treatment guidelines, depression severity is an important consideration in treatment decision-making. For example, the NICE guidelines[5] discourage the use of antidepressant medications as the initial treatment option for mild depression, whereas they recommend it, along with empirically supported psychotherapies, for moderate and severe depression. The third edition of the American Psychiatric Association's guidelines[6] recommends either psychotherapy or pharmacotherapy for mild and moderate depression, and pharmacotherapy (with or without psychotherapy) for severe depression.

If clinicians are to follow treatment guidelines and base initial treatment selection on the severity of depression, then it is important to have a consistent method of determining that severity. Based on a review of the available evidence, the following severity ranges have been suggested for the 17-item HAM-D: 0-7 for no depression, 8-16 for mild depression, 17-23 for moderate depression, and >24 for severe depression[82].

However, a rating scale such as the 17-item HAM-D takes too much time to administer to be suitable for use in routine clinical practice. A 6-item version of this scale, which is purported to assess the core features of depression, has been found to be superior to the full-length scale at detecting differences between active drug and placebo[83]. This version of the scale might be more suitable for clinical use. However, cutoff scores to demarcate categories of severity on this version are not established.

In clinical practice, it is more likely that self-administered questionnaires will be used to quantify the severity of depressive symptoms. Self-report scales that assess the symptoms of depression and are available for clinical use at no cost include the Clinically Useful Depression Outcome Scale (CUDOS)[84], the QIDS[24], the Patient Health Questionnaire-9 (PHQ-9)[85], and the 8-item PROMIS Depression Short Form (www.dsm5.org). However, there is a marked disparity among these tools in the classification of depressed patients into severity groups, making their use to guide treatment selection problematic[86].

So, overall, while treatment guidelines emphasize depression severity as a key consideration in treatment decision-making, there is no agreement about how this severity should be assessed in ordinary clinical practice. Reaching this agreement represents today a major unmet need.

Approximately a decade ago, two analyses of the US Food and Drug Administration (FDA) database found that drug-placebo differences were largest in antidepressant trials with the highest mean baseline severity on the HAM-D, whereas the differences in the trials with lower mean baseline scores were modest and clinically insignificant[87,88]. More recently, large pooled analyses of patient level data from published and unpublished studies have found that antidepressants are effective across a range of severity[9,89]. However, these studies do not include patients across the full range of symptom severity, because they require a minimum score on a symptom severity scale for study entry. Thus, the lower bound of symptom severity associated with antidepressant efficacy has not been established. Nonetheless, at the present time, it is reasonable to conclude that the efficacy of antidepressants is not limited to the small group of patients who score highest on symptom severity scales.

Regarding the impact of severity on the efficacy of psychotherapies for depression, a meta-analysis of 132 controlled studies of various types of psychotherapy found that higher mean baseline symptom scores did not predict poorer response[10]. More recently, an individual patient data meta-analysis[90] of pooled data from 16 studies compared antidepressants and cognitive behavioral therapy: severity was not associated with differential treatment outcome.

The results of these more recent analyses are thus not consistent with clinical lore and current treatment guidelines which recommend medication as the first line treatment for severe depression. However, interpretation of these data must be tempered by the recognition that studies often truncate the range of severity included. More studies of psychotherapy than pharmacotherapy of depression limit the upper range of severity[91]. Thus, the most severely depressed patients may not have been included in at least some controlled psychotherapy treatment studies. Furthermore, the above studies are based on scales assessing symptom severity without consideration of the degree of functional impairment.

The use of scales assessing symptom severity to monitor the course of treatment is supported by research demonstrating that measuring outcome in clinical practice results in improved outcome[92,93]. However, which scales should be used in routine clinical practice for this purpose currently remains uncertain. For practical reasons, self-administered questionnaires may be more suitable.

NEUROCOGNITION

Cognitive deficits are a core dimension of the depressive syndrome and have been identified in both first- and multiple-episode patient populations[94]. They may be antecedent to the formal diagnosis of depression and persist during "asymptomatic" states[95]. Their magnitude (i.e., expressed as effect sizes) ranges from small to large and is clinically relevant[96]. Moreover, it has been empirically shown that a significant degree of psychosocial impairment and reduction of workplace productivity in adults with depression is mediated directly by cognitive impairment[97].

Neurocognition may be disaggregated into executive functions, attention/concentration, learning/memory, and processing speed[98]. Executive functions can be further subdivided into the planning, initiation, sequencing, monitoring and inhibition of thoughts, moods and behavior[99].

Replicated evidence indicates that cognitive deficits may be progressive in patients with depression especially in the subdomain of learning/memory[100]. This observation aligns with a separate body of evidence documenting volumetric reduction in memory substrates (e.g., hippocampus) in adults with depression[101]. Conceptually, the progression of cognitive deficits in subpopulations of patients may provide an explanatory framework for the attenuated response to antidepressants in cohorts of adults with depression later in the illness trajectory[102].

The prevalence, persistence, as well as the mediational effect of cognitive deficits on quality of life, psychosocial and workplace function, as well as response to treatment, suggests the need for systematic screening and measurement of neurocognition in adults presenting with clinically relevant depressive symptoms. The lack of a significant correlation between self- and objectively-measured cognitive functioning in depression indicates that the exclusive reliance on self-reported cognitive functions will insufficiently characterize the magnitude and complexity of cognitive disturbances in affected individuals[98].

Conventional rating instruments of depressive symptoms – such as the PHQ-9 and the QIDS – rely on patient self-report, contain relatively few items assessing cognition and, importantly, do not fully capture the ecological manifestations of cognition in an affected individual's everyday life. Consequently, it is recommended that adults with depression be specifically asked about the presence of cognitive deficits and their impact on their quality of life and psychosocial/workplace functioning. It is also suggested to supplement the clinical assessment with a validated, reliable and sensitive objective measure suitable for use in ordinary practice[103].

Most cognition assessment tools are too time-consuming for clinical use and many require professional interpretation, often with cost. The THINC-integrated tool (THINC-it) is an instrument with satisfactory psychometric properties whose administration is feasible in routine practice[104]. It has been validated both as a screening tool for cognitive impairment in depression and as a measure to detect change in cognition with treatment. It evaluates executive functions, information processing speed, attention/concentration, learning/memory, as well as self-reported cognitive functions. It is free of charge and downloadable to a smart device, and takes approximately 5-8 min to complete.

The presence of cognitive impairment in a patient with depression has significant implications for the formulation of the management plan. Psychotropic drugs that are known to interfere with cognitive functions should be discontinued. These include antidepressants with anticholinergic activity (e.g., tricyclic antidepressants), antipsychotics with significant anti-histamine properties, and benzodiazepines[98]. Moreover, recreational substances (e.g., cannabis) that interfere with cognition should be avoided. Improving sleep quality would also be expected to ameliorate cognitive functions in depressed patients. Treating both psychiatric (e.g., alcohol misuse) and medical (e.g., diabetes mellitus, obesity) comorbid states should be prioritized as part of a "cognitive preserving" approach to managing depression[105].

Treatments specifically targeting cognitive functioning in depression have been hitherto insufficiently evaluated. Cognitive remediation has been found to improve attentional capacity in adults with depression, but its benefit across other domains of cognitive functioning awaits further documentation[106,107]. Aerobic exercise shows some promise in preserving and improving cognitive functions in adults with age-related cognitive decline, but its efficacy in improving cognition in adults with depression remains just a testable hypothesis[108]. Neurostimulation (e.g., repetitive transcranial magnetic stimulation) may also improve subdomains of cognition in individuals with depression independent of mood symptoms[109].

Available evidence suggests that the antidepressants vortioxetine and duloxetine may have direct and independent effects on cognitive functions. Vortioxetine has been reported to improve executive functions, attention, learning/memory and processing speed[110], while duloxetine has been found to have a favorable impact on learning/memory[111]. Psychostimulants, anti-inflammatory agents, and possibly ketamine may be pro-cognitive in select individuals[98].

New technologies, such as ecological momentary assessment, may help in the assessment of neurocognition in patients with depression, by providing a more precise characterization of an individual's cognitive abilities in real time across different environments[112].

FUNCTIONING AND QUALITY OF LIFE

When defining the depressive syndrome, classification systems go beyond symptoms and require that these symptoms "cause clinically significant distress or impairment in social, occupational, or other important areas of functioning" (DSM-5)[7] or "result in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning" (ICD-11)[8].

Since these functional aspects are not well defined, the clinician is left with hesitancy as to how to assess them. A study in primary care in which physicians were asked to include patients with major depression showed that 95% of the included patients had, as requested, at least five of the nine DSM depressive symptoms, but that only 72% met the criterion of at least moderate impairment in occupational, social or family functioning[113]. Assessing functioning appropriately could therefore improve diagnostic accuracy.

The growing interest in functioning and in quality of life (QOL) goes hand in hand with the recent emphasis on shared decision-making, where the patient and the physician should agree upon the treatment goals. In fact, in depression, the main patient expectations are restoration of positive emotions, functioning and meaningfulness of life rather than merely symptom relief, far away from what is usually assessed in randomized controlled trials[114,115].

Numerous scales and questionnaires have been proposed for the assessment of functioning and QOL (over one thousand QOL scales have been published), but they are rarely used by clini-

cians. They are often overly comprehensive and therefore only suitable for use in research settings, or they are a mix of symptoms and functioning, or they contain some items or subscales (i.e., self-care, mobility) which make them useful in a very severe patient population but not in the majority of outpatients.

Another problem is that some scales make it difficult to differentiate between impaired functioning caused by the depressive disorder and the problems causing or maintaining the disorder: for example, impairment in occupational functioning caused by the depressive mood state versus difficulties and conflicts at work leading to or maintaining the depressive mood state.

The concept of QOL is even more confusing. The relevant literature differentiates between objective and subjective QOL[116]. Objective QOL refers to a functionalist approach: the ability to perform roles that are considered normal for people (i.e., occupational, social, family life), aiming for an optimal level of functioning defined externally by society. Subjective QOL refers to a needs-based approach: the ability and capacity to satisfy one's needs (physical, emotional or social), which involves a personal cognitive-emotional appraisal and mediates between objective indices (living conditions, symptoms and side effects) and personal expectations and aspirations[117].

The latter comes close to the concept of "life satisfaction", which is influenced by the excess of negative affect and lack of positive affect in depression[117]. Satisfaction with one's life implies a contentment with or acceptance of one's life circumstances, or the fulfilment of one's wishes and needs for one's life as a whole[117]. It comes also close to the concept of eudaimonic well-being: a sense of having meaning and purpose in one's life, considered very important from the patients' perspective[115].

Among the various scales available for the assessment of functioning and QOL, we do not recommend the Global Assessment of Functioning (GAF)[118], because it reflects too closely symptom severity, nor the 36-item Short Form Survey (SF-36)[119], which mixes symptoms and functioning. Some very well-developed scales – such as the World Health Organization (WHO) Disability Assessment Schedule[120] (36-item WHODAS 2.0), the International Classification of Functioning (ICF)[121], the WHO Model Disability Survey (MDS)[122], and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[123] – may be too comprehensive to be used in daily practice. Even the 12-item version of the WHODAS 2.0 is not well suited for the majority of depressed outpatients, due to the inclusion of items such as "washing your whole body" and "getting dressed" that are likely to be not relevant.

More suitable for routine practice may be one tool for assessing both functioning and life satisfaction and two tools for assessing life satisfaction.

The tool for assessing both functioning and life satisfaction is taken from the Leuven Affect and Pleasure Scale (LAPS)[124]. Four items are considered: "I can think clearly, I can focus well. I can make decisions and my memory is good"; "I can function well (occupational, social and family life)", "I feel my life is meaningful", "I feel happy". For each item, the respondent is asked "To what extent did you experience this during the past week?". The ratings are: "0 (not at all)", "1 to 3 (a little bit)", "4 to 6 (moderately)", "7 to 9 (quite a bit)", and "10 (very much)".

A first tool for assessing life satisfaction is based on the Organisation for Economic Co-operation and Development (OECD) guidelines[125]. Two items are considered: "Overall, how satisfied are you with life as a whole these days?"; "Overall, to what extent do you feel the things you do in your life are worthwhile?". The rating is from "0 (not at all satisfied)" to "10 (completely satisfied)".

A second tool for assessing life satisfaction is based on the finding that the subscale "Inner experiences" from the Quality of Life Self-Assessment Inventory (QLS-100)[126] is the most impaired in patients with depression[127]. The subscale includes five items: "Feeling at ease", "Being pleased with life", "Sense of fulfilment", "Being of use" and "Being understood by others". The rating on each item can be "Satisfactory" or "Unsatisfactory".

A routine assessment of these aspects of functioning/QOL/life satisfaction in clinical practice is important for multiple reasons. First, it can improve diagnostic accuracy: in defining depression, both the DSM-5 and ICD-11 go beyond symptoms, and assessing functioning can reduce the number of false positive diagnoses[113]. Second, shared decision-making and patient-centered care have gradually become integrated in medicine, where "what matters to you" has become as important as "what is the matter": concordance on the treatment goals (what does the physician as well as the patient expect from treatment) has been shown to result in better outcomes six months later, at both the symptom and the QOL level[128-130]. Third, medicine is about curing and caring: although cure is the ultimate goal of treatment, many patients can achieve a meaningful QOL and an acceptable level of life satisfaction despite (residual) symptoms.

CLINICAL STAGING

Clinical staging indicates where a person stands along the continuum of the course of depression[131]. Furthermore, it takes into consideration the response of the disorder to specific therapies, with particular reference to treatment resistance[132].

A staging model of depression was first presented in 1993[131] and updated twenty years later[132] (see Table 3).

The prodromal phase (stage 1) is characterized by either aspecific symptoms (generalized anxiety, irritability, sleep disorders) with mild functional change or decline (stage 1a), or subthreshold depressive symptoms (stage 1b). There is a large inter-individual variability in this prodromal phase; however, for a specific patient, different depressive episodes tend to share a similar prodromal symptomatology.

At stage 2, the patient presents the first depressive episode. Then a residual phase (stage 3) may occur. This phase may be marked by aspecific symptoms (sleep disturbance, generalized anxiety, irritability, anorexia, impaired libido) (stage 3a), or by residual depressive symptoms (depressed mood, guilt, hopelessness) (stage 3b), or by the occurrence of dysthymia (a mild chronic depressive syndrome) (stage 3c).

Residual symptoms are a strong predictor of relapse[132]. Cer-

Table 3 Clinical staging of depression

STAGE 1	Prodromal phase a. Aspecific symptoms (generalized anxiety, irritability, sleep disorders) with mild functional change or decline b. Subthreshold depressive symptoms
STAGE 2	First depressive episode
STAGE 3	Residual phase a. Aspecific symptoms (sleep disturbance, generalized anxiety, irritability, anorexia, impaired libido) b. Residual depressive symptoms (depressed mood, guilt, hopelessness) c. Dysthymia (mild chronic depressive syndrome)
STAGE 4	a. Recurrent depression b. Double depression (depressive episodes superimposed on dysthymia)
STAGE 5	Chronic depressive episode (i.e., episode lasting at least two years without interruptions)

This staging is a modification of that proposed by Cosci and Fava[132]

tain prodromal symptoms may be overshadowed by the acute manifestation of the disorder, but persist as residual symptoms and progress to become prodromes of relapse. A model for relating prodromal and residual symptomatology, based on the so-called rollback phenomenon, has been proposed[133]: as the episode remits, it progressively recapitulates, in reverse order, many of the symptoms that were seen during the time it developed. The rollback phenomenon has been substantiated in depression[132].

Stage 4 is characterized by recurrent depression or by double depression (i.e., depressive episodes superimposed on dysthymia). The link between dysthymia and relapse of depressive episodes has been widely confirmed[134]. At stage 5, the patient has a chronic depressive episode (i.e., an episode lasting at least two years without interruptions).

This longitudinal view of depression entails two important clinical implications. First, let us consider a patient who currently presents with depressive symptoms that are not sufficient to formulate the diagnosis of a depressive episode. Staging allows to determine whether such symptoms are a residual symptomatology of a previous episode (thus indicating a high risk of relapse) or can be viewed as manifestations of mild or subthreshold depression.

A second implication is concerned with treatment planning. Staging allows selection of a specific treatment geared to the phase of development of depressive disorder[135]. In particular, the sequential model is an intensive, two-step approach, where one type of treatment (i.e., psychotherapy) is employed to address symptoms which another type of treatment (i.e., pharmacotherapy) has been unable to improve[136]. The sequential model has been found to prevent depressive relapse in a number of randomized controlled trials[135,136]. Furthermore, chronicity (stage 5) has been reported to be a predictor of a better response to the combination of pharmacotherapy and psychotherapy vs. either treatment alone[137].

Different methods to stage degree of treatment resistance in patients with depression have been suggested.

In the five-stage model[138], patients are classified according to the number and classes of antidepressants that failed to produce a response, with staging moving from more common to less common treatments. Thus, for instance, stage I is characterized by failure of at least one adequate trial of one major class of antidepressants.

A second model is the European approach[139]. Stage A represents no response to one adequate antidepressant trial lasting 6-8 weeks. Treatment-refractory depression (stage B) is defined by the failure of two or more adequate trials of different antidepressants given in adequate dosages for a period of at least 12-16 weeks, but no longer than one year. Chronic resistant depression (stage C) is marked by failure of several antidepressant trials, including augmentation strategies, lasting one year or more.

The Massachusetts General Hospital model[140] considers both the number of failed trials and the intensity of each trial, without assumptions on the hierarchy of antidepressant classes. This model generates a score reflecting the degree of treatment resistance and ranging from 0 to 5.

Finally, the Maudsley Staging Method[141] incorporates, in addition to the number of failed treatment trials, factors considered to be closely related to the depressive disorder itself, such as duration and severity, as well as the use of augmentation or electroconvulsive therapy. The stage of treatment resistance is represented as a single score ranging from 3 to 15.

An attempt to integrate the four models is proposed in Table 4, which also includes psychotherapeutic approaches[135]. Stage 0 is defined by no history of failure to respond to a therapeutic trial. Stages 1 to 3 are characterized by failure of one, two or at least three adequate therapeutic trials of a specified duration. Stage 4 is defined by the failure of three or more adequate trials, with at least one involving augmentation/combination or electroconvulsive therapy. In this model, the expression "therapeutic" means either psychopharmacological therapy or psychotherapy.

In summary, staging allows to characterize a patient with a diagnosis of depression with respect to both the phase of the development of the disorder and its response to specific therapies, and can therefore be useful in clinical practice.

Table 4 Staging of depression according to levels of treatment resistance

STAGE 0	No history of failure to respond to a therapeutic trial
STAGE 1	Failure of one adequate therapeutic trial (duration: 6-8 weeks for medication; 36 weeks-1 year for psychotherapy)
STAGE 2	Failure of two adequate therapeutic trials (duration of each trial: 12-16 weeks for medication; 36 weeks-1 year for psychotherapy)
STAGE 3	Failure of three or more adequate therapeutic trials (duration of each trial: 12-16 weeks for medication; 36 weeks-1 year for psychotherapy)
STAGE 4	Failure of three or more adequate trials, with at least one involving augmentation/combination or electroconvulsive therapy (duration of each trial: at least 3 months)

This staging is a modification of that proposed by Cosci and Fava[132]

PERSONALITY TRAITS

Personality traits should be routinely assessed in a person with a diagnosis of depression. These traits, particularly neuroticism, may have provided a dispositional vulnerability for the onset of the depression, and additional traits may impact on how the patient responds to treatment. However, the assessment of personality traits while the person is clinically depressed can often be problematic, as the depressed mood will influence the patient's self-description.

The predominant model for the description of personality structure is the Five Factor Model (FFM)[142], consisting of the five broad domains of neuroticism, extraversion (vs. introversion), openness (or conventionality vs. unconventionality), agreeableness (vs. antagonism), and conscientiousness (or constraint vs. disinhibition).

Neuroticism is particularly important as a precursor for major depressive episodes, as it concerns the disposition to experience negative affects, including sadness as well as anger and anxiety[143]. Persons with elevated levels of neuroticism respond poorly to environmental stress, interpret ordinary situations as threatening, and can experience minor frustrations as hopelessly overwhelming[144]. A clinician may need to treat the patient's personality to the extent that the current depression is secondary to the neuroticism. There is now a manualized psychotherapy for the treatment of neuroticism[145]. Techniques that help reduce neuroticism include cognitive therapy, exposure, and mindfulness[145,146].

Personality traits can also impact treatment. Persons who are highly conscientious are more likely to adhere to demanding treatment regimens, whereas persons who are low in conscientiousness (i.e., disinhibited or lax) are more likely to drop out. Persons who are high in openness will be more receptive to exploratory insight; persons who are extraverted are more likely to be comfortable and active within group therapy; and persons who are antagonistic are likely to be disruptive within inpatient settings and oppositional or argumentative within individual therapeutic sessions, whereas persons who are agreeable are more likely to be compliant[147]. There are empirically supported strategies to treat maladaptive traits: for example, goal planning to increase conscientiousness, social skills training to decrease detachment, and cognitive restructuring to decrease antagonism[146].

There has been a study reporting that depressed patients with higher scores on neuroticism are more likely to respond to pharmacotherapy than to cognitive behavioral psychotherapy, suggesting a potential usefulness of treatment sequencing (i.e., initial treatment with medication and subsequent introduction of psychotherapy when the patient is better able to benefit from cognitive behavioral strategies)[148].

The maladaptive trait models included in the Section III of the DSM-5 (negative affectivity, detachment, disinhibition, antagonism and psychoticism) and in the ICD-11 (negative affectivity, detachment, disinhibition, dissocial and anankastia) are aligned conceptually and empirically with the FFM. For example, ICD-11 negative affectivity aligns with FFM neuroticism, detachment with introversion, dissocial with antagonism, anankastia with conscientiousness, and disinhibition with low conscientiousness[149].

Given that these traits are maladaptive variants of the FFM, one can infer their likely impact on the treatment of depression. For example, the same implications for treatment apply to ICD-11 negative affectivity, detachment, dissocial and disinhibition that occur for FFM neuroticism, introversion, antagonism and low conscientiousness, respectively. The DSM-5 and ICD-11 trait models do not include adaptive personality strengths (e.g., extraversion and conscientiousness) and so will not indicate how positive personality traits can facilitate treatment response.

Personality disorder syndromes, such as borderline and antisocial personality disorders, are constellations of maladaptive personality traits and can therefore impact on treatment. Patients with borderline disorder may form intense relationships with their therapist, sometimes leading to violation of professional boundaries; patients with dependent disorder may become overly attached and reliant; patients with histrionic disorder may be overly flirtatious and provocative; patients with narcissistic disorder may be critical and devaluing; and patients with antisocial disorder may be deceptive, disruptive and oppositional. Cognitive behavioral, dialectical, schema, and psychodynamic therapies are efficacious for personality disorders[150]. Pharmacotherapy can also be effective for borderline personality disorder, but the treatment will have to be maintained.

The co-occurrence of a diagnosis of personality disorder with that of depression has been found to be associated with a better response to a combination of pharmacotherapy and psychotherapy than to pharmacotherapy alone[151]. In patients with avoidant personality disorder, cognitive behavior psychotherapy has been reported to be superior to interpersonal psychotherapy[152].

There are many alternative measures for the assessment of FFM personality traits, the DSM-5 and ICD-11 maladaptive trait models, and the personality disorder syndromes. The predominant and most well validated self-report measure of the FFM is the NEO Personality Inventory - Revised (NEO PI-R)[153]. This is a 240-item self-report commercially published measure. A closely comparable (and freely available) measure is the International Personality Item Pool - NEO (IPIP-NEO)[154]. Both the NEO PI-R and IPIP-NEO, though, are relatively long. There are several abbreviated measures, including the Five Factor Model Rating Form (FFMRF)[155] and the Big Five Inventory-2[156]. The FFMRF is a one-page rating form that can be completed as a self-report measure or as a clinician assessment tool.

There is only one instrument for the assessment of the DSM-5 trait model: the Personality Inventory for DSM-5 (PID-5)[157], freely available online from the American Psychiatric Association. The Personality Inventory for ICD-11 (PiCD)[158] was developed to assess the ICD-11 trait model. The PID-5 can also be used to assess the ICD-11 trait model, but its coverage for anankastia is more limited than in the PiCD.

There are also many alternative measures of the personality disorder syndromes. The most commonly used is the freely available Personality Diagnostic Questionnaire-4 (PDQ-4)[159], consisting of 99 items. Other possible measures have potential limitations,

such as being relatively expensive, lengthy and/or lacking in full coverage.

One of the most well-recognized problems in the self-report assessment of personality is the potential impact of clinical depression on a person's self-image and self-description[160]. Persons will provide inordinately negative self-descriptions when they are clinically depressed. Clinicians should focus their interview assessment of personality on the patient's life prior to the onset of the depression.

ANTECEDENT AND CONCOMITANT PSYCHIATRIC CONDITIONS

While there are multiple antecedent psychiatric conditions over-represented in persons with depression, the list is somewhat elastic depending on source material.

A representative study[161] reported that adult depression was increased in those who had had anxiety conditions (i.e., generalized anxiety, separation anxiety), disruptive states (e.g., conduct disorder, oppositional defiant disorder) and substance-related disorders in childhood or adolescence. Such narrow lists most commonly reflect a limited set of candidate conditions being studied by the researchers.

In contrast, the DSM-5[7] states that "essentially all major nonmood disorders increase the risk of an individual developing depression", before noting that "substance use, anxiety, and borderline personality disorder are among the most common of these". The manual also points out that depression developing against the background of another mental disorder often follows a more refractory course.

The number of antecedent conditions is also likely to be related to how depression is defined, in that there may be a small set of antecedent conditions experienced by those who develop melancholic depression and a broad set if depression is defined at a low threshold of severity.

Multiple mechanisms for such associations can be postulated and should be contemplated, as they have the potential to shape management models. First, the conditions may have independent status. Second, having a psychiatric condition can be depressogenic *per se*. Third, those with "acting-out" conditions (e.g., conduct disorder) or who have substance use conditions are more likely to be expelled from school, lose their job or experience divorce, with such secondary social factors being depressogenic. Fourth, some antecedent conditions may operate via a biological conduit (for example, alcohol excess and some illicit drugs can be distinctly depressogenic). Fifth, a "staging model" may be operative, in which the clinical phenotype is linked to the extent of disease progression. For instance, there may be a prodromal phase in the development of depression, marked by "increased aggression and augmented anxiety"[131].

Turning to concomitant conditions (and it is perhaps important to note that "comorbid" strictly means coterminous and excludes antecedent conditions), virtually all psychiatric disorders can be associated with depression. The most common ones are anxiety states, with patients reporting the onset of, or an increase in, generalized anxiety, panic attacks or social anxiety during depressive episodes, and with such conditions generally returning to their premorbid status when recovery from depression occurs.

In terms of mechanisms, concomitant psychiatric states may again reflect chance, or the pathoplastic impact of a stressor (e.g., a traumatic event might cause depression, a set of anxiety disorders including post-traumatic stress disorder, and illicit substance use). Furthermore, the concomitant presentation may reflect a common genetic determinant providing a pleiotropic risk. A high genetic correlation between anxiety and major depression has been indeed documented[162], although those two might be conjoined by genetically determined neuroticism.

In terms of tools for diagnostic assistance and clarification, the SCID-5[60] provides a guidance to the clinician, but its administration takes about 90 min and requires considerable training. Thus, clinicians are more likely to rely on taking a comprehensive clinical history from patients (and optimally from relatives as corroborative witnesses) to determine what conditions have diagnostic status, and their onset, ranking and current standing.

The DSM-5 has a patient- or informant-rating "cross-cutting" symptom measure, best viewed as a screening measure for potential more detailed inquiries. While principally designed to assess symptoms in the two previous weeks and prospectively, its 12 probe questions for adults capture several salient domains (i.e., anxiety, psychosis, obsessive-compulsive disorder, personality functioning, and substance use), so allowing retrospective applicability[7].

The PDSQ[61] is a screening instrument covering multiple psychiatric disorders, including mood, anxiety, substance abuse, eating and somatoform disorders. Tools focusing on specific disorders, to be used when their presence is suspected, are the Generalized Anxiety Disorder 7-item scale (GAD-7)[163], the Penn State Worry Questionnaire[164], the Liebowitz Social Anxiety Scale[165], the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[166], the PID-5[157], the Posttraumatic Stress Diagnostic Scale (PDS)[167], the Conners Adult ADHD Rating Scales (CAARS)[168], the Alcohol Use Disorders Identification Test (AUDIT)[169], and the Drug Abuse Screening Test (DAST-10)[170].

In persons with depression, identifying other conditions should help shaping management. If the two conditions are judged to be independent, then both are likely to require condition-specific treatments. If interdependent, five principal models come into play.

First, a sequential model. For example, for a patient with depression and a borderline personality disorder, stabilizing the depression might be the initial priority before addressing the other condition.

Second, a hierarchically-weighted model. A single treatment may address a higher-order factor and thus ameliorate downstream concomitant conditions. For example, an SSRI and/or cognitive behavioral therapy may be of benefit for comorbid states of depression and anxiety, or depression and obsessive-compulsive disorder.

Third, a severity-weighted model. Treatment of a primary de-

pressive episode might correct any secondary conditions or consequences. For example, if anxiety has emerged only with onset of a severe melancholic depressive episode, then treating the primary state is the optimal model, with the hypothesis being that, on its recovery, there will be no residual anxiety requiring treatment or, if present, it will become more responsive to treatment.

Four, a "motivational bypass" model. For example, an individual with an acting-out personality style leading to brief explosive depressive states may have no motivation to attend psychotherapy or to take medication (which, moreover, may involve a risk for overdose), but be prepared to engage in an anger management program.

Fifth, a risk management model. For example, if an individual with depression has a primary conduct disorder and/or is under the influence of an illicit substance, then hospitalization and other salient strategies for ensuring the patient's and/or relatives' safety may be the immediate priority.

The reality of depression being associated with multiple antecedent and concomitant conditions challenges the clinician to contemplate a range of causal and treatment models, and to avoid seeking a parsimonious single diagnosis.

The scientific data base informs us about candidate conditions, but their detection relies on diagnostic skills and tools, while management invokes the therapeutic "art" of determining the relevant explanatory model and then providing a management model that "fits" with the putative linking mechanisms.

PHYSICAL COMORBIDITIES

Compelling evidence indicates that the depressive syndrome is highly associated with physical comorbidities, particularly cardiometabolic diseases[171]. A variety of factors, including unhealthy lifestyles and the use of antidepressants, increase the risk of physical complications/disorders in people with this condition[172]. In clinical practice, however, such comorbidities are routinely overlooked[173].

The poor clinical management of these comorbidities drastically reduces life expectancy, and increases the personal, social and economic burden of depression across the lifespan[174]. Improving the management of physical health conditions in people with depression, with the aim of decreasing morbidity and premature mortality, is therefore essential.

Approximately one third of people with a diagnosis of depression has metabolic syndrome[175], characterized by the simultaneous occurrence of several metabolic abnormalities (abdominal obesity, glucose intolerance or insulin resistance, dyslipidemia and hypertension). Meta-analytic data show that, compared with the general population, people with depression have a 1.6 times higher risk of developing this syndrome[175].

As the individual components of metabolic syndrome are critical in predicting the morbidity and mortality of cardiovascular disease, type 2 diabetes mellitus, cancer and other related diseases, they should be checked at baseline and measured regularly thereafter[176].

Clinicians should monitor the weight of every patient at every visit. However, assessment of central/abdominal adiposity, by measuring waist circumference, has a stronger correlation with insulin resistance and better predicts future type 2 diabetes mellitus and cardiovascular diseases than total body weight or body mass index. This assessment can easily be done with a simple and inexpensive waist tape measure.

As the cost for measuring is low and hypertension is a risk factor for cardiovascular disease, blood pressure ought to be assessed routinely with an inflatable or digital blood pressure cuff. A checklist for accurate measurement is provided by the American College of Cardiology/American Heart Association (ACC/AHA)[177]. Importantly, at least two separate, independent measurements are required for the diagnosis of elevated blood pressure/hypertension. Moreover, the ACC/AHA guidelines recommend out-of-office measurements to confirm this diagnosis[177].

Finger prick tests should be carried out to capture early cases of hyperglycemia at baseline and after three months, and then at least yearly. Ideally, blood glucose measurement should be conducted in the fasting state, because this is the most sensitive measurement for the detection of developing glucose abnormalities.

Lipid parameters, especially triglycerides and high density lipoprotein (HDL)-cholesterol, should also be assessed at baseline and at 3 months, with 12-monthly assessments thereafter. More frequent screening is unnecessary, unless in case of abnormal values. Fasting is not routinely required for the determination of a lipid profile.

The diagnosis of depression is a risk factor for cardiovascular disease[178]. According to a large-scale meta-analysis, depression increases the risk for coronary heart disease by 1.6-2.5 times[179]. Identifying and managing modifiable cardiovascular risk factors in people with depression – such as smoking, an unhealthy diet, obesity, sedentary lifestyle, alcohol consumption, hypertension, diabetes mellitus, and dyslipidemia – will reduce their risk for premature morbidity/mortality[180,181].

People with depression are more likely to smoke and have significantly poorer diet quality than the general population. Around 60-70% of them do not meet physical activity guidelines and are sedentary for 8.5 hours or more per day. Around 30% have or have had alcohol use disorder[173].

Patients with high risk for cardiovascular disease can be identified by one of several "cardiovascular risk calculators", including the WHO cardiovascular risk prediction charts, the Joint British Societies risk calculator (JBS3), and the Framingham risk score (FRS-CVD), some of which are available online[182-184]. The WHO risk prediction charts, for example, quantify the 10-year risk of a fatal or non-fatal major cardiovascular event (i.e., myocardial infarction or stroke), according to age, gender, blood pressure, smoking status, total cholesterol and presence or absence of diabetes mellitus[183]. The value of such prediction is to help communicate risk, so that patients can receive advice (and treatment if necessary) appropriate to their risk level.

Depression is also a well-acknowledged risk factor for diabetes mellitus[185]. Meta-analytic data have found that the risk for type 2 diabetes mellitus is 1.5 times higher in people with a

depressive syndrome, compared to the general population[185]. Clinicians who provide care to people with depression should understand the clinical features of diabetes mellitus and be able to identify potential life-threatening episodes. The clinician should check whether patients have significant risk factors (family history, body mass index ≥25, waist circumference above critical values).

Physical comorbidities of depression have important implications for the formulation of the management plan. Patients should be taught about healthy lifestyles and receive psychoeducational packages (e.g., nutrition education) and support (e.g., dietary support) to facilitate them. Training on smoking cessation is now freely available online (e.g., the e-learning tool from the National Centre for Smoking Cessation and Training)[186]. Patients should be advised to engage in at least 30 min of moderately vigorous activity on most days of the week. The importance of consuming healthy food, such as fresh fruit and vegetables, fish, and lean meats in a balanced way, should be stressed by clinicians whenever possible[187].

If lifestyle interventions do not succeed, medication may be indicated. First-line pharmacological therapy for type 2 diabetes mellitus or pre-diabetes is metformin monotherapy. For the pharmacological management of hypertension, any of the following medication classes can be used as first-line treatment: thiazide diuretics, long-acting calcium-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor antagonists. Statin therapy should be offered for primary prevention of cardiovascular disease if the 10-year risk of developing cardiovascular disease is ≥10%[173]. In cases where physical comorbidities, such as hyperglycemia or hyperlipidemia, are secondary to antidepressant medication, dose reduction or switching to an antidepressant with a lower risk profile should be considered, if safe and feasible.

Preventing physical comorbidities of depression is a more efficient strategy than attempting to reverse them once they have developed[188]. The Diabetes Prevention Program is an example of a gold-standard lifestyle intervention with a key focus on prevention[189]. Emerging evidence indicates that mHealth, i.e. the use of digital technology (such as smartphone apps and fitness trackers) in health care delivery, can play an important role in preventing those comorbidities. A comprehensive lifestyle assessment would inform patients of specific lifestyle changes they could make to protect their physical health. Unfortunately, no suitable digital tools are as yet available for clinicians to comprehensively assess lifestyle factors (e.g., exercise, diet, sleep) all at once[190].

In summary, clinicians have a duty today to ensure that patients with depression are adequately evaluated with respect to their physical health, and are given access to evidence-based lifestyle interventions from the start of treatment.

FAMILY HISTORY

Assessing the family history in a patient with depression can assist in refining the diagnosis and identifying management priorities, and it may have utility in clarifying possible comorbid conditions. It can also be of importance to some patients in advancing understanding of their condition.

A meta-analysis of six twin studies quantified heritability of DSM-defined major depression at 37%, with an apparently higher rate in women than men[191]. However, DSM-defined major depression is likely to be a heterogeneous diagnosis, subsuming quite different depressive conditions, presumably with varying degrees of genetic contribution – including perhaps none. A higher concordance rate for DSM-defined major depression has been reported in melancholic than in non-melancholic cotwins, with the risk for major depression in the melancholic subset also being higher in monozygotic than in dizygotic twins[192].

Obtaining a family history of depression and/or bipolar disorder may weigh the likelihood of a melancholic condition in a patient with a diagnosis of depression (and may thus prioritize the use of antidepressant medications, in particular broad-action ones). Any such probability is further advanced if a family member is reported as having been hospitalized or committed suicide, or if a relative received (and, especially, benefitted from) electroconvulsive therapy.

For patients with a unipolar melancholic pattern, a family history of bipolar disorder does not by itself argue for diagnostic revision (to bipolar status). Any history of a relative receiving an antidepressant medication is of limited utility in refining the depressive subtype, in light of the wide use of these drugs across quite varying depressive (and other) conditions in recent times.

In depressed patients with prominent comorbid anxiety, a family history of anxiety or of relatives being distinct "worriers" (and no distinct family history of depression) may weigh a diagnosis of a non-melancholic depression and implicate anxiety as a highly likely predisposing factor. In such scenarios, management options include a sequential approach (i.e., treat the depression and then address the predisposing anxiety) or a transdiagnostic treatment model (e.g., prescribe an SSRI and/or initiate cognitive behavioral therapy) to address both conditions concurrently.

In depressed patients with certain hereditary-weighted comorbid conditions (e.g., attention-deficit/hyperactivity disorder, conduct disorder), the diagnostic probability of such disorders is advanced if there is a family history.

If a family history of a mood disorder is identified, then establishing medications that have been of benefit for a relative would appear theoretically useful in determining treatment choice for the patient. However, at the clinical level, such information does not seem to provide a distinct specificity "signal", and there are only few studies documenting a high concordance of antidepressant response in members of the same family[193]. However, a family history of depression and/or bipolar disorder has been consistently shown to indicate a greater likelihood of responding to lithium augmentation in those with treatment-resistant depression[194].

Pursuing a family history is initially best addressed by seeking such information from the patient, but a false negative report is not uncommon as a consequence of the family "hiding" such information from the patient, most commonly reflecting stigma or cultural factors.

While a corroborative witness interview with one or more

family members is generally wise for any initial assessment, it can be particularly important in such cases. One remains struck by the high frequency of a family member nominating a relative who was hospitalized for depression or committed suicide, or who even nominates himself/herself as having depression, when the patient has failed to report any family history.

Some instruments for the assessment of family history in patients with depression have been used for research purposes, such as the Diagnostic Interview for Genetic Studies[195] and the Family Informant Schedule and Criteria[196], but they take several hours to complete for an average sized family. Brief screening instruments have also been proposed, such as the Family History Screen (FHS)[197], which could be suitable for use in clinical settings. This screen is administered to a family informant, who reports about himself/herself and other biological relatives (parents, siblings and offspring). It takes about 5 to 20 min to administer, as each question is posed only once about all family members as a group.

The patient's concern about any role of genetic factors in contributing to his/her depressive condition allows a potentially therapeutic dialogue. For those with melancholia, information that its cause is likely to reflect genetic "hard wiring" (akin to developing a genetically determined physical disease such a type 1 diabetes) is often reassuring if they have previously judged their condition as reflecting a personality limitation, as well as advancing adherence to medication. For patients with a non-melancholic depression, dialogue about genetic "causes" may concede weaker direct and even indirect genetic links (e.g., a family history of anxiety predisposing them to increased anxiety and, in turn, to depression) or may allow the clinician to formulate the greater salience of psychosocial as against genetic factors. Some patients are intrigued by studies demonstrating gene-environment interactions, with such data allowing the clinician to inform them that depression should not be viewed as necessarily "all environmental" or "all genetic".

Overall, a comprehensive family history can assist diagnostic clarification and so lead to prioritized management modalities. While gathering such background information, the clinician is also afforded the opportunity to become aware of and moderate any concerns from the patient of "passing on" his/her mood disorder and so strengthen the therapeutic alliance.

EARLY ENVIRONMENTAL EXPOSURES

There is a consistent and growing evidence base supporting an association between early childhood adversity and subsequent depression. A systematic review[198], focusing on prospective cohort studies, calculated a pooled odds ratio between maltreatment in childhood and depression of 2.03, with population attributable fractions indicating that over one-half of global depression cases are potentially attributable to self-reported childhood maltreatment.

Specific questions continue to be explored, including associations of different types of early adversity with depression, causal mediators between early adversity and subsequent depression, and associations of early adversity with different features of depression[199].

Early life adversity includes exposures to either abuse (sexual, physical or emotional) or neglect (physical or emotional). Emotional abuse and neglect may be particularly strongly associated with depression[200,201]. Other parental factors, such as less warmth or over-involvement, that are associated with depression in young people, may be more subtle[202].

Timing of adversity may also be important, with increased vulnerability during particular developmental phases, although further work is needed to delineate such windows more precisely[203].

Causal mediators between early adversity and subsequent depression involve gene-environment interaction, and may lead to neurobiological changes (e.g., alterations in brain structures and connectivity, in neuroendocrine systems, and in inflammatory pathways) and cognitive-affective changes (e.g., hypervigilance to threat, emotional dysregulation, low responsivity to reward)[204]. Causal mechanisms may differ across threat-related and deprivation-related adversity[205]. Importantly, some predictors of depression after childhood maltreatment, e.g., interpersonal relationships, may be modifiable[206].

Early adversity has been associated with risk for depression onset, maintenance and recurrence. In addition, it has been related to an increased comorbidity of depression with other mental disorders, increased suicidality, and greater treatment refractoriness[199]. Population-attributable risk proportions suggest that eradication of childhood adversities would lead to a 22.9% reduction in mood disorders, with a higher reduction in early onset than in later depression[207].

Given this literature, assessing the history of childhood adversity is a crucial component of the comprehensive characterization of a patient with depression. However, a number of key issues must be kept in mind. First, reports of adversity are necessarily subjective, and there is the possibility of recall bias. Second, it is important to explore not only the events that occurred, but also key aspects of the subjective experience and meaning assigned. Third, personality and sociocultural background may influence both the experience and reporting of early adversity. Obtaining a history of childhood adversity that also includes a focus on coping and resilience may be useful in helping to address these issues.

The Childhood Experience of Care and Abuse (CECA) is a comprehensive interview measure for the assessment of childhood adversity[208]. Although it allows for detailed collection of information, it is time-consuming to administer and requires interviewer training. Moreover, information on its clinical utility is limited.

Several shorter self-report questionnaires have been used in research settings, and can be considered in clinical practice. These include a shorter self-report questionnaire based on the CECA (CECA.Q)[209], and the Childhood Trauma Questionnaire[210]. The short form of the Childhood Trauma Questionnaire has 28 items, assessing five domains of childhood adversity: emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse.

A number of measures are also available to assess the parent-

ing patterns of early caregivers. The Young Parenting Inventory (YPI) has been used in schema therapy, and provides a useful way of assessing early parenting styles, and how these might be related to an individual's early maladaptive schemas[211]. The inventory has 72 items that retrospectively assess perceived parenting experiences in respect of each key caregiver. This measure is designed to be used in conjunction with the Young Schema Questionnaire (YSQ)[212], which assesses 18 early maladaptive schemas.

The presence of early adversity may impact on treatment planning for depression in a number of ways. First, the presence of early adversity may be associated with premature treatment termination[213], perhaps because of a weaker therapeutic alliance. This association may be present across psychotherapies; any particular therapy would therefore need to consider how best to address this issue, in accordance with its own theoretical framework.

Second, specific evidence-based psychotherapies developed for patients with childhood adversity, such as trauma-focused treatment for depression, can be considered in order to ensure more specific targeting of the impact of such adversity. However, such interventions have been developed only recently, and the evidence base for their efficacy remains preliminary[214].

Third, the presence of early adversity may be associated with a decreased response to both pharmacotherapy and psychotherapy[215]. This does not impact choice of treatment *per se*, but rather indicates the need for robust management. Indeed, many patients with depression and early adversity respond well to pharmacotherapy and/or psychotherapy over time, and it is therefore key to encourage patients to stay in treatment[216,217].

RECENT ENVIRONMENTAL EXPOSURES

Environmental stressors can play a role in precipitating depression. The literature on this association has benefited from increasingly sophisticated study designs[218], and has included work on a range of stressors, studies of stress appraisal, research on vulnerable populations, and gene-environment interaction studies.

Stressors associated with depression include major life events (e.g., serious physical disease, natural disasters, intimate partner violence), chronic stressors (e.g., community violence, job insecurity, racial discrimination), and daily hassles. Other environmental factors reported to be associated with depression include negative aspects of the work environment[219], increased social media and screen time[220,221], unfavorable living environments[222], increased air and noise pollution[223,224], and higher ambient temperatures[225].

Individual response to stressors differs, in part due to differences in stress appraisal. Causal factors relevant to stress appraisal are genetic as well as environmental (e.g., previous exposure to stressors). The relevance of stressors differs across the lifespan, in part due to what is considered most stressful at a particular developmental stage[226,227].

Populations with higher vulnerability to stressors include patients in long-term care[228], caregivers, postpartum women[229,230], individuals with a housing disadvantage[231], immigrants and refugees[232]; lesbian, gay, bisexual and transgender people; and other stigmatized individuals[233]. Among caregivers at particularly high risk are those taking care of children with intellectual and developmental disabilities, or family members with dementia[234].

History of environmental exposures is therefore a crucial component of a comprehensive assessment in persons with depression, particularly those from vulnerable groups. Semi-structured interview measures such as the Life Event and Difficulty Schedule (LEDS)[235] are mostly used in research settings. They involve questions to assess objective aspects of the severity of life events and chronic stressors, as well as the person's subjective experience of how threatening or disruptive they were.

A range of self-rated checklist measures for assessing life events and chronic stressors may be suitable for use in clinical practice. These include the Psychiatric Epidemiology Research Interview (PERI) Life Events Scale (PERI-LES)[236], the List of Threatening Experiences (LTE)[237], and the Questionnaire of Stressful Life Events (QSLE)[238], each of which has been carefully validated by psychometric research.

The PERI-LES lists 102 events, and has been widely used in epidemiological research. The LTE was specifically developed in order to be shorter; it assesses 12 recent life events that are associated with long-term threat. The QSLE was developed to cover the lifespan; it assesses 18 life events that occur during childhood, adolescence and adulthood, noting the age at which they occurred and their impact. Thus, it may be a helpful clinical adjunct. Additional work to assess the clinical utility of such measures is warranted.

Targeted clinical questions regarding aspects of the work and neighborhood environment, including social media and screen time, may be useful as part of the clinical interview. There is also ongoing attention to the use of ecological momentary assessment to measure daily life stressors and responses. Although these are typically restricted to research settings, a range of apps can now be used by clinicians and patients to collect such information[239,240].

Mobile technologies have potential advantages over traditional diaries in several respects, including automating the process, allowing a more engaging experience, and providing real-time feedback to patients and clinicians[241]. In research settings, self-reports from ecological momentary assessment can be integrated with data from both embedded sensors and wearable biosensors. Few clinical studies have, however, focused on these technologies, and further work is needed to mould research approaches for clinical purposes[239,240].

A comprehensive clinical interview in a patient with depression should include a careful assessment of the patient's family and social networks, and the quality of relationships. The use of an interpersonal inventory is a key strategy in interpersonal therapy, but may be useful in ordinary clinical practice as well. The original Inventory of Interpersonal Problems comprised 127 items, but a number of shorter (e.g., 32-item) versions are now available, and may be helpful in assessing interpersonal behaviors[242].

The presence of environmental stressors may impact on treatment planning of depression in a number of ways. First, occur-

rence and perception of ongoing chronic stressors and daily hassles will inform the therapeutic work. In interpersonal therapy, the presence of interpersonal stressors is specifically targeted. In cognitive behavioral therapy, it may be noted that stressors and hassles trigger particular schemas or thoughts, which in turn lead to maladaptive emotions.

Second, for major stressors, trauma-focused treatment for depression may be considered[214]. Depression, like post-traumatic stress disorder, may be marked by intrusive and distressing memories of traumatic events, and these can then be targeted by trauma-focused interventions. However, such interventions have been developed only recently, and the evidence base for their efficacy remains preliminary.

Third, while a relationship between severe and enduring environmental stressors and less robust responses to pharmacotherapy and psychotherapy may be hypothesized, many patients with depression and environmental stressors do respond well to pharmacotherapy and/or psychotherapy over time. The presence of ongoing severe environmental stressors does not impact choice of treatment, but rather highlights the need for rigorous management that includes a clear focus on addressing such stressors.

PROTECTIVE FACTORS/RESILIENCE

There is a growing body of work on factors that protect against the onset or continuation of depression. This work includes development of theoretical frameworks for conceptualizing different kinds of protective factors, exploration of causal pathways and mechanisms that mediate increased resilience, and investigation of protective factors and resilience in particularly vulnerable populations.

Protective factors against depression range from those involving the individual and his/her family to those pertaining to the larger community. They include being employed[243], using positive coping strategies[244], having closer family relationships[245], residing where one's own ethnic density is higher[246], and having more social interactions[247].

Work on causal pathways and processes underlying resilience against depression is at a surprisingly early stage. Investigation of genetic and environmental factors is needed to delineate these pathways, which may involve specific cognitive-affective processes, neuronal circuitry and molecular mechanisms. Some findings have clear clinical relevance: for example, work on mechanisms underlying the protective impact of healthy diet and weight[218,248], reduced substance use[249], increased cardiorespiratory fitness[250], and positive work and living environment[219,222].

Importantly, there is a growing literature on the supports and "uplifts" associated with well-being in particularly vulnerable populations, such as postpartum women[251], caregivers[229], and lesbian, gay, bisexual and transgender people[252].

A comprehensive clinical interview in a patient with depression should include a history of protective factors and resilience against stressors. Nesse[253] has used the acronym SOCIAL to refer to key protective factors that should be addressed in such a history: Social resources, including friends, groups and social influence; Occupation, whether paid work or other social roles; Children and family, including relatives; Income and sources of material resources; Abilities, appearance, health, time, and other personal resources; and Love and sex in an intimate relationship.

For each of these resources, several follow-up questions may help the clinician to understand the person and his/her resources better. Thus, for example, are there secure ways to get sufficient amounts of this resource, how important is this resource to you, is there a gap between what you want and what you have, and what are the main things you are trying to do, get, or prevent in this area?

A number of self-report measures of resilience have been developed for use in research settings[254]. The Connor-Davidson Resilience Scale[255] may be of particular interest to clinicians, because it appears sensitive to change during treatment. A 10-item version of this scale has been studied in a range of populations; these items reflect the ability to tolerate experiences such as change or personal problems[256]. The Brief Resilience Scale[257] is focused on the ability to bounce back from the stressors of life; it is a 6-item scale that again could be considered for clinical use.

Self-report measures of perceptions of social support, such as the Multidimensional Scale of Perceived Social Support (MSPSS)[258], and perceptions of social rank, such as the McArthur Subjective Social Status Scale (MSSSS)[259], may also be useful for assessing protective factors, although further work on clinical utility is needed. The MSPSS is a 12-item self-report measure of subjectively assessed social support from family, friends and significant others. The MSSSS is a two-item visual scale of subjectively assessed social rank. The instrument comprises a drawing of two ladders on which people place themselves; the first assesses placement in society and the second evaluates placement in community.

Knowledge about protective factors may impact on the management plan for depression. Where protective factors are present, their maintenance can be encouraged, and conversely, where modifiable protective factors are absent, addressing this may be part of treatment targeting. There is, for example, a growing evidence base on the value of a healthy diet and of exercise in the management of depression[260].

Treatments of depression that include a focus on enhancing resilience can be considered[261-263]. There is an increasing evidence base, for instance, on the value of mindfulness-based cognitive therapy (MBCT) and acceptance and commitment therapy (ACT) in the management of depression, although further work is needed to determine which patients might benefit most from these therapies[264-266].

DYSFUNCTIONAL COGNITIVE SCHEMAS

Depressed patients tend to have dysfunctional cognitive schemas characterized by themes of loss, failure, worthlessness and rejection, which lead to negative perceptions of themselves, the

world and the future (the cognitive triad) and to negative information-processing biases[267,268].

The formulation of dysfunctional cognitive schemas has paved the ground for the development of cognitive therapy[268] and subsequent psychotherapeutic refinements subsumed under the rubric of cognitive behavioral strategies[269]. Cognitive restructuring is a central part of this approach: schemas can be modified in the course of psychotherapy to achieve a functional role[268,269].

In addition to a life history interview and the use of a diary, inventories are available to identify dysfunctional cognitive schemas[269]. Both detailed questionnaires, such as the Dysfunctional Attitude Scale[270], and brief checklists, such as the Schema Inventory[269], have been developed and validated.

In people with depression, cognitive negative biases are frequently associated with impaired ability to use past memories to mitigate current mood states[271]. Attention has been drawn on cognitive schemas that in depression hinder balanced levels of psychological well-being (i.e., environmental mastery, personal growth, purpose in life, autonomy, self-acceptance, and positive relations with others)[272]. A widely used and validated self-rating inventory, the Psychological Well-Being Scales[273], is geared to detecting such impairments.

Specific instruments for assessing euthymia (the presence of positive affects and psychological well-being, i.e., balance and integration of psychic forces, a unifying outlook on life which guides actions and feelings, and resistance to stress) are also available[272,274]. They include a brief self-rating scale (the Euthymia Scale) and a Clinical Interview for Euthymia[272,274].

It is a common assumption that assessment of dysfunctional cognitive schemas in depression is only relevant to the performance of cognitive behavioral therapies[269] or well-being enhancing psychotherapeutic strategies[272]. There is evidence to call such views in question.

In the setting of a depressive episode, exploration of cognitive biases may provide incremental information on challenging clinical issues such as suicidal ideation and mental pain[267,275,276], and the weight of stressful environmental circumstances[277]. For instance, severe hopelessness and lack of purpose in life may increase suicidal risk[267,275]. A patient who displays good symptom control with pharmacotherapy, but is exposed to major life events and has dysfunctional cognitive schemas, may be in need of additional psychotherapy.

Prospective studies have shown that more negatively biased self-referential processing is associated with a worse clinical course[271]. Conversely, the presence of unaffected areas of psychological well-being may predict a more favorable course[278].

The importance of assessing dysfunctional cognitive schemas increases when patients have achieved improvement of their symptomatology with pharmacotherapy and/or psychotherapy. Negative schemas may remain present, even though at a latent level, after remission from a depressive episode[267], and trigger negative automatic thoughts when they are activated by life events, leading to recurrences of illness.

Dysfunctional cognitive schemas have been reported to be predictive of the onset of a new depressive episode[279]. During the stage of remission, their assessment may suggest the use of cognitive behavioral therapies and/or well-being enhancing psychotherapeutic strategies to improve residual symptomatology and thus long-term outcome in depression[135].

Furthermore, dysfunctional cognitive schemas (e.g., "no matter what I do, it will not work", "I must always be in control") are likely to affect individual attitudes to medication[280]. If a patient has problems with adherence to antidepressant drugs, this is a clinical area that is worth exploring. The Drug Attitude Inventory is a brief questionnaire[280] that may facilitate such exploration.

In summary, assessment of dysfunctional cognitive schemas during the acute manifestations of depressive disorder, and particularly after remission, may demarcate major differences relevant to prognosis and treatment among patients who otherwise seem to be deceptively similar since they share the same diagnosis.

DISCUSSION

This paper provides a systematic description of the salient domains that should be considered in the currently ongoing effort to personalize the management of depression. The assessment instruments that have been developed for the evaluation of these domains are reviewed, with a special attention to their suitability for use in routine clinical practice. The preliminary research evidence on the relevance of each domain to treatment decisions is summarized, and the main unmet needs that have to be addressed by further studies are emphasized. Where the available evidence provides indications about how the management of depression can already be personalized to some extent in the current situation of uncertainty, these indications are highlighted.

The aims of this endeavor are: a) to reinforce the currently re-emerging interest in the personalization of the management of depression; b) to help in the identification of the variables to be considered when developing machine learning approaches or other complex prediction models in this area; c) to help in the selection of simple, preferentially self-report assessment instruments that can be included in comprehensive questionnaires or batteries of measures to be tested in large observational studies; d) to support clinicians in their attempts to personalize treatment of depression even today, in the absence of standardized decision tools validated by research.

One could argue that most clinicians are aware that depression is a heterogeneous syndrome, and that some of them have developed their own criteria for the selection of the optimal antidepressant and/or psychotherapy in the individual patient. These criteria are usually based on their personal experience, their interaction with experienced colleagues, or papers or meeting presentations focusing on the mechanisms of action of antidepressants, which often represent a guidance for clinical decision-making beyond the evidence provided by clinical trials[281]. So, the majority of clinicians are likely to welcome the ongoing effort to make the characterization of the individual patient who has received a

diagnosis of depression more systematic. This will more probably happen if different levels and modalities of characterization are envisaged, taking into account different real-world scenarios in terms of available resources, sociocultural context (including the needs of special populations such as ethnic minorities), organization of the health care system, and clinical traditions.

It is true that many clinicians do not like using formal assessment instruments in their ordinary practice, and that even formal diagnostic systems are not routinely used in clinical settings. However, our experience with the DSM-III and its successors is very telling in this respect. Although these diagnostic manuals are not frequently used in routine practice, several elements of their description of individual mental disorders have actually been incorporated by most clinicians in their personal prototypes of these disorders, which has arguably made the reliability of psychiatric diagnosis, although far from optimal, certainly better than it was in the 1970s. Something similar may happen if decision support tools are developed for the personalization of management of depression and other psychiatric conditions: although these tools may be formally used only by a minority of clinicians, several of their elements may be incorporated by most clinicians in their characterization of individual patients, making this characterization more reliable and useful than it is today.

Regulatory agencies have encouraged in recent decades the documentation of the "equivalence" of any newly developed antidepressant medication to an already consolidated one, implicitly discouraging the search for the "differences" between those medications and consequently the pursuit of a matching between the characteristics of the individual depressed patients and the individual available interventions. Not surprisingly, in clinical trials, the characterization of the recruited depressed patients is often somewhat coarse, mostly limited to the administration of a depression rating scale. Comparisons between antidepressant medication and psychotherapies, and between different psychotherapeutic techniques, have suffered from the same limitation, thus generating a research evidence which seems to suggest that almost all treatments for depression, being "equivalent", are interchangeable with each other. However, even in the presence of such a limited information from clinical trials, recent secondary analyses of available databases are documenting that there may indeed be clinical variables associated with the response to different antidepressant drugs, and or to antidepressant medication vs. specific psychotherapies[11,12]. The present paper aims to encourage and support these developments, which clearly require large patient samples (i.e., pooling the results of different studies using the same assessment instruments) and the use of innovative strategies of data analysis.

Our review also indicates that the management of patients with a diagnosis of depression can be personalized even today, in several respects, beyond the choice of a given antidepressant medication or psychotherapy. Several sections of the paper, such as those on neurocognition and on physical comorbidities, highlight that the modern management of depression is becoming increasingly complex, and that some of its components may already be reliably personalized in routine clinical practice on the basis of the available research evidence.

We would like to emphasize once again that the focus of this paper on clinical variables does not mean that we are undervaluing the currently ongoing effort to identify biological markers that may help in the personalization of treatment of depression. There may be different views about the current status of this line of research, but we think that no biological marker is as yet ready for use in routine clinical practice. On the other hand, we do believe that a more precise clinical characterization of depressed patients, beyond the syndromal diagnosis, may significantly support the development of those markers, as well as the identification of more homogeneous subtypes of depression.

The endeavor reflected in this paper is obviously a work in progress. We welcome comments and additions from the field that may be considered in a future update of this publication.

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Adaptation of evidence-based suicide prevention strategies during and after the COVID-19 pandemic

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Suicide is preventable. Nevertheless, each year 800,000 people die of suicide in the world. While there is evidence indicating that suicide rates decrease during times of crises, they are expected to increase once the immediate crisis has passed. The COVID-19 pandemic affects risk and protective factors for suicide at each level of the socio-ecological model. Economic downturn, augmented barriers to accessing health care, increased access to suicidal means, inappropriate media reporting at the societal level; deprioritization of mental health and preventive activities at the community level; interpersonal conflicts, neglect and violence at the relationship level; unemployment, poverty, loneliness and hopelessness at the individual level: all these variables contribute to an increase of depression, anxiety, post-traumatic stress disorder, harmful use of alcohol, substance abuse, and ultimately suicide risk. Suicide should be prevented by strengthening universal strategies directed to the entire population, including mitigation of unemployment, poverty and inequalities; prioritization of access to mental health care; responsible media reporting, with information about available support; prevention of increased alcohol intake; and restriction of access to lethal means of suicide. Selective interventions should continue to target known vulnerable groups who are socio-economically disadvantaged, but also new ones such as first responders and health care staff, and the bereaved by COVID-19 who have been deprived of the final contact with loved ones and funerals. Indicated preventive strategies targeting individuals who display suicidal behaviour should focus on available pharmacological and psychological treatments of mental disorders, ensuring proper follow-up and chain of care by increased use of telemedicine and other digital means. The scientific community, health care professionals, politicians and decision-makers will find in this paper a systematic description of the effects of the pandemic on suicide risk at the society, community, family and individual levels, and an overview of how evidence-based suicide preventive interventions should be adapted. Research is needed to investigate which adaptations are effective and in which contexts.

Key words: Suicide, suicidal behaviour, mental health, COVID-19, socio-ecological model, universal prevention, selective prevention, indicated prevention

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Approximately 800,000 people die of suicide each year[1], with a rate of 10.5 per 100,000 people (males: 13.7 per 100,000; females 7.5 per 100,000)[2]. This number is underestimated, due to variations in the methods of monitoring and death registration as well as cultural factors[2]. Suicide is the second leading cause of death among people aged 15-24 worldwide, and for each death by suicide 10 to 20 suicide attempts are estimated[1,3].

It has been reported that, during times of natural disasters, war, or epidemics such as the severe acute respiratory syndrome (SARS), suicide rates may momentarily decrease[4-6]. However, after the immediate crisis has passed, suicide rates increase[4,6]. The COVID-19 pandemic poses a special challenge to people around the world, as it affects both physical and mental health[7-15], economy[16], and social life[17,18].

Physical distancing[19,20] and lockdown measures[21], work disruptions[22] and school closures[23,24] have suddenly changed social life and daily routines. A major effect of these measures has been the reduction of social contacts, with a consequent increase in social isolation and feelings of loneliness, both in turn associated with increased anxiety, depression and suicidal behaviour[25,26].

Even if some positive outcomes related to staying at home have been highlighted, such as the adoption of healthier eating habits and the increase of sleep hours[27], reports show that movement restrictions aimed to stop the spread of the virus are causing a worldwide increase in family problems and domestic violence[28,29]. A systematic review[30] documented that family conflict is the most commonly reported precipitant of suicidal acts among children. A high prevalence of domestic violence victimization has been reported among people seeking treatment for self-harm in the UK[31]. Furthermore, intimate partner violence[32] and childhood abuse and neglect[33] have been found to be associated with suicide attempts.

As a consequence of the lockdown and other public health measures implemented in many countries, a global economic crisis at least as bad as the one occurring in 2008 is expected[16]. In the European Union, the unemployment rate is predicted to rise from 6.7% in 2019 to 9% in 2020[34]. In the US, more than 20 million people lost their jobs in April 2020. The unemployment rate increased to 14.7%, while it was 3.5% in February 2020, before the spreading of the virus in the country[35].

According to the United Nations, the pandemic hit the Latin America and the Caribbean in a period in which their economy was already weak and indebted[36]. Consequently, a 3.4% increase in the unemployment rate for 2020 (from an already high 8.1% rate in 2019) is forecast, resulting in an increase of 44.7 million people in poverty or extreme poverty. Furthermore, at least 11 million people will fall into poverty across East Asia and the Pacific[37], and 27 million people will face extreme poverty in Africa[38].

There is consistent evidence of an association between economic crises and increased suicide rates, especially in high-income countries, such as those in Europe and North America[39], and among men in working age or unemployed[40]. Analyzing data between 1970 and 2007 for 26 European Union countries, it has been estimated that every 1% increase in the unemployment rate

is associated with a 0.79% rise in suicides at ages below 65, with 60 to 550 potential excess deaths[41]. An estimate of the impact of the COVID-19 recession forecasts a 3.3% to 8.4% increase in suicide rate in the US[42]. However, previous research also shows that policy responses and governmental expenditures may be able to mitigate the impact of unemployment and economic crises on suicide rates[41,43].

According to the World Health Organization (WHO)[44], as of August 30, 2020, there were more than 838,000 confirmed deaths worldwide attributable to COVID-19. Other analyses suggest that the real death toll of the pandemic is higher than what official statistics show[45-47]. COVID-19 deaths lead to bereavement overload, because of the frequent multiple deaths within the families, and the impossibility to visit and assist the dying person or even join the funeral or ritual ceremonies due to the prohibition of public gatherings[48]. The accumulation of deaths and the fact that COVID-19 mortality mostly affects the elderly may induce, in the society, indifference and attitudes to overlook the deep pain and distress of bereaved families, further contributing to complicate the grief.

Reports predicting a rise in suicide rates as well as in mental health problems call for appropriate actions during and after the crisis[9,49-53]. Suicide is an unnecessary death and can be prevented by using evidence-based methods[54]. However, a broad approach according to the socio-ecological model is needed[55].

The aim of this paper is to systematically evaluate the influence of the COVID-19 pandemic on risk and protective factors for suicide at the societal, community, relationship and individual levels. Adjustments of evidence-based universal, selective and indicated suicide prevention strategies are recommended to provide guidance to clinicians, public mental health professionals, politicians and decision-makers.

IMPACT OF THE COVID-19 PANDEMIC ON RISK AND PROTECTIVE FACTORS FOR SUICIDE

According to the WHO, risk and protective factors for suicidal behaviour are categorized, in line with the socio-ecological model, into four levels: society, community, relationship and individual[55].

Risk and protective factors are likely to be influenced by the COVID-19 pandemic in different ways. Some risk factors, such as a family history of suicide[55], will not be affected at all. Many modifiable risk factors may be exacerbated, leading to an increase in the risk of suicide over time[56]. The prevalence of stress, sleep disturbances, anxiety, depression, alcohol and drug abuse, with suicide as their utmost consequence, is likely to increase[17,57,58]. Financial problems and worries about the uncertain future and unemployment will also contribute to an increase in suicide rates[16,17,53].

Protective factors for suicide have been described, such as effective mental health care, strong personal relationships, a supportive social network, life skills and ability to adapt, practice of positive coping strategies, and religious or spiritual beliefs[55,59].

Protective factors may be influenced positively or negatively, depending on the economic and social actions that will be taken by politicians and decision-makers in response to the COVID-19 pandemic. Strategies may be of varying effectiveness in different regions or countries. With an adequate and effective response, the pandemic may even represent an opportunity to strengthen suicide preventive efforts[50,52].

The expected effects of the pandemic on each risk and protective factor at the society, community, relationship and individual level are summarized in Tables 1-4.

Table 1 Risk and protective factors for suicide at the societal level and possible impact (positive or negative) of the COVID-19 pandemic on these factors

	Impact of COVID-19 pandemic	
Risk factors		
Economic downturn	• Increased financial problems, unemployment, worries about the future	–
Barriers to accessing health care	• Increased pressure on health care systems	–
	• Increased delegation of resources towards the acute response to the pandemic	–
	• Decreased focus on mental health care	–
	• Reduced help-seeking due to containment measures	–
	• Reduced help-seeking due to fear of being infected	–
	• Stigma related to the infection or to mental health problems	–
Access to suicidal means	• Increased buying and stockpiling of medications or firearms	–
Inappropriate media reporting	• Speculations on the reasons for specific suicidal acts; sensationalizing of pandemic-related suicides	–
Protective factors		
Effective mental health care	• Closure or reduced activity of mental health services	–
	• Increased resources for telemedicine and digital tools	+
Legislations concerning economy and social inequalities, welfare measures, health care accessibility, national prevention programs	• Decreased emphasis on prevention programs due to the economic impact of the pandemic	–
	• Increase of government funds for health policies in general	+
	• Increase of short- and/or long-term welfare measures	+
	• Opportunities to strengthen mental health care systems	+

+ = positive impact, – = negative impact

Table 2 Risk and protective factors for suicide at the community level and possible impact (positive or negative) of the COVID-19 pandemic on these factors

	Impact of COVID-19 pandemic	
Risk factors		
Discrimination	• Deprioritization of mental health	–
Stresses of acculturation and dislocation	• Increased stress in individuals currently fleeing from conflicts or staying in refugee camps during the pandemic	–
	• Decreased effectiveness of containment measures in such settings	–
Protective factors		
Social integration, social living conditions, local prevention, rehabilitation programs	• Deprioritization of preventive activities	–
	• Opportunities to increase resources for preventive activities	+

+ = positive impact, – = negative impact

Table 3 Risk and protective factors for suicide at the relationship level and possible impact (positive or negative) of the COVID-19 pandemic on these factors

	Impact of COVID-19 pandemic	
Risk factors		
Loneliness	• Increased isolation and lack of social support	–
Relationship conflict, discord, loss	• Increased conflict and discord as additional strains are put on relationships	–
	• Decreased opportunities for contact with people outside home who can provide support	–
	• Loss of significant others	–
Trauma and abuse	• Increased interpersonal violence and abuse within families or households as people are confined to their homes	–
	• Decreased access to help	–
Protective factors		
Strong personal relationships	• Reduced opportunities for communal experiences and activities	–
	• Improved relationships through new ways of connecting or having more time available to connect with other people	+
	• Improved relationships in families due to more time available to do activities together (both children and adults)	+

+ = positive impact, – = negative impact

EVIDENCE-BASED SUICIDE PREVENTION STRATEGIES DURING THE COVID-19 PANDEMIC

The universal-selective-indicated (USI) model, in which different populations are targeted depending on the level of suicide risk, is mostly used for the categorization of suicide preventive interventions[60,61].

Universal suicide preventive strategies target everyone in a defined population (e.g., a nation, a county, a local community). They are aimed at increasing awareness about suicide and mental health, removing barriers to care, promoting help-seeking behaviours and protective factors such as social support and coping skills, and mitigating the impact of economic downturns. Examples of universal interventions include awareness campaigns and educational programs, limiting access to suicide means, guidelines for responsible media reporting, and governmental measures to address economic crises.

Selective suicide preventive strategies are meant for specific groups who are at increased vulnerability for suicidal behaviour, such as people with mental health problems, alcohol and drug abusers, prisoners, victims of physical and sexual violence, members of the lesbian, gay, bisexual, transgender and queer (LGBTQ) community, migrants, and the bereaved. Screening programs in health care or other facilities, gatekeeper training for frontline helpers, psychological support and treatment of mental health problems and substance abuse in people who do not display signs of suicidality as yet, are all considered selective suicide preventive interventions.

Indicated suicide preventive strategies target high-risk individuals who are displaying signs of suicidal behaviour, and are aimed at timely and appropriately assessing and dealing with the suicide risk using case management, referral to psychiatric treatment and care, skill-building interventions and support groups.

The suicide preventive interventions proven to be most effective include: restriction of access to lethal means, policies to reduce harmful use of alcohol, school-based awareness programs, pharmacological and psychological treatment of depression, chain of care and follow-up of at-risk individuals, responsible media reporting, and policy responses to mitigate the impact of economic downturns[55,62,63]. Other interventions, such as gate-

Table 4 Risk and protective factors for suicide at the individual level and possible impact (positive or negative) of the COVID-19 pandemic on these factors

	Impact of COVID-19 pandemic	
Risk factors		
Mental disorders (anxiety, depression, post-traumatic stress disorder)	• Increased incidence of mental disorders	–
	• Worsened symptoms of existing mental disorders	–
	• Reduced treatment adherence	–
Financial problems	• Job or financial loss due to the economic crisis	–
Hopelessness	• Increased hopelessness through potential loss of friends and family, loss of job, and general uncertainty	–
Harmful use of alcohol/drugs	• Increased use of alcohol/drugs	–
Chronic pain	• Worsened chronic pain through reduced care and increased stress	–
Protective factors		
Life skills and lifestyle practice: problem solving, positive coping, ability to adapt	• Increased awareness of self-care strategies and positive coping through media and Internet support	+
	• Increased time to practice self-care	+
	• Adoption of maladaptive coping strategies (e.g., denial, self-blame)	–
Religion or spiritual beliefs	• Difficulties in participating in religious ceremonies due to containment measures	–
	• Increase in individual practice of religion or spirituality at home	+
Food and diet	• Increased opportunities for a healthier diet	+
	• Negative impact on diet through irregular eating patterns and frequent snacking	–
Physical activity	• Decreased physical activity due to containment measures	–
	• Increased physical activity due to greater availability of leisure time	+
Sleep	• Improved sleep patterns through new work routines	+
	• Poor sleep due to worries, increased anxiety and stress	–

+ = positive impact, – = negative impact

keeper training, are also theoretically valid, even if conclusive evidence of their effectiveness on reducing suicidal behaviour is not yet available[64].

All preventive strategies require adjustments and adaptation in the light of the new challenges that are posed by the COVID-19 pandemic.

Universal interventions

Mitigating the impact of unemployment, poverty and inequalities

Unemployment, poverty and inequalities represent major risk factors for suicide which are considerably exacerbated by the current global crisis. Studies from high-income countries on the association between social protection policies and suicide rates[65] show that the various policies may have a different impact.

Active labour market policies, including job search assistance, job training and subsidized employment, have a positive impact on health and quality of life[66]. More specifically, at the individual level, job search assistance programs with a psychological component, such as improving self-confidence and self-efficacy, have been found to exert positive effects on mental health, such as reduced depression, anxiety and distress symptoms. At the national level, increases in government spending on active labour market policies have been shown to reduce the effect of unemployment on suicide rates[41,67,68]. It has been calculated[41] that, for each US$10 per person increased investment in these policies, the effect of unemployment on suicides was reduced by 0.038%. In another study, it has been reported that the same amount of increased spending would correspond to a 0.026% decrease in male suicide rate[67]. If spending for active labour market policies were higher than US$190 per person per year, rises in unemployment would have no effect on suicide rates[41]. These findings advocate for specific governmental actions.

In the US, the maximum allowable unemployment benefit was found to be associated with a reduced impact of economic downturns on suicide rates[69]. Similarly, in European countries, the unemployment protection system was reported to mitigate the negative impact of unemployment on suicide rates[70]. In this context, the adoption of policies related to universal basic income (UBI) during and in the aftermath of the COVID-19 pandemic could significantly decrease its social and psychological costs. UBI is defined as "a periodic cash payment unconditionally delivered to all on an individual basis, without means-test or work requirement"[71]. Interventions which unconditionally provided substantial cash transfers to individuals or families have been found to have positive effects on educational participation and on some health outcomes, including mental health[72,73]. In Indonesia, a cash transfer program providing between $39 and

$220 per person annually was found to reduce the yearly suicide rate by 0.36 per 100,000 people, corresponding to an 18% decrease[74].

Housing loss may represent a significant trigger for suicidal crisis. For example, eviction- and foreclosure-related suicides doubled between 2005 and 2010, during the US housing crisis[75], and significantly contributed to the increase of suicide rates[76]. Housing interventions, such as relocating disadvantaged people to less deprived areas or improving physical housing conditions, are reported to be successful in reducing mental health problems[77]. Policies to subsidize housing costs have been used during the pandemic in some countries and their effect on mental health should be evaluated.

Restricting access to lethal means of suicide

There are few reliable data on suicide methods. One global overview[78] showed several differences in preferred suicide means between countries and even between different regions in the same country, with hanging, self-poisoning and firearms as the most frequently used methods. A recent systematic review[79] of 16 studies confirmed that hanging (81.3%), firearms (56.3%), poisoning/overdose (43.7%) and jumping from a height (18.7%) are the most common reported suicide methods.

In most European countries, hanging is reported to be the predominant method of suicide. Pesticide self-poisoning accounts for around 20% of suicides globally and 48.3% of those in low- and middle-income countries in the Western Pacific region[80]. Firearms account for 50.5% of suicide deaths in the US, followed by suffocation (28.6%) and self-poisoning (12.9%)[81]. Although jumping from a height is a relatively uncommon method of suicide in most countries, it plays an important role in urban settings such as Hong Kong, Singapore, Luxembourg and Malta[78,82,83], and is considered a highly lethal method[84].

Restricting access to lethal means of suicide entails various points of application, such as limitations in the size of packs of medications, use of antidepressants which are not dangerous in overdose, safety procedures and safer room design for hospitals and prisons (e.g., not wearing belts or shoes with laces, minimizing the number of suspension points available for hanging), more stringent firearm regulations, installation of barriers and safety nets at jumping sites, and limitation of access to highly lethal pesticides[62,85]. The effectiveness of these strategies is supported by robust evidence[63]. Planned suicidal acts may be delayed if people are precluded from implementing the chosen method, increasing the chance of suicide prevention[86]. Moreover, in impulsive suicidal acts, people tend to use the most readily accessible method. If there are no lethal methods available, the suicidal crisis may pass or the use of a less lethal method may result in non-fatal outcomes.

During the COVID-19 pandemic, policies restricting the access to suicidal means should be reinforced. It is possible that an increase of stockpiling of medications occurs in order to prepare for a possible shortage[87]. Furthermore, an increased purchasing of firearms due to worries about an increase in crime generated by the pandemic may take place[88,89].

Governments, at the national and regional level, are advised to restrict and increase monitoring of sales of lethal means for suicide, such as firearms and pesticides. Additionally, temporary restrictions on the amount of some medications (e.g., analgesics) bought per person should be considered. Public awareness strategies and policies to ensure or reinforce safe storage of firearms and medications at home as well as pesticides at warehouses are of importance[90]. Public awareness should be increased by informing about the significance of reducing access to lethal means of suicide[49].

Policies to reduce harmful use of alcohol

Evidence exists that alcohol use is associated with increased risk of suicidal behaviour[91-93]. Reducing harmful use of alcohol through policies and interventions has been shown to reduce suicide rates effectively[94,95], especially for males. The best example was probably the restructuring of the former Soviet Union (*perestroika*), when heavy restrictions of alcohol use were introduced: between 1984 and 1990, suicide rates decreased for males by 32%, in comparison with 8% in Europe[96].

The WHO global strategy to reduce the harmful use of alcohol identified ten areas for national action: leadership, awareness and commitment; health services' response; community action; drink-driving policies and countermeasures; availability of alcohol; marketing of alcoholic beverages; pricing policies; reducing the negative consequences of drinking and alcohol intoxication; reducing the public health impact of illicit alcohol and informally produced alcohol; and monitoring and surveillance[97].

Psychosocial crises boosted by the COVID-19 pandemic, such as family conflicts, unemployment and financial problems, may trigger alcohol abuse, that in turn enhances suicidal risk by increasing impulsivity, aggressiveness, loneliness and hopelessness[98].

Governments, at the national and regional level, are encouraged to monitor the consumption of alcohol during the pandemic; increase public awareness about the negative outcomes of alcohol use; defuse the myth that alcohol consumption may protect from COVID-19 infection[99]; and restrict availability if necessary.

Increasing follow-up consultations of individuals at risk for alcohol abuse, promotion of safe drinking[49], and online tools for monitoring alcohol intake may counteract the increase of harmful alcohol use.

Public awareness about mental health and suicide

Over the last decades, public attitudes have changed, showing improved mental health literacy and higher acceptance of professional help for mental health problems[100]. This is most probably at least in part due to international, national and local mental health awareness campaigns. Nevertheless, a similar improvement has not been observed in stigma and discrimination related to mental health problems[100,101].

As a result of the increasing concerns for the mental health consequences of the COVID-19 pandemic, international organizations, such as the WHO[102] and the United Nations[103], and national and local authorities[104,105] are releasing resources and guidelines for the promotion of mental health and raising awareness about the potential increase of mental health problems and suicide during the pandemic.

Besides increasing mental health knowledge and literacy, key aspects of suicide prevention resources should empower the general population with coping skills by providing useful advice, promoting help-seeking behaviour and making information available about where to get help.

School-based interventions

Young people are a vulnerable group for risk of suicide. Suicide is the second leading cause of death worldwide among the 15-24 year old[1]. Evidence suggests that 13.4% of children and adolescents have a diagnosed mental disorder[106]. A much higher proportion reports mental health symptoms such as depression or anxiety (30.4% and 23.3%, respectively)[107,108].

Strong evidence for the effectiveness of school-based interventions has been shown in increasing help-seeking behaviour[109,110], enhancing awareness about mental health and risk and protective factors for suicide[110-113], and decreasing the incidence of suicide attempts and severe suicidal ideation[111,113].

During the COVID-19 pandemic, schools have frequently been closed or physical attendance has substantially decreased, which has been reducing or completely stopping school-based mental health interventions[23,24,114]. Schools have a major role in children and adolescents' social development. During the pandemic, peer relationships, which are important to foster autonomy and independence in adolescence, are substantially affected. The increased use of social media, substituting real-life peer relations, may result in pathological Internet use[115], a higher risk of cyberbullying[116] and other negative health outcomes, such as anxiety, depression and suicidality[117]. Feelings of anxiety and distress may also arise as a consequence of the uncertainty about final exams and future school re-opening.

Governments, at the national and regional level, are encouraged to resume school-based interventions as soon as schools re-open. Availability of online resources for youth mental health, such as helplines and information about how to get support, should be increased. Additionally, teachers and parents are advised to discuss the pandemic and feelings about it with children and adolescents.

Responsible media reporting

Irresponsible media coverage may promote suicidal behaviours in recipients by sensationalizing suicide or paying unproportioned attention to spectacular suicides[118,119]. However, protective effects may be established through responsible reporting of suicide as well as public education[63,120].

Basic principles of responsible media reporting include avoiding to sensationalize or normalize suicide, especially when reporting celebrity suicides, limiting the description of methods and locations, avoiding to show photos, videos and social media links, and providing information about the effectiveness of suicide prevention and where to get help[121].

During the COVID-19 pandemic, specific additional considerations should be made when reporting increased suicide risk, suicide rates, or an individual suicide, especially if it is related to the pandemic[122]. In this sense, oversimplifications of the issue and speculations on what is the reason of the specific suicidal act should be avoided. Instead, the public should be informed about the complexity of suicidal behaviour, in which biological, psychological, social and environmental factors interplay, and about preventive and treatment possibilities.

During the pandemic, it is advised to raise awareness of journalists about existing WHO guidelines for responsible media reporting[121], and develop and disseminate locally adapted guidelines to reduce sensationalizing of suicide, especially if pandemic-related[49,122].

The time spent on media to search for information may increase significantly during crisis events, and this increased media exposure has been shown to enhance distress. Thus, it is recommended to limit media exposure during the pandemic[123].

Access to health care

Appropriate and accessible care for mental disorders, substance use, and physical illnesses is effective in reducing suicide risk[55,124]. Due to increased pressure on the health care system during the COVID-19 pandemic, an adequate care for mental disorders may be deprioritized. An additional reduction in access is likely due to closed practices and increased sick-leave of mental health care professionals.

The mental health problems and suicidal behaviour of frontline health care professionals, first responders (e.g., ambulance operators) and other health care workers may increase due to their crucial role during the pandemic, associated with high stress[5,17,125-129].

Actions are required to provide financial support to mental health services, ensure accessibility, increase staff, develop digital services, and provide tools for self-care online. Moreover, the local health care systems are encouraged to plan and adjust resources to maintain or improve treatment and follow-up of patients with mental disorders, and adopt and reinforce the use of telemedicine[52,130].

Selective interventions

Gatekeeper training

Gatekeeper training is a widely used strategy to reduce suicide risk[64], even if supportive evidence for its effectiveness mostly

comes from uncontrolled studies[131]. It entails training of key people, such as teachers, first responders, or human resource managers, to identify suicidal individuals and refer them to appropriate services[55,64].

Most of the already trained gatekeepers probably belong to frontline responders (e.g., general practitioners, nurses, officers) and, for this reason, they are full-time involved in the emergency battle against the virus or even sick themselves. On the other hand, gatekeepers belonging to the general population (e.g., religious officials, teachers) may be prevented to identify and interact with suicidal individuals due to lockdown measures. Furthermore, a decrease in the availability of gatekeepers may be the result of paused or reduced gatekeeper training during the COVID-19 pandemic.

During the pandemic, continued training online or in person, in line with local regulations about appropriate physical distance, should be ensured. Also, actions to increase the number of volunteers to participate in the programs is advised. Successful examples of the adaptation of standard gatekeeper training to the current situation are the Alliance Project[132] and the Zero Suicide Alliance[133], that are offering brief online trainings. The Mental Health First Aid[134] is an Australian gatekeeper training evolved into global initiatives, and now organizes online courses. It proved to be effective in improving knowledge, attitudes and helping behaviours towards adults with mental health problems[135].

Interventions for vulnerable groups

Individuals with psychiatric conditions are recognized as those most severely impacted by the psychosocial effects of the pandemic[136-138] and, due to the existing association between psychiatric disorders and health risk behaviours (e.g., smoking, obesity, alcohol use, low adherence to precautionary measures), they are also at increased risk of infection and its complications. Outreach interventions and a closer follow-up of patients with severe psychiatric disorders may allow to enhance treatment adherence and to timely identify and intervene on psychiatric emergencies. The creation of online networks may provide adequate social support and mitigate the temporary unavailability of community services.

Besides increasing the unemployment rate[42,139], the current global crisis is exacerbating existing socio-economic inequalities. Indeed, migrants, different cultural and ethnic minorities as well as socio-economically disadvantaged groups have been found to be less able to adhere to "stay at home" recommendations[140] and, consequently, to be more affected by the virus[141-143]. These groups largely overlap with those at increased risk for suicide.

Specific interventions are needed for these vulnerable populations aimed at increasing access to health care and reducing socio-economic inequalities through labour and welfare policies. Reinforcing crisis helplines may be also pivotal to timely identify and intervene on emerging psychosocial crises potentially leading to suicidal behaviour.

Another important effect of this global crisis is the increase in domestic and intimate partner conflicts and violence[29]. Public health actions to prevent domestic violence are needed and should be adapted to the current situation[144]. Surveillance methods through text messages, hidden smartphone notifications or other methods that allow victims of domestic violence to safely ask for help should be used. Police and health records can be linked according to local legislation to timely identify individuals at risk. Adequate surveillance should be ensured through routine inquiries and remote consultation with the health care system. To mitigate and prevent the negative mental health impact, victims of domestic and intimate partner violence should be referred to online or in person evidence-based interventions, such as those based on cognitive behavioural therapy[145].

COVID-19 patients[10,146] and frontline health workers[147,148] are also particularly vulnerable to negative psychological outcomes. Therefore, interventions to increase mental health awareness, promote effective coping skills, reduce primary and secondary post-traumatic stress disorder (PTSD) symptoms and decrease social isolation should be implemented. Mental health screenings and assessments should be scheduled, and referral to evidence-based treatments be ensured.

Bereavement from COVID-19 may be very challenging[149-152]. Traumatic death, a lack of preparation for the death, and low social support[153,154] have been described as risk factors for complicated grief, which in turn results in increased risk for suicidal behaviours, independently from other psychiatric disorders such as major depressive disorder and PTSD[155,156].

Finally, the previously described impact of the pandemic in increasing social isolation and loneliness becomes particularly concerning when considering older people. A recent study[157] reported that being 59-80 years old was significantly associated with higher levels of depression, anxiety and PTSD symptoms during the pandemic, compared to the younger age groups. Phone calls and online platforms may represent valuable instruments to mitigate the sense of loneliness and social isolation, even if there might be disparities in access to or literacy in digital resources among older people[158].

Indicated interventions

Treatment of mental disorders

Strong evidence for the effectiveness of pharmacological and psychological treatment of psychiatric disorders in order to reduce suicidal behaviour exists[55,63,159-163]. National and regional pharmaco-epidemiologic studies show a protective effect of the prescription of antidepressants on suicide[164]. Antidepressants have been reported to decrease suicidal thoughts and behaviours in adult and geriatric patients[165,166]. Literature consistently reports anti-suicidal effects of lithium, both in clinical samples and in the general population[167,168]. Other mood stabilizers, such as valproate, lamotrigine and carbamazepine, may also have an anti-suicidal effect[169]. It has been reported that second-

generation antipsychotics are effective in reducing suicidal risk in patients with schizophrenia[170-172]. Promising results[173,174] are reported for the use of ketamine: a single infusion was found to rapidly reduce suicidal thoughts, within one day and for up to one week, in depressed patients with suicidal ideation[175], but long-term effects are not yet evaluated.

Among psychotherapies, individual cognitive behavioural therapy has been reported to significantly reduce suicidal thoughts and behaviour compared to treatment as usual[162,176]. In a recent meta-analysis[177], dialectical behaviour therapy was found to be effective in reducing suicidal behaviour and re-attempt, especially in females with borderline personality disorder. Brief interventions, focused on the identification of warning signs, coping skills and available social support, professional help and crisis planning, have been shown to be effective in preventing suicidal thoughts and behaviour[178,179]. The brief intervention and contact (BIC) implemented in the WHO Multisite Intervention Study on Suicidal Behaviours (SUPRE-MISS) randomized controlled trial showed a significant decrease in suicide after 18-month follow-up in comparison with treatment as usual[180].

During the COVID-19 pandemic, containment measures affect treatment availability, as practices and other psychiatric services may be closed[181]. A worsening of symptoms of mental disorders – such as anxiety, depression and PTSD – among psychiatric patients, and an increase in mental health disorders in the general population, including first responders, may occur[13,14,17,49,182]. Consequently, suicidal behaviour may increase[9].

Due to the likely rise in mental disorders, mental health care providers are advised to continue treatment and assessment in person (if possible) or online and increase assessment of at-risk individuals[49]. The local and national health care systems are encouraged to offer guidelines for remote assessment of mental disorders and suicide risk. Since untreated individuals have a higher risk of suicide[55,183], appropriate care should be provided for anxiety, depressive and PTSD symptoms, alcohol and drug abuse, psychotic and other psychiatric disorders. Furthermore, online interventions to manage psychiatric symptoms should be offered.

Chain of care and follow-up

Chain of care is an integrated model in which the effectiveness of care is ensured by the overall coordination between different services and activities[184]. In this model, primary care, hospitals and community services are linked and integrated through local agreements to create pathways for the identification, treatment and management of specific disease or long-term conditions.

A continuous and functioning chain of care, with adequate follow-up of patients, has been shown to be effective in reducing suicide for at-risk individuals[63,180]. Due to the increasing demands on health care systems during the COVID-19 pandemic, a disruption of the chain of care and delayed follow-up of psychiatric patients is likely to occur, with potential negative effects on suicide risk.

Critical in continuity of care is the promotion of treatment engagement. Providing patients with psychoeducation regarding the importance of follow-up treatment and an outpatient appointment within the first week after discharge[185,186] are recommended strategies for engaging suicidal individuals. Post-discharge follow-up contacts, including phone calls, postcards, letters and technology-based methods (e.g., e-mails and texting) have showed promising results in enhancing treatment adherence and reducing suicidal behaviour[187,188].

Appropriate actions are required to develop new helplines and reinforce the existing ones for suicidal patients and individuals affected by the pandemic and to increase the training of volunteer workers in mental health. The use of telemedicine appears to be critical in maintaining an effective chain of care surrounding suicidal patients.

TELEMEDICINE DURING THE COVID-19 PANDEMIC

During the ongoing pandemic, mental health care faces significant challenges related to staff shortages, decrease of resources, and the risk of health care services becoming hotspots for contagion. Telemedicine is one of the best tools to tackle these challenges and simultaneously address the expected increase in demand for mental health care.

Telemedicine is defined as the remote delivery of health care with the aid of technology[189]. It usually includes two-way audio and video remote communication[190] between patients and health care professionals. However, other forms, such as self-help applications or websites, may support the tele-mental health care and offer additional opportunities for treatment[191].

There are several advantages of expanding telemedicine in mental health care. First, psychiatric diagnosis and treatment constitute a reasonable setting for telemedicine because they are conducted through interviews as opposed to physical assessment[192]. Second, costs of telemedicine may be lower compared to traditional mental health care[193,194]. Third, other barriers of traditional approaches to mental health care, such as stigma, are reduced[194,195]. The potential to increase care has also been recognized for suicide prevention efforts[196,197].

Barriers that limit the use of telemedicine include the lack of access to the Internet[198], the required electronic devices, or the technological capabilities of recipients, especially individuals in old age or with serious mental health illnesses[199]. The coverage of telemedicine through insurances may be limited[200], and integration into the health care systems is required to ensure the broad availability of digital medical services to the population[201,202].

Legal and ethical challenges are related to the storage and sharing of sensitive personal data, security of the communication with patients, privacy for the patient at the location where the remote consultation is held, and difficult choices in situations in which a traditional in-person visit is required to achieve the best treatment effects[191,196]. The remote management of patients with acute suicide risk poses very significant ethical questions and should be managed by involving the family and the

social network. Direct communication with emergency services should be available when the attempts to motivate the suicidal person to seek help are unsuccessful. Legal regulation for telemedicine is missing in most countries and is urgently required.

There is some evidence for the effectiveness of technology-enhanced suicide preventive interventions[203]. Unguided digital self-management interventions have shown to reduce suicidal ideation and suicide-related symptoms in individuals with severe psychiatric difficulties[194] or self-harm[204], while others showed reductions of suicidal ideation, but not of self-harm or attempted suicide, compared to wait-list controls or self-management interventions[205-207]. Technology-enhanced suicide preventive interventions may be more effective in younger people, due to their higher acceptance and affinity with technology[208]. Brief texting contact has shown potential to reduce re-attempt after a suicide attempt through initiating contact with crisis support[209].

The agreement of psychiatric diagnoses between in-person and telemedicine assessment appears to be high, indicating its potential utility[210]. Additionally, telepsychiatry has been found to be cost-effective[211] and appears to be useful as crisis intervention[212]. Hence, various advantages of implementing telemedicine and some evidence for its use in suicide prevention are available. Due to the limited methodologies used in previous studies about telemedicine[205], more high-quality research is required.

During the COVID-19 pandemic, it has become apparent that a large number of visits can be managed on distance[213], that the infrastructure for telemedicine is widely available[213,214], and that the pandemic itself represents an opportunity to expand the use of telemedicine[215]. It has been reported that telepsychiatry may be efficient to screen for mental health symptoms in COVID-19 patients and to optimize treatment[216], or that online assessments are helpful prior to appointments and as follow-up[217]. Continued care is, thus, enabled in a time when the health care systems are overwhelmed[218].

Existing and additional challenges to utilizing telemedicine in mental health care have become apparent as well. New protocols for assessment and therapy must be established quickly[213,217]. Privacy, confidentiality and access issues remain[217]. Quiet places and headphones are required and, in case of limited privacy, yes/no questions should be adopted[217]. These issues may affect certain people more than others. For example, lower socio-economic status may result in smaller living spaces and consequently reduced privacy. Lack of access to electronic devices may occur for elderly patients[217]. Disabilities and technology illiteracy pose a major obstacle to access[219,220]. Social aspects of traditional medical approaches are lost with telemedicine, and this may be a significant problem for some categories of psychiatric patients[221].

The continued evaluation of telemedicine is essential. The infrastructure requires improvement and growth to counter the unique challenges during the pandemic in the short term. The prospect to sustain these changes in the long term and improve care[222,223] is a valuable opportunity that should guide the efforts of policy-makers. Even though evidence for telemedicine designed specifically for suicide prevention is limited, some advantages have already been highlighted[197,203].

CONCLUSIONS

The continued and strengthened implementation of suicide preventive measures during and after the COVID-19 pandemic is of global importance. Suicide prevention should be a priority for policy-makers and health care professionals alike and should not be postponed while facing this pandemic. This paper aims at informing the scientific community, health care professionals, policy-makers and politicians about plausible adaptations and/or reinforcements of evidence-based suicide preventive strategies, which should be undertaken due to the severe impact of the pandemic on everyday life.

The analysis of risk and protective factors shows that most of them are affected and the pandemic may have both positive and negative impacts. However, the negative effect appears to be greater. Thus, the foreseen increase of mental health issues and suicides[9,13-15,17,49-53,224] is likely to happen.

Selecting suicide prevention strategies based on strong evidence remains essential throughout this crisis. However, we face unique challenges due to the need of urgent measures and lack of evidence that indicates how interventions should be adapted. The adaptations and reinforcements may be more effective in some regions or countries compared to others, due to differences in local suicide rates, interventions already in place, the status of the local health care and mental health care system, or local and national policies. Confirmatory research is needed to investigate which adaptations are effective taking the different cultural, economic and health care context into account.

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COVID-19 health anxiety

Much has been written about the mental health consequences of the COVID-19 pandemic. The anticipated need to develop new services for post-traumatic stress disorder, for suicide prevention and for prolonged grief have filled many paragraphs of newspaper space, and these have been reinforced by weighty papers from experts across the medical disciplines[e.g.,1]. But there is something missing from these accounts – health anxiety – and this cannot be ignored.

It is perhaps easy to explain why. Health anxiety is a relatively new concept. It derives from the much better known condition called hypochondriasis. The reason why health anxiety has been separately identified is that it is primarily an anxious disorder, whereas hypochondriasis covers a much larger range, including significant depression and even psychotic symptoms such as delusions.

People with pathological health anxiety have excessive fear of getting, or having, a disease[2]. But, as we all know in the health professions, anxiety itself leads to psychological and bodily symptoms that, all too frequently, are misinterpreted as evidence of organic illness. These are present across the wide range of disease and can simulate disorders in every medical speciality, which is why they were in the past included under the generic title of "medically unexplained symptoms". So, in the case of people with health anxiety preoccupied with respiratory disease, somatic symptoms such as cough, dizziness, difficulty in getting one's breath, and need to breathe more rapidly, are all present. But of course, most of us, in the present circumstances, would at least contemplate the possibility that, if we had these, they might be incipient coronavirus symptoms.

This is where COVID anxiety differs from ordinary health anxiety; at present it is probably justified and so cannot be regarded as pathological. But it is only a matter of degree. In the middle of the pandemic it is perfectly reasonable for people experiencing these symptoms to attribute them to coronavirus infection. But what happens later? COVID-19 is not going to disappear suddenly. There will be a long period, possibly extending over several years, in which there will still be the danger of infection, and this is when pathological COVID anxiety will occur.

Every symptom, no matter how small, will be given sinister significance. In classical health anxiety, sufferers become their own monitors of health, but, as they are never convinced that they are doing the job properly, they also need reassurance from relatives and friends, and often will present their symptoms to medical personnel. Because there is some doubt over the accuracy of tests, even a negative result for COVID-19 will not remove their fears. Once established, health anxiety leads to continued vigilance, often associated with checking of the body, repeated requests for reassurance, and browsing on social media, followed by the vicious cycle of increased anxiety, greater symptomatology and more misinterpretation.

It is difficult to predict what will happen with the COVID pandemic in the future, but all the evidence points towards a likely second outbreak during this autumn. If so, this will be a peak period for pathological health anxiety. In the absence of a vaccine, there will continue to be fear of getting infected, even in those who may have already been tested, as even those who have tested positive will not know if they still have immunity.

Those with severe health anxiety are likely to become abnormally avoidant, continuing to isolate and practise repeated hand washing, checking their body temperatures, respiratory function, and even testing their ability to smell (as this is a recognized symptom of the infection) over and over again. There is considerable overlap between obsessional symptomatology and health anxiety[3], and a relentless concern with safety seeking behaviours may come to dominate some people's lives.

What can be done to prevent or reduce the impact of COVID health anxiety? We do not yet know, but there are worrying signs that handicap its prevention. One of the strong drivers of health anxiety is cyberchondria, the malign influence of the Internet and social media in promoting fears about illness. This may be behind the rise in pathological health anxiety in recent years[4]. As COVID-19 now dominates every news medium, it is going to be impossible to escape this particular reinforcement of health anxiety.

One of the positive signs is that now we have effective psychological treatments, after regarding hypochondriasis as untreatable for many years. Psychopharmacology is unlikely to help in this condition, unless depression becomes a marked symptom. The most effective established treatments are cognitive behaviour therapy adapted for the condition[5], and acceptance and commitment therapy[6]. These can be given face to face and over the Internet very successfully[6,7], and in most cases the response is rapid and encouraging. Nurses have also been shown to be highly effective in giving this treatment[8], and it is likely that many other health professionals may be able to act as therapists for this condition.

What is not clear is how long COVID health anxiety is likely to persist. Other forms of health anxiety tend to last for many years and show little fluctuation. The symptoms often arise after a trigger event that threatens health and, paradoxically, COVID health anxiety might be even more prominent in those who have already experienced infection or have tested positive. Untreated, symptoms persist and can lead to a significant degree of depression[9]. Currently, we are carrying out a remotely given intervention for COVID health anxiety based on experience with previously successful short-term cognitive behaviour therapy for health anxiety (CBT-HA).

Much will depend on the arrival of a vaccine and further evidence about the degree and length of immunity after recovered infection. Once the current uncertainty is resolved, the situation will be clearer and we can then expect the prevalence to fall. In the meantime, the following advice might be given to those with an abnormal degree of health anxiety linked to COVID, and indeed all those who already have health anxiety: limit unnec-

essary contact with health professionals of all types, only listen to the news for a short time each day, do not wash your hands repeatedly if you have had no possible contact with another person, and keep yourself occupied as much as possible.

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Smartphone relapse prediction in serious mental illness: a pathway towards personalized preventive care

Imagine a smartphone app that knows when a patient is at risk of relapsing on alcohol use based on geolocation data indicating proximity to a liquor store and real-time surveys suggesting elevated craving. The smartphone detects this imminent risk, alerts a clinician, and the patient receives a personal check-in within minutes. Such a system does not sound futuristic in 2020, neither was it a decade ago, when the Alcohol - Comprehensive Health Enhancement Support System (A-CHESS) study, described above, was conducted[1]. Ten years later, smartphone relapse prediction systems are catalyzing a paradigm shift in mental health care that is now further accelerated by the COVID-19 pandemic. As these approaches continue to enable dynamic and longitudinal modeling of risk, personalized preventive care is within reach.

The evidence for smartphone relapse prediction across major mental disorders is impressive. Today it is possible to build dynamic digital proxies for symptoms, functioning, cognition and physiology using smartphones and wearables – often referred to as digital phenotyping[2]. For example: passive smartphone data from sensors like global positioning system (GPS) can inform about location; accelerometer about sleep; active data from surveys (often referred to as ecological momentary assessment) can capture real time symptoms; metadata from phone interactions can characterize cognition; and data from wearables can inform on physiological measures.

Capturing these diverse data streams is highly feasible. Open-source and free platforms such as mindLAMP have permitted teams across the world to engage in this work[2]. Using varying combinations of these digital data streams, studies have shown clinically actionable assessment of relapse risk in schizophrenia[3], depression[4], bipolar disorder[5] and substance abuse[1]. Furthermore, data around spoken and written language as well as social media use (often accessed via smartphones) is also augmenting relapse prediction. Since at least 2018, an effort has been made to predict suicide attempts in the US through real time natural language processing[6].

The success in accurate assessment of relapse risk is encouraging and highlights the need for the field to advance towards studies of predictive validity and reproducibility. In the suicide prevention field, a recent review highlighted that even the good global classification accuracy of current suicide risk models still yields a predictive validity of less than 1%[7]. The predictive validity of smartphone relapse models remains untested, but targets for ensuring reproducibility have already emerged, including data accessibility, standards and methods.

Data accessibility from smartphones is constantly in flux, as Apple and Google (which control over 99% of the world's smartphone operating systems) change accessible data sources each year in response to both technical and privacy considerations. For example, in June 2020, both Apple and Google announced that access to Bluetooth data (which can be used to infer social context – a key element in many relapse models) would become limited given growing privacy concerns. Balancing ethical data uses and surveillance risks from this work requires renewed attention. For available data streams, differences in sensors and phone models and brands often yield divergent metrics for the same behaviors, generating a need to control for device characteristics in a standardized way.

Furthermore, assuming a case where all smartphone sensors are sampling at 10Hz, theoretically up to 65GB of data can be generated for one patient in one month. Appropriate use of statistical methods is critical, as spurious findings should be considered the norm with this amount of digital data. Sharing data – a challenge in this work given the personal and identifiable nature of digital phenotyping data – will be critical to success, and new efforts in the spirit of the openfMRI project (see https://openfmri.org) are necessary. Ensuring that these new dynamic models of relapse are not biased, as is being realized today for some medical treatment algorithms that misuse race[8], will require diverse and representative research.

Careful assessment of the prospective validity, reproducibility and clinical applicability of these new smartphone relapse prediction models is a clear next step. Many current models are not utilized in routine care because they are based on static risk factors (e.g., age and gender) and explain a low percentage of relapse variance. While there are some sophisticated models that allow for time varying factors, they often assume that mental health processes are ergodic, i.e. that group level data are generalizable to an individual[9]. In the past, when data collection was limited at the individual level, this assumption has been necessary, but now it is recognized to be incorrect[9].

With new access to unprecedented amounts of data over intervals that can range up to years per individual, the methods used to analyze data need to evolve alongside the technology that has enabled this new potential data resource. Digital phenotyping creates the potential for a new generation of relapse prediction models that do not fall victim to the ergodic fallacy, and can make personal and more preventive psychiatry a reality.

This reality is approaching faster now, as the COVID-19 pandemic has accelerated the field's use of telehealth and acceptance of smartphone data to supplement care. As patients can no longer fill out paper-and-pencil surveys and hand them to clinicians, use of patient-reported outcomes captured via computers and smartphones has become necessary for everyday care. As barriers to using smartphone data continue to fall, and the evidence for benefit continues to expand, the real question is not when but how relapse prediction data will be used.

While it is easy to imagine ideal uses for smartphone relapse prediction, as outlined in the A-CHESS study, the broader realities must also be considered. In Fall 2019, the concept of using smartphone prediction not towards relapse, but rather violence prediction among people with serious mental illness, was floated. This idea was met with concerns around ethics, feasibility and stigma, but highlights how easily a seeming boon to the field can turn into a potential liability.

Another pressing challenge is how health systems can respond to smartphone relapse prediction data. Relapse may happen at 2am on Sunday morning, and the clinical team can be alerted at the same time. The real solution is designing new clinical services that are able to respond to digital data. Designing these new services along with new technologies in an inclusive, collaborative, iterative manner across disciplines will result in solutions that will bridge the research to practice (or code to clinic) gap and help prevent relapse.

The digital clinic of tomorrow may not look like the traditional clinic of today. Our teams in Boston, New York and Philadelphia are piloting digital clinic models where we have learned first-hand the rewards and challenges of this approach. In relapse prediction, the new technology can offer a first line of response with just-in-time adaptive interventions in a stepped care manner – in some cases removing the need for an immediate personal response from the clinical team. But there is always the need for a personal connection with every patient. For example, a patient recently appeared at risk for a manic relapse given elevated levels of phone activity but, upon reaching out, he informed us that he had started letting his roommate use his smartphone when working the night shift. This explained the lack of sleep and increased activity captured by the smartphone, which had been interpreted incorrectly as elevated risk. Fully automated interventions could be problematic with respect to false positives and should instead be seen as complementary to the human element of care.

The potential of personalized preventive mental health care is within reach with smartphone-based relapse prediction. As the next generation of studies explore prospective validity, the clinical need for these models will drive further innovation. The convergence of these approaches is not a decade away, but will likely be as swift as it is transformative.

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Brain networks and cognitive impairment in psychiatric disorders

Cognitive impairments are a prominent feature of all psychiatric disorders. The goal of mapping each disorder to individual brain areas has now been largely abandoned, and supplanted by systems neuroscience approaches which focus on distributed circuits and large-scale brain organization[1].

Although the nature of cognitive impairments varies across disorders, a common underlying feature is the inability to adaptively regulate or control behavior in relation to changing goals and saliency of external stimuli and internal mental events. Dysregulation of the brain's cognitive control systems thus lies at the crux of most behavioral impairments. Cognitive control is a dynamic process, which relies on flexible goal-relevant modulation of brain networks, and investigations of dynamic network interactions are advancing fundamental knowledge of the neurobiological basis of psychiatric disorders[2].

The human brain is intrinsically organized into networks, each consisting of a distinct set of cortical and subcortical areas linked by temporally synchronous neural activity[1]. The intrinsic connectivity of brain networks displays close correspondence with task-related co-activation of brain regions, and this correspondence has allowed intrinsic and task-related connectivity to be demarcated and studied under a common systems neuroscience framework[3].

Brain networks not only provide a unifying framework for characterizing functional organization of the neurotypical brain, but also for probing the neurobiological basis of psychiatric disor-

ders. In particular, aberrations in large-scale brain networks that implement cognitive control have now been shown to transdiagnostically underpin virtually all psychiatric disorders.

Cognitive control processes are implemented by distinct large-scale brain networks, each with unique spatial and temporal properties. Three brain networks have received considerable attention in the context of impairments of cognitive control in psychiatric disorders: the salience network (SN), anchored in the anterior insula and dorsal anterior cingulate cortex, with prominent subcortical nodes in affect and reward processing regions; the fronto-parietal (FPN) "central-executive" network, anchored in dorsolateral prefrontal cortex and posterior parietal cortex; and the default mode network (DMN), anchored in the medial posterior cingulate cortex, ventromedial prefrontal cortex, medial temporal lobe, and angular gyrus[4,5].

The SN network is crucial for "salience mapping", i.e., detecting salient external stimuli and internal mental events and facilitating engagement or disengagement of brain systems relevant for goal-relevant behaviors. The FPN is involved in active maintenance and manipulation of information in working memory. The DMN is typically suppressed during focused attention to external stimuli, and is involved in self-referential and autobiographical processes. These networks are fundamental to human cognition and are critical for regulating adaptive goal-directed behaviors[6,7].

A synthesis of findings over the past decade has led us to propose a triple network model of psychopathology, which posits that aberrant functional organization of the SN, FPN and DMN and their dynamic interactions underlie a wide range of psychiatric disorders[2]. Dysfunction in one or more of these networks has been reported in many psychiatric disorders, including autism, anxiety and mood disorders, schizophrenia, bipolar disorder and substance abuse.

The model specifically hypothesizes a central role for the SN in aberrant salience assignment and mapping of external and internal events, leading to altered dynamic temporal interactions with the FPN and DMN. Misattribution of salience and the resulting dysregulation in engagement of appropriate task-relevant brain networks is thus predicted to be a proximal factor underlying cognitive impairments, and evidence in support of this model has been accumulating over the past decade in multiple psychiatric disorders.

Critically, integrative between-network communication is crucial for efficient cognitive control and adaptive behaviors[6-8]. Models incorporating cross-network dynamics have identified robust neurobiological features capturing cognitive phenotypic characteristics in psychiatric disorders. These models better reflect aberrations in the waxing and waning of network-wide co-activation patterns arising from externally and internally driven mental events. The temporal evolution of the ensuing dynamical states captures clinical symptomatology and cognitive impairments better than static network features.

In a recent study, we examined whether aberrant functional organization of the SN, FPN and DMN contributes to psychosis in schizophrenia[9]. We found that dynamic SN-centered cross-network interactions were significantly reduced, less persistent, and more variable in patients with schizophrenia compared to neurotypical controls. Moreover, dynamic time-varying measures of cross-network interactions were correlated with cognitive dysfunction and positive, but not negative, symptoms. Thus, aberrations in time-varying engagement of SN with FPN and DMN are a clinically relevant neurobiological signature of psychosis in schizophrenia. The discovery of dysregulated brain dynamics in the triple-network salience model further highlights the value of theory-driven systems neuroscience approaches for characterizing core cognitive impairments and clinical symptoms associated with schizophrenia.

Delineation of the brain network basis of cognitive control impairments in the developing brain holds particular promise for early intervention. The earliest manifestations of major psychiatric disorders typically occur in childhood and adolescence, and cognitive, affective and behavioral deviations are often seen years before illness onset and clinical diagnosis. The neural signatures of these deviations have been reported in multiple brain networks, and evidence that aberrations in dynamic interactions of cognitive control networks contribute both to general cognitive impairments and specific phenotypic features is accumulating in studies of autism, attention-deficit/hyperactivity disorder and many other neurodevelopmental disorders. Characterization of the developmental trajectories of cognitive control networks, and in particular early identification of network dysfunction, has the potential to improve early diagnosis, treatment and outcomes.

A primary goal of psychiatry is identifying psychological and biological factors underlying cognitive impairment that cut across diagnoses and explain fundamental aspects of mental illness. Impairments in cognitive control systems that regulate the ability to adaptively engage with and respond to changing goals and contexts have emerged as a hallmark of psychopathology. A convergence of empirical findings and theoretical frameworks for examining aberrations in brain networks that underlie cognitive impairments have provided foundational information about transdiagnostic circuits and promising targets for intervention. Brain network models also provide critical insights into sources of variability in the expression of clinical symptoms, behavioral phenotypes, and their neurodevelopmental bases.

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RDoC at 10: changing the discourse for psychopathology

From 1990 to 2010, researchers lamented the problems of comorbid conditions and heterogenous syndromes in psychiatric diagnoses. A volume from the American Psychiatric Association detailing a research agenda for DSM-5 collectively captured these views, as well as the accompanying lack of progress to connect integrative neuroscience with psychiatric diagnoses[1].

Amid growing concerns, the Research Domain Criteria (RDoC) project was proposed by the US National Institute of Mental Health (NIMH) to offer an alternative strategy[2]. The NIMH convened researchers and stakeholders to identify psychopathology-relevant constructs from the experimental literature. Conditions for empirical support were set, including well-elucidated neural circuits and demonstrated validity for functional behavior. Relevance for human suffering was also a requisite.

Since its introduction, RDoC facilitated a new scientific discourse about precision medicine in psychiatry, as evidenced by thousands of citations in studies or commentaries and as a keyword in over 400 National Institutes of Health (NIH)-funded grants. It cleared a path for alternative designs for translational research, offered new tactical approaches to explicate disruptions in psychopathology mechanisms, and invited robust international dialog[3].

An RDoC Unit at NIMH now helps advance the aims of the project in many ways. For example, sponsoring meetings to update original domains and constructs, to evaluate relevant tasks for RDoC research, and to strengthen integration of developmental processes and environmental events. An internal working group adds to the discourse, and National Advisory to Mental Health Council subcommittees provide oversight.

Before RDoC, diagnoses constructed of clinically-observed symptoms (DSM/ICD) were the routine to define patient groups studied in translational research. Now, the assumption that clinical syndromes will be validated by corresponding internal mechanisms in a one-to-one way is accepted as untenable. RDoC offers new directions to understand psychopathology as dimensional deviations from normal performance (neural systems and behaviors). It captures mechanisms inherent to normal-range functioning, and then determines how disruptions correspond to psychopathology. It expands consideration of what constitutes an independent or dependent (outcome) variable.

RDoC research calls for samples of patients broadly exhibiting a range of related symptom patterns, primarily focusing on connecting a neural mechanism with behavior, while tracking variations in co-occurring diagnoses, degrees of functional impairment, and levels of subjective distress. RDoC research does not require DSM/ICD diagnoses to select patient groups, and allows focus in a study on one or more such clinical syndromes.

An RDoC strategy gaining considerable traction is to pool a broader band of participants with a range of potentially related syndromes, and then study dimensions of reliable biomechanisms as independent (or predictor) variables in relation to outcome. For example, researchers have redistributed patients with various anxiety and mood-related diagnoses into quintiles based on psychophysiological response elicited by startle, and the regrouping predicted a number of psychopathological indices, including reports of distress and transdiagnostic severity[4]. P3 amplitude was graduated: lower among those reporting the most distress and demonstrating more comorbid disorders, and higher for those reporting less distress and more circumscribed symptom patterns, with control participants placing in the center quintile, suggesting clinical relevance for fear responses that deviate in either direction[4].

Another study found that this inverse pattern held when dividing participants in quintiles based on amygdala response using a different task, comparing emotional and neutral images during functional magnetic resonance imaging[5]. Participants with the least differential (emotional minus neutral) self-reported higher trauma risk scores, whereas those with the largest differential reported lower trauma scores, with controls again placing in the middle quintile.

That fear circuitry figured more prominently in these studies for more circumscribed conditions (lower transdiagnostic severity and less complex trauma histories, respectively) is clinically relevant, suggesting when exposure therapies would be more efficacious. In contrast, those with a broader symptom range (more comorbidity, more complex trauma) may have more elaborate disruptions among internal mechanisms. This adds to our understanding of poorer outcomes and higher dropout rates for exposure treatment in people with multiple trauma post-traumatic stress disorder.

RDoC has also helped to change the way clinical trials are conducted, including those for regulatory approval. Regulatory bodies, once bound to DSM disorders as the standard for outcome, now allow indications targeting transdiagnostic constructs such as anhedonia, cognitive functions, and suicidal behaviors[6]. For example, patterns of activity in ventral striatum, implicated in reward anticipation, have been investigated as primary outcome measure in the development of therapeutic agents for anhedonia in a mixed patient group of depressive and anxiety disorders[7]. Other researchers reported wider-spread activations in cognitive control regions, specifically bilateral parietal cortex activity in pediatric anxiety, and are now investigating these brain-behavior dimensions to predict cognitive behavioral therapy outcomes[8].

RDoC introduced structure by grouping constructs within superordinate domains (rows), and suggesting units of analysis ranging from neuroscience to behavior (columns). Constructs and elements of the matrix were offered as exemplars, with expectations for change with accumulation of new findings. However, the format was susceptible to the interpretation that the framework incorporated a goal to curate a fixed set of constructs that constrained research. We have previously clarified that RDoC can serve instead as a nomological network to theoretically organize psychopathology data[3]. Advances in computational neuroscience offer dynamic ways to model hypothesized brain-behavior

mechanisms. These models could use RDoC as a scaffold to extend data-driven approaches to identify new clinical phenotypes.

Models of failure might detail the implications of disruptions in one or more internal mechanisms[9]. It could be that a failure in either one of two distinct mechanisms leads to a similar clinical presentation, or that a poor clinical prognosis requires multiple failures. Another possibility is that a mechanism could fail (e.g., glutamatergic pathways in the amygdala associated with fear acquisition), yet clinical manifestation of that failure could be shielded by compensatory mechanisms (e.g., ventromedial prefrontal cortex circuits associated with fear extinction).

Exemplar RDoC dimensions offer a platform for a first generation of mathematical models to integrate data describing relations of neural circuits and behavior. Such developments can advance multiple aspects of the needs for precision diagnosis. Experimental paradigms developed with computational models are showing the potential to delineate specific aspects of behavior, and to relate these various aspects to their implementation, coordinated by increasingly well-specified brain circuits[10]. This development capitalizes on the RDoC principle to explain relations across units of analysis in order to clarify psychophysiological constructs and the critical relationships among interrelating response systems.

Over the first ten years, RDoC provided a structure to unharness researchers from diagnostic categories for funding applications and treatment approval in order to open new avenues for discovery. Going forward, RDoC may provide ways to leverage the development of computational models of psychopathological systems that integrate neural and psychological mechanisms with developmental processes and environmental influences.

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Perinatal mental health: a review of progress and challenges

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Perinatal mental health has become a significant focus of interest in recent years, with investment in new specialist mental health services in some high-income countries, and inpatient psychiatric mother and baby units in diverse settings. In this paper, we summarize and critically examine the epidemiology and impact of perinatal mental disorders, including emerging evidence of an increase of their prevalence in young pregnant women. Perinatal mental disorders are among the commonest morbidities of pregnancy, and make an important contribution to maternal mortality, as well as to adverse neonatal, infant and child outcomes. We then review the current evidence base on interventions, including individual level and public health ones, as well as service delivery models. Randomized controlled trials provide evidence on the effectiveness of psychological and psychosocial interventions at the individual level, though it is not yet clear which women with perinatal mental disorders also need additional support for parenting. The evidence base on psychotropic use in pregnancy is almost exclusively observational. There is little research on the full range of perinatal mental disorders, on how to improve access to treatment for women with psychosocial difficulties, and on the effectiveness of different service delivery models. We conclude with research and clinical implications, which, we argue, highlight the need for an extension of generic psychiatric services to include preconception care, and further investment into public health interventions, in addition to perinatal mental health services, potentially for women and men, to reduce maternal and child morbidity and mortality.

Key words: Pregnancy, postpartum, perinatal mental disorders, maternal mortality, suicide, child outcomes, psychological interventions, antidepressants, preconception interventions, public health interventions, service delivery

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Perinatal mental ill-health has been a focus of interest for centuries, but until recently this interest has mainly centered around postpartum psychosis and depression, with relatively little funding for research into individual level treatments as well as for investment in specialist services and public health interventions. This is, however, changing.

In January 2016, the UK Prime Minister announced a strategic >£290 million investment into new specialist perinatal mental health services (services for women with mental disorders in pregnancy and the first year postpartum)[1]. Since then, additional funds have been promised, with the aim of ensuring that women in all parts of the UK have access to specialist community services and psychiatric inpatient mother and baby units, and extending service provision up to two years postpartum. The ambition is to provide care concordant with the Antenatal and Postnatal Mental Health Guidelines produced by the National Institute for Health and Care Excellence (NICE)[2] to all women needing it. In other countries, there have also been investments in specialist outpatient and/or community perinatal mental health services and/or in mother and baby units[3,4].

Perinatal mental disorders are common – indeed, the commonest complication of child-bearing – and are associated with considerable maternal and foetal/infant morbidity and mortality[5-7]. In addition, there is a huge cost burden, particularly to health and social care, estimated in the UK to be £75,728 and £34,840 per woman lifetime for perinatal depression and anxiety respectively, with an aggregate cost for the country of £6.6 billion. Around 75% of this economic burden is associated with subsequent childhood morbidity[8].

While these estimates inevitably are subject to various assumptions, the World Health Organization (WHO) has highlighted the urgent need for "evidence based, cost effective, and human rights oriented mental health and social care services in community-based settings for early identification and management of maternal mental disorders"[9].

The current classifications of perinatal mental disorders are confusing, which partly reflects the debate on whether these disorders are unique in terms of their causes and psychopathology, or the same as mental disorders at other times of a woman's life. Recent evidence suggests that, even within individual diagnostic constructs such as postpartum depression, there are different phenotypes, potentially needing different interventions and services[10].

In this paper, we summarize and critically examine the epidemiology of mental disorders in relation to childbirth and their impact on the foetus/infant/child, and then focus on the evidence base for interventions during pregnancy and postpartum, as well as in the preconception period, at the individual and population level. We also review the evidence base on service delivery models and discuss implications for research.

In particular, we explore whether, in view of the current evidence base, investment in services can be expected to make a meaningful and lasting difference for women and their families, how service delivery could be optimized, and what the implications can be for general psychiatric services and research.

PREVALENCE OF MENTAL DISORDERS IN THE PERINATAL PERIOD

The early postnatal period is at high risk for new and recurrent episodes, particularly of severe mental illness[5,11-13], with around one to two women in 1,000

requiring admission in the first few months after birth[5].

A seminal study by Kendell et al[12] (replicated by several groups) found that women were around 22 times more likely to have a psychiatric admission in the month following birth than in the pre-pregnancy period. This increased postnatal admission risk is found amongst women both with and without prior psychiatric illness, but more so among women with a pre-existing severe mood disorder[11]. A systematic review of 37 studies (including 5,700 deliveries in 4,023 women) found that 20% of women with pre-existing bipolar disorder experience a severe postnatal mental illness (i.e., psychosis, mania and/or hospitalization)[14].

For less severe mental disorders (predominantly mild to moderate depression and anxiety disorders), the evidence for postpartum triggering is less clear[6,11]. Some studies have found an increased rate of disorders requiring outpatient contact and/or psychotropic treatment in the postnatal period, particularly for depression and obsessive-compulsive disorder (OCD)[15,16]. This may reflect an under-detection and/or under-treatment of these disorders during pregnancy, as studies find that postpartum depressive and anxiety symptoms frequently begin during or before pregnancy[17,18], but women are less likely to receive treatment during pregnancy than postnatally[11]. Nevertheless, it has been estimated that, for each woman requiring psychiatric admission following birth, 2.5 require outpatient treatment and 12 receive pharmacological treatment in primary care[11]. Therefore, "common mental disorders" (namely, depression and anxiety) represent a significant component of treatment need in the postnatal period.

A systematic review of 58 studies (N= 37,294 previously healthy women) reported an incidence estimate for postnatal depression of 12% (95% CI: 4-20) and a prevalence of 17% (95% CI: 15-20)[19]. In general, the prevalence is higher in low- to middle-income countries (LMIC) than in high-income countries (HIC)[20].

Recent systematic reviews report a prevalence of 15-20% for antenatal and 10% for postnatal anxiety disorders[21,22], with higher rates in LMIC versus HIC settings. Self-reported anxiety symptoms are very common, and increase across the trimesters of pregnancy (with a mean prevalence of 25% in the third trimester)[21].

Perinatal eating disorders are relatively rare, but there is a history of an eating disorder in up to 15% of pregnant women, who may therefore need support with re-emerging symptoms precipitated by pregnancy or postpartum[23].

The evidence is not consistent concerning the relapse rate of prior depression and bipolar disorder during pregnancy. Around 10-20% of pregnant women with prior depression seem to experience a depressive relapse, but with a broad range of estimates (from <5% to 75%)[24,25]. For bipolar disorder, a systematic review of 14 mainly small studies (including a total of 2,345 women, but with only two studies with a sample size of >100) suggests that around one in five women experience a relapse during pregnancy[24], with a possible predominance of depressive and mixed episodes (in contrast to prominent manic episodes in the postnatal period)[5,24,25]. However, a recent electronic health record study reported a relapse rate of 10%[26], possibly reflecting different populations.

There is some indirect evidence that the prevalence of perinatal mental illness has increased in recent years. A study using UK primary care data has reported that the proportion of children exposed to maternal mental illness increased from 22.2% (95% CI: 21.9-22.4) between 2005 and 2007 to 25.1% (95% CI: 24.8-25.5) between 2015 and 2017[27].

This could be due to increase in primary care attendance (due to greater awareness of mental health problems) and/or increased detection, and/or different populations. However, it is likely to reflect at least in part a real increase, as similar findings of an increase of common mental disorders in young women has been found in population surveys[28]. Moreover, a multi-generational pregnancy cohort[29] has reported that depression in pregnancy was on average 51% more common among young mothers in the recent generation than among their mothers' generation 25 years ago. We also recently reported a population prevalence estimate of common mental disorders of 45.1% (95% CI: 23.5-68.7) in pregnant women less than 25 years of age, compared with 15.5% (95% CI: 12.0-19.8) in women aged 25 years of more (adjusted odds ratio: 5.8, 95% CI: 1.8-18.6)[30].

Obviously, young pregnant women are now living in circumstances different from their mothers: some have pointed to the fast pace of modern life, changes in technology (including social media use which may amplify experiences of abuse and bullying through "sexting"), isolation, and insecure employment as potential contributors to this[29].

Alcohol is a major teratogen, and a recent high-quality systematic review estimated that globally around one in ten women use alcohol in pregnancy, with one in 67 having a child with foetal alcohol syndrome[31]. In the UK, Confidential Enquiries into Maternal Deaths[32] have recently highlighted the increasing prevalence of substance misuse among women who died in the perinatal period and the poor maternity and mental health care they often received.

The historical focus on mothers' perinatal mental health reflects a variety of epidemiological, scientific, service-related and sociological factors. Recently, fathers' mental health has rightly gained greater attention, with epidemiological evidence suggesting an unmet treatment need for paternal depression and anxiety[33,34]. There is also growing evidence on the adverse effects of untreated paternal mental illness on mothers' mental health[35], and its association with adverse child emotional and behavioural outcomes[36,37] and child maltreatment[38], particularly when children are exposed to a combination of parental mental illness, parental substance misuse and inter-parental conflict[7,36].

ASSOCIATION BETWEEN PERINATAL MENTAL DISORDERS AND MATERNAL AND CHILD MORBIDITY AND MORTALITY

Maternal mortality, suicide and self-harm

Perinatal mental disorders are associated with deaths from suicide, substance misuse complications and the misattribution

of physical symptoms of life-threatening complications (e.g., pulmonary embolism) to mental illness in women with, for example, anxiety disorders or schizophrenia[32]. In addition, as mental disorders are associated with poverty, physical health complications, interpersonal violence and other forms of disadvantage, women with mental illness are more likely to experience life-threatening complications (sometimes referred to as "near misses") than those with no mental illness[32]. Of note, evidence from the US National Violent Death Reporting System found interpersonal violence among nearly half of the mothers who died by suicide, in addition to deaths from domestic homicide[39].

While suicide is a leading cause of death during the perinatal period in HICs (accounting for 5 to 20% of maternal deaths)[40], it is a modest contributor to deaths in LMICs: in a systematic review and meta-analysis, the pooled prevalence was 1.00% for suicide (95% CI: 0.54-1.57) and 5.06% for injuries (95% CI: 3.72-6.58)[41]. Reclassifying the leading suicide methods from injuries to suicide increased the pooled prevalence of pregnancy-related deaths attributed to suicide to 1.68% (95% CI: 1.09-2.37)[41].

The Eastern Mediterranean (3.55%, 95% CI: 0.37-9.37), Americas (3.03%, 95% CI: 1.20-5.49) and Southeast Asia (2.19%, 95% CI: 1.04-3.68) regions have the highest prevalence of suicide in the perinatal period, with the Western Pacific (1.16%, 95% CI: 0.00-4.67) and Africa (0.65%, 95% CI: 0.45-0.88) regions having the lowest[41]. However, rates may be underestimated, due to different definitions of maternal mortality (e.g., during pregnancy and up to six weeks after birth, or during pregnancy and up to one year after birth), and because rates are based on whether the death certificate records pregnancy or recent childbirth.

In 2012, the WHO introduced the International Classification of Diseases for Maternal Mortality (ICD-MM), which recommended the significant change of classifying all suicides in pregnancy and up to 12 months postpartum as direct obstetric deaths, in order to reduce underreporting and improve data collection[42].

Suicide risk in the perinatal period is drastically increased in women with moderate to severe mental illness as compared with mothers with no psychiatric history[43] (mortality rate ratio = 289.42; 95% CI: 144.02-581.62). Suicide risk is related particularly to severe depression[40,44]. Suicides may occur less commonly in women with other diagnoses, including bipolar disorder, schizophrenia and personality disorder[44]. Deaths more often occur in the second half of the first postpartum year. Recent studies have highlighted that women may not be receiving active psychiatric treatment at the time of their death[44].

A significant proportion (a quarter in the past three months according to one study)[44] of women self-harm before suicide, and self-harm in women with first-onset severe mental disorder is a risk factor for later suicide[45]. Self-harm in the perinatal period has only recently been highlighted as a public mental health issue[46]. A systematic review of 39 studies (reporting on 19,191,431 pregnancies)[47] found that perinatal self-harm is relatively rare (though this may partly reflect detection bias) other than in women with severe mental illness. Indeed, in a study using secondary care electronic health records of women with psychotic mood disorder and schizophrenia, 8% self-harmed during pregnancy[48].

Self-harm history is an important marker for perinatal mental disorders[49,50], and is associated with adverse obstetric and neonatal outcomes[47]. However, it is not routinely asked about in women during pregnancy and postpartum.

Obstetric and neonatal outcomes

It is well established that women with both common mental disorders and severe mental illness have an increased risk for adverse obstetric and pregnancy outcomes, including preterm births and foetal growth impairments[51-55]. Furthermore, women with severe mental illness also have increased risks of pre-eclampsia, antepartum and postpartum haemorrhage, placental abruption and stillbirths[53-55].

It is also increasingly clear that these risks are elevated regardless of pharmacotherapy during pregnancy[51,52,56], suggesting causality beyond medication[55]. This is unsurprising, given the higher prevalence of well-established obstetric risk factors among women with perinatal mental illness, including distal risk factors (such as domestic violence, and poor or delayed antenatal care) and proximal risk factors (such as obesity, gestational diabetes, hypertension and smoking)[5,6,55,57].

In general, the risks are greater among women in LMICs than HICs, among those with chronic severe mental illness, and among those with important concomitant conditions such as smoking, substance misuse, poverty and domestic violence.

Infant and child outcomes

There is a large evidence base on associations between perinatal mental disorders and childhood adverse mental health outcomes, particularly for perinatal depression[58] and antenatal alcohol misuse[59]. The association between prenatal alcohol exposure and childhood cognitive impairment is not only supported by observational data, but also by at least one randomized controlled trial (RCT) and 16 quasi-experimental studies (including nine Mendelian randomization studies and seven "natural experiment" studies)[60].

Our understanding of the effects of antenatal depression exposure on the offspring is largely reliant on preclinical (animal) research and observational studies (that are problematic due to genetic and environmental confounding and other biases such as recall bias or limited follow-up)[61,62]. The available evidence suggests that *in utero* exposure to both depression and antidepressants is independently linked to biological changes in the developing foetus, affecting the serotonergic system and the hypothalamic-pituitary-adrenal axis, hypothesized to be related to maternal-placental-foetal stress-related mechanisms, including maternal immune activation[61-64]. Clinically, exposure to antenatal depression has been associated with childhood cognitive and behavioural problems, attention-

deficit/hyperactivity disorder (ADHD) and autism[7,61,65]. However, there is limited understanding of protective factors that account for the large proportion of unaffected children, despite exposure to significant antenatal maternal illness.

Antenatal anxiety is associated with a small increase in emotional problems in early and middle childhood. However, in several studies, these associations are attenuated or no longer evident after adjustment for confounders. Moreover, in the studies that included multiple informants, these associations were found using maternal but not teacher-reported child outcomes[66], suggesting recall bias. Interestingly, women with anxiety disorders in one study perceived themselves to have bonding problems, yet the quality of their observed mother-infant interactions at three months postpartum was similar to the general population[67].

Conversely, women with personality dysfunctional traits have been found to be less sensitive during observed interactions, but they may not perceive themselves as having problems as measured by the Parental Bonding Questionnaire[68]. Other studies also highlight the importance of personality disorder with respect to adverse outcomes such as higher levels of dysregulated infant behaviour[69].

There is less consistent evidence on posttraumatic stress disorder (PTSD) impacting on maternal sensitivity and mother-infant interactions[70]. Mothers with eating disorders often have comorbid anxiety and depression, and some studies have found that this comorbidity mediates the association with emotional and conduct problems in their children[71]. This reflects a more general finding that at-risk children are generally those whose mothers have a cluster of psychiatric, psychosocial and physical concomitant conditions[7].

Postnatal mental disorders often begin during or before pregnancy, and it is difficult to disentangle the effects of genetics, prenatal exposure and broader familial/social confounding from the discrete effects of postnatal mental illness. However, a key mechanism for transmission of risk to infants, with substantial theoretical and empirical support, is impaired attachment related to low maternal sensitivity and "parental mentalization"[72,73]. Insecure or disorganized attachment is associated with externalizing (and, to a lesser extent, internalizing) childhood problems [74,75].

Importantly, impaired attachment is more closely related to mothers' experience of early trauma (including emotional neglect) than to specific maternal diagnoses[72], underlining the need for a careful developmental history in perinatal settings. Mental illness in both parents and inter-parental conflict are clearly red flags for adverse child outcomes, but positive parenting by a healthy co-parent (mother or father) can buffer children against the adverse effects of perinatal mental illness [7,36].

Research has also highlighted the additional impact of risk factors associated with maternal depression (including young age, low educational level, interpersonal violence, poor social support, substance misuse), which explain a significant proportion of the association between maternal illness and children's externalizing and internalizing disorders. A study using a large English pregnancy cohort found that exposure to each additional risk factor increased the odds for an internalizing and externalizing disorder[76], underlining the need for multidisciplinary treatment approaches.

In terms of physical health impact in infancy, a recent systematic review found that postnatal depression was associated with increased mortality and hospitalization among children in the first year of life[77]. In LMIC settings, an association was found between postnatal depression and one of the leading causes of infant mortality, diarrheal illness, but confounders were not adequately addressed in the included studies[78].

Whilst there are plausible causal mechanisms linking postnatal depression to infant morbidity, including poor maternal care and reduced help-seeking, the evidence for direct causation is limited[79,80]. Nonetheless, perinatal mental disorders are likely to be a marker for high-risk infants, particularly in LMICs and, for severe mental illness, in HICs.

INTERVENTIONS

Perinatal individual level interventions

Efficacy of psychological and psychosocial interventions

Recent systematic reviews provide robust evidence (>49 RCTs) that psychological and psychosocial interventions for postnatal depression are effective and cost-effective[81,82].

Most psychological intervention trials have tested cognitive behavioural therapy (CBT) modified for postnatal depression, but there is also evidence of clinical effectiveness for a range of other interventions, including interpersonal therapy (IPT), listening visits, and exercise. Some uncertainties remain regarding effect sizes, but there is consistent evidence of improvement in depressive symptomatology.

RCTs of interventions using new modalities for delivery, namely online CBT or behavioural activation, for perinatal depression have also demonstrated robust effects in several countries[83-85].

There is a smaller but similar literature on treatment of mental disorders during pregnancy. A systematic review of 29 trials (2,779 patients)[86], predominantly of depression (28 trials), reported a moderate treatment effect of CBT (seven trials) and to a lesser extent IPT (four trials). This review highlighted the lack of controlled studies for mental disorders other than depression. Recent small trials of guided self-help for antenatal depression provide preliminary evidence of efficacy of low-intensity interventions[87,88].

A systematic review of studies of interventions for perinatal anxiety disorders similarly highlighted the limited data (and high levels of heterogeneity), but found evidence of significant reductions in anxiety symptom severity with interventions also used at other times in a woman's life[89]. There is also some evidence from small trials suggesting that CBT can reduce symptoms in women with blood and injection phobias in pregnancy[90], PTSD and depression in mothers who have babies on a neonatal intensive care unit[91,92], and post-

natal OCD[93].

There is a parallel literature examining the impact of transdiagnostic interventions for the intergenerational cycles of developmental trauma often associated with perinatal mental disorders[73,94]. In addition, some perinatal interventions target depression, anxiety and/or trauma symptoms *and* other risk factors for adverse child outcomes, such as substance misuse, smoking and unsafe infant care practices, with promising results[95].

Most trials have been conducted in a Western country (usually Australia, US or UK), but some high-quality RCTs have also been carried out in low-resource settings, documenting that CBT-based interventions delivered by trained community mental health workers[96] or peers[97] can be effective and cost-effective when compared to enhanced usual care only[98], though this was not found in all settings[99].

In addition to the effect on depression in mothers, trials have also examined subsequent impact on infants, though with mixed findings. For example, a systematic review found evidence from 13 studies in LMIC settings that psychosocial interventions for perinatal depression delivered by supervised non-specialists were not only effective at reducing maternal depressive symptoms, but also led to improved infant growth and vaccine uptake as well as reduced diarrheal disease in some studies[100]. Some small trials in HICs also suggest that psychological interventions for depression may be associated with improved infant outcomes such as stress reactivity[101], but larger RCTs are required to detect clinically meaningful effects.

While women clearly need interventions tailored for pregnancy and subsequent relationships with their infant, there seems to be no reason to assume that treatments which are effective at other times in a woman's life would not be effective in the perinatal period. Many different tailored manuals for perinatal interventions have been developed, but some have argued that the most important aspects of psychological interventions are experience and flexibility of therapists[102].

In summary, there is a reasonably good evidence base on psychological and psychosocial interventions, particularly for perinatal depression, largely mirroring the evidence on interventions outside the perinatal period.

Efficacy of pharmacological interventions

In the general population, the rate of psychotropic drug use has roughly doubled in the past two decades, with a disproportionate increase among young women, of whom around one in ten are prescribed an antidepressant in HIC settings[103,104]. There is concern that psychotropics are overused in these young women, particularly those with mild symptoms or with psychosocial risk factors that could be better addressed by non-pharmacological interventions[105,106].

To our knowledge, there are no published RCTs of psychotropic drug use during pregnancy, due to concerns regarding the ethics of such trials. The challenge is to reach a consensus among researchers, clinicians and patients on the group of women for whom there is clinical equipoise that would justify such trials. There are, however, ongoing trials evaluating antidepressants in pregnancy, with some focusing on child safety rather than efficacy for the mother as a primary outcome[107].

The much larger observational evidence base on psychotropic drug use in pregnancy has also placed a greater emphasis on safety for the exposed child than on efficacy for the mentally unwell mother[55]. This focus on risk of harm to child is reflected in high rates of psychotropic drug discontinuation during pregnancy in women with bipolar disorder[108-110], exceeding discontinuation rates of the same medications for epilepsy[110].

The available evidence suggests that there is both an overuse of psychotropic medications among women with milder disorders or for a broader range of conditions than is supported by research[111,112], as well as an underuse and inappropriate discontinuation for women with more severe disorders associated with a high relapse risk[14,113].

A recent systematic review identified five small studies on lithium continuation and one study on lamotrigine continuation (with a total of 126 women across all six studies), and found that mood stabilizer continuation was associated with up to two-thirds lower risk of relapse during pregnancy[24].

There is an even smaller evidence base for antidepressant continuation during pregnancy, with findings from two studies suggesting that these medications may be protective for women with severe depression but not for those with milder depression[111,113]. There are limited efficacy data for other conditions and medication groups. Confounding is possible: women with stable social situations and insight into their illness may be more likely to remain on prophylactic medication.

There is also reasonable evidence from RCTs for efficacy of antidepressants in the postnatal period, but little data on efficacy of antipsychotics. A recent large cohort study using electronic medical records did not find a beneficial independent effect of prophylactic medication in women with affective or non-affective psychosis in the first three months postpartum[114].

Clinical guidance emphasizes the need for individual risk-benefit analyses regarding psychotropic use in pregnancy[2,55], reflecting a move towards individualized decisions for antidepressant use in the general population[115]. As with all finely-balanced clinical decisions, the emphasis is on good-quality counselling, addressing risks of both treated and untreated illness, giving clear information regarding absolute (not relative) risks of adverse outcomes, and enabling women to make informed decisions.

There is some evidence that women often over-estimate medication (including antidepressant) teratogenic risks[116], and that evidence-based counselling can enable them to restart medication where needed[117]. Two recent pilot trials of a decision aid to help women decide whether or not to use antidepressants in pregnancy have reported preliminary evidence of efficacy[118,119].

Adverse outcomes

As with other psychotherapy research, the perinatal literature on psychological

and psychosocial interventions rarely reports adverse outcomes, and it is not clear whether this is due to lack of these outcomes or a failure to record them. By contrast, there is an extensive literature on potential risks of antidepressants, mood stabilizers and antipsychotics.

Over the last two decades, there has been an improvement in the quality of observational harm studies, with the use of advanced statistical techniques and more robust methodological approaches that aim to isolate the effect of *in utero* medication exposure. In general, better designed studies have reported smaller or null harm effects compared with earlier, smaller or less well-designed studies[55,120]. However, the possibility of residual confounding needs to be understood by clinicians and women.

There is clear evidence of teratogenic and neurodevelopmental harm from valproate, mainly from research into treatment of epilepsy in pregnancy, with a recent European regulatory ban on its use in all women of childbearing age, unless use is unavoidable and women are enrolled in a pregnancy prevention programme[121].

For other psychotropics, the evidence suggests less significant harm, but is more challenging to interpret. In general, recent systematic reviews indicate that, once confounders are taken into account, selective serotonin reuptake inhibitors (SSRIs) are not associated with a clinically important increase in the risk of congenital malformations[122] or growth impairment[123]. SSRIs and other antidepressants may be associated with a small risk of prematurity, especially when used in the 2nd and 3rd trimesters[123-125], though this could reflect residual confounding by indication.

SSRIs have been linked to an increased risk of a severe respiratory neonatal condition (persistent pulmonary hypertension of the unborn), but with a small absolute risk of around 3 in 1,000 reported in a recent systematic review[126].

There is considerably less evidence on longer-term neurodevelopmental outcomes, but an emerging consensus that findings from preclinical (animal) studies may not apply to the human population[127]. For example, an initially concerning safety signal of an association between *in utero* exposure to SSRIs and autism spectrum disorder[128] is not supported by more recent, better quality evidence that takes into account confounding by underlying illness and familial variables[125,129].

Children of women with antenatal depression are at increased risk of autism spectrum disorder, and the risk is similar for siblings with and without *in utero* antidepressant exposure[129], and following maternal antidepressant use pre-pregnancy as well as during pregnancy[130], again suggesting the absence of a causal association.

The safety of antipsychotics has been less well studied, but evidence may be prone to even greater confounding by indication and comorbidity. In general, there is no evidence that antipsychotics are major teratogens, but their use may be associated with greater metabolic risks for the mother and growth impairment in infants (including risk of being large for gestational age among babies exposed to second-generation antipsychotics)[55].

There is a striking lack of evidence on psychotropic use for perinatal mental disorders in LMICs, with one recent systematic review identifying only one RCT that investigated psychiatric medications[98]. This is an important evidence gap, since medications may have a different impact in women at risk for nutritional deficiencies and low body mass index.

Efficacy and safety of other interventions

Electroconvulsive therapy (ECT) may be considered for women with life-threatening complications of perinatal mental disorders (e.g., catatonia, no food or fluid intake, suicide risk), in whom the key consideration is the balance of risks of untreated illness versus ECT risks[7]. Data from case series indicate that ECT is overall safe in these clinical emergencies, but may be associated with pre-term birth.

Other physical treatments, such as transcranial magnetic stimulation, have limited clinical indications[131], may not have sustained benefits beyond a few weeks post-treatment, and have limited pregnancy safety data[132], so that further research is warranted.

The novel medication brexanolone, a neurosteroid that acts as a positive neuromodulator at GABA-A receptors[133,134], has been developed for postpartum depression and approved by the US Food and Drug Administration for this condition in 2019[135]. Small RCTs (N=246) compared the efficacy and safety of a 60-hr brexanolone infusion vs. placebo infusion, with the primary outcome being the mean Hamilton Depression Rating Scale (HAM-D) score at the end of the infusion period. Lower mean HAM-D scores in the intervention group immediately post-infusion and at 30-day follow-up were reported[134].

Caution regarding the use of this new medication has been suggested on scientific, clinical and cost-effectiveness grounds[135], including concerns that findings reflect statistically significant but not clinically meaningful differences.

Limitations of current research into individual level perinatal interventions

Several limitations of current research into individual level perinatal interventions can be pointed out. As with other research[136], there is limited use of clinically significant patient-defined outcome measures. Moreover, infant care itself can generate symptoms that in some studies are attributed to perinatal mental disorders (e.g., the HAM-D three items on sleep). Evidence of safety is dependent on long-term outcomes, which are rarely collected.

The Edinburgh Postnatal Depression Scale[137], the most commonly used scale in perinatal RCTs, has been translated into more than thirty languages and has reasonable diagnostic accuracy. However, many studies of this diagnostic accuracy have used methods subject to bias. An individual participant data meta-analysis is underway to address some of these problems[138]. In addition, many translated versions have lower precision in LMICs: in a systematic review of 12 studies, only one study met all criteria for culturally sensi-

tive translations[139].

Research into the psychometric properties of quality of life measures finds that the Short-Form Six-Dimension (SF-6D) may better capture the effectiveness of perinatal interventions than the more frequently used EuroQol-5D-5L (EQ-5D-5L)[140], though replication is needed to inform future studies of cost-effectiveness.

There has been little research on interventions for women across the diagnostic spectrum and for interventions that target concomitant conditions. When these conditions are identified, there is promising evidence that they may be sensitive to treatment. For example, integrative collaborative care can improve PTSD symptoms[141], in addition to the main target of depression; and guided self-help can include modules on smoking and partner abuse, in addition to a focus on depressive symptoms[87], with reductions found in both symptoms and comorbid problems[142].

Indeed, integrated interventions following comprehensive assessment are essential for holistic perinatal care, but relatively few have been developed. For example, in clinical practice, pregnant or postnatal women with mental disorders and multiple comorbid problems may need to be referred to separate smoking cessation, weight management and substance misuse services.

The development of a core outcome set[143,144] for perinatal treatment trials across the diagnostic spectrum, and for interventions that target comorbid problems, could facilitate the agreement among researchers on optimal measures and ensure comparability of results in future trials. One such set for perinatal depression is underway[145].

A powerful narrative has argued that intervention in the perinatal period would protect children from long-term adverse developmental outcomes, with significant health and economic gains. However, the direct evidence base for perinatal mental health interventions improving child outcomes is limited, and needs to be considered in the context of concomitant exposure to other familial adversities[146].

In addition, some disorders (e.g., perinatal depression) are known to be associated with poorer quality mother-infant interactions (a key mediator of child behavioural outcomes). So, an important research question is whether effective treatment of depression (or other disorders that impact on mother-infant interactions) remove the need for additional support with parenting. To our knowledge, little research directly examined this issue. However, research analyzing outcomes of young children of women treated for depression in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found that remission of maternal depression after three months of medication treatment was significantly associated with reductions in the children's diagnoses and symptoms[147].

Furthermore, in a trial in which an intervention effectively treating depression was associated to either an additional parenting video-feedback therapy intervention or a control treatment of progressive muscle relaxation, child development outcomes were in the normal range in both treatment groups[148]. This trial suggests that additional therapy may not be needed when effective treatment for postnatal depression is available[149]. Further research is needed on whether and which women with perinatal mental disorders would benefit from help with parenting, in addition to treatment of the disorder.

Preconception individual level interventions

There is an emerging literature reporting an association between preconception mental health and perinatal depression[18], mother-infant bonding[50], and infant and child outcomes[150-152]. Clinical guidelines and public health professionals are increasingly highlighting the opportunity for improving preconception health when women *plan* a pregnancy.

Traditionally, the focus of preconception interventions has been on optimizing nutrition in early weeks of pregnancy, but more recently this has been extended to include mental health[153] and other psychosocial factors[154]. Perinatal mental health professionals in HIC settings are increasingly offering preconception advice, though with a primary focus on optimizing medication, rather than a broader spectrum of preconception interventions for nutrition, obesity, interpersonal violence and other relevant factors.

There have been no trials, to our knowledge, that have examined whether preconception mental health interventions improve distal maternal and infant outcomes, but there is a growing literature on what women with mental disorders would like from preconception care. Qualitative studies involving women with psychotic and mood disorders highlight their wish to receive non-judgmental care, better family planning information from generic services, as well as information on adverse effects of medicines on foetal and infant development, on genetic risk to future children, and on risk of relapse if prophylactic treatment were to be stopped[155-159].

Women have also commented on previous traumatic experiences of being told not to get pregnant at all[155,156]. For most, if not all, women with severe mental illness, the centrality of motherhood in their lives is clear.

Women also expressed dislike of the terminology of "high risk", which they found unhelpful and anxiety provoking[155]. Similarly, warnings about preconception health can be potentially damaging, reduce feelings of agency and choice, and at worst push women further into destructive practices. For example, women with eating disorders have described how warnings regarding the impact of their condition on fertility led them to further dietary restriction and purging[160].

Many women with severe mental illness (and in the general population) have unplanned pregnancies, so it is unrealistic to expect more than a small proportion of women to access preconception care even where it is available. We have, therefore, recently suggested that generic adult psychiatric services should include routine preconception discussions within usual care[161]. Medication reviews, for example, could be an opportunity to discuss physical and mental preconception health, including pregnancy planning, relationships, nutrition, physical exercise, weight management, smoking, substance misuse, and folic acid supplementation.

People with severe mental illness may

not respond to traditional public health campaigns, and therefore targeted interventions may be key. Thinking about pregnancy early could also minimize safeguarding concerns. Indeed, pregnancy planning could be a central part of recovery. Currently, the right to a family and optimizing medication for a future pregnancy may still be often met with discouragement or prohibition[155,157].

Public health interventions

The perinatal mental health literature is focused on individual women as the main agent for change. However, social determinants of mental health – poverty, racism, gender disadvantage and other structural inequalities, food insecurity, gender-based violence, poor housing, limited education and social networks – are all of critical importance for women in the perinatal period.

Indeed, interventions often include addressing these determinants at the individual level (e.g., referring to smoking cessation services, writing letters of support for better housing or secure migrant status, referring to local community groups to increase social networks).

Moreover, psychiatrists have an important role in advocating for, and implementing, policies that target social determinants across different sectors[162]. These will vary depending on the context, but could include policies involving the criminal justice system (particularly in relation to domestic violence or trafficking), minimum alcohol pricing to reduce foetal alcohol syndrome and family violence, smoking bans, and welfare benefits.

Within a conceptual framework that includes the United Nations Sustainable Development Goals, psychiatrists can also: a) help design policies that attenuate risks of perinatal mental health problems (e.g., provision of targeted support for low-income young families, parenting support including free child care, microfinancing in LMICs); b) carry out research on the effectiveness of interventions that aim to address the social determinants of mental disorders; c) examine the mechanisms by which social determinants affect perinatal mental disorders; d) examine how best to implement interventions at scale; e) examine cost-effectiveness of universal vs. targeted interventions[163].

While the focus of this review is on treatment rather than prevention of perinatal mental disorders, we agree with recent arguments in this journal[164] that current prevention programmes for depression do not target the strongest determinants of risk and are not structurally embedded in major social systems. This is also the case for perinatal mental disorders. In addition, the focus on women overlooks the role of fathers' parenting skills, and the impact of family violence on children. There is a risk of "blaming" mothers for the health of future generations[165], when the need for family and system level interventions is clear.

Paternal interventions

In view of the growing recognition that paternal mental health is also a cause of morbidity for the family, and the increasing involvement of fathers in parenting, interventions for expectant and new fathers are seen increasingly as an important focus for research.

The most recent systematic review of paternal interventions[166] identified only 11 studies (including eight RCTs). Most studies evaluated psychosocial programmes (predominantly in the antenatal period), but several of them had significant methodological limitations.

An alternative approach is family interventions. A recent systematic review found two small treatment trials of couple interventions which were associated with improvements in maternal depressive symptoms[167]. As with research into maternal interventions, a core outcome set would be useful to improve methodological rigour.

Beyond this literature on paternal-specific interventions, international guidelines on perinatal mental health recommend that services primarily supporting women involve and support their partners and wider families too. While the evidence reviewed in this paper is clear that partners and families have an important influence on women's perinatal mental health, there is a smaller evidence base on their influence on women's access to care and their own interactions with services.

A meta-synthesis of 20 studies of the experiences of fathers reported that services tend to focus on individual women (and babies), with a marginalization and neglect of women's partners and an unmet need for information by these partners[168]. A recent qualitative study, based on separate interviews with women with mental illness and a participant-nominated "significant other", also emphasized the complexity of involving and supporting partners and families, particularly when relationships are poor[169].

SERVICE DELIVERY

Research into the effectiveness of different perinatal mental health service delivery models is in its infancy. The public health and clinical challenge for both general and perinatal psychiatry is to develop services designed to provide personalized medicine with timely assessment and treatment of perinatal mental disorders and comorbid problems, including avoidance of unnecessary medication at the expense of evidence-based psychological therapies, whilst identifying which women with moderate to severe illness would benefit from psychotropic prophylaxis/treatment and/or parenting support.

Furthermore, in light of the high prevalence of the experiences of trauma in pregnant women with mental disorders, trauma-informed interventions in the perinatal period need systematic evaluation[94]. If a key aim of perinatal mental health services is to minimize intergenerational psychopathology, then a family-focused, rather than a mother-focused individual approach, is likely to better meet this aim[36].

Preconception care

Preconception advice is highly valued by women with severe mental illness[155]. The relative effectiveness of provision of preconception interventions in generic vs. specialist care is not known, but in

general it is perinatal psychiatrists who offer preconception advice, and research is underway to explore its effectiveness in the UK.

Initial evaluations of innovative case management interventions for women with repeated custody loss also show promising results[170].

Case identification in universal/ primary care services

Early identification of perinatal mental disorders necessitates detection in universal services, which vary by country but can include primary care, midwives/ obstetricians and home visiting nurses/ paediatricians. Mental health care is accessed by only a small proportion of women with mental disorders[171], and there have been many debates on screening, with divergence in national recommendations[172-175]. Further systematic reviews are underway[176]. However, case identification by trained staff (who can be supported by use of screening tools) is good clinical practice, and the evidence suggests that it would be cost-effective in HIC settings where there are services to provide treatment.

There is less clarity on whether use of screening tools by health practitioners who are not experienced/trained/skilled in talking about mental health is helpful or potentially harmful, and whether it is cost-effective. Some would also argue that identification of the extent of psychological morbidity in pregnant and postnatal women, even where services are limited, is an important public health first step in leverage for efficient stepped perinatal mental health care[177].

Routine enquiry into mental health may require careful consideration of how to prepare the maternity environment, particularly for mental health task-shifting initiatives in LMICs[178]. In HICs, most women welcome the opportunity to talk about mental health[179], and there are no differences in acceptability of different modes of screening tool (e.g., paper vs. iPad)[179,180], as long as women are given the opportunity to talk and are referred appropriately[179]. Some women, however, particularly those with mental health problems or histories of trauma, find disclosure difficult and routine enquiry less acceptable[179,180]. In LMICs, there may be additional cultural barriers and stigma[181,182].

Case identification of perinatal depression is often facilitated in universal services by tools such as the self-administered Edinburgh Postnatal Depression Scale, the Patient Health Questionnaire-9, or the two depression screening questions (the Whooley questions)[183]. However, there is a high prevalence of other mental disorders in the perinatal period, which, in addition to perinatal depression, are also associated with considerable morbidity. So, some have suggested the use of other tools to detect these disorders.

There is very limited evidence to support this. A recent study on the diagnostic accuracy of the Generalized Anxiety Disorder 2-items (GAD-2) suggests that its use would be unhelpful, due to the high number of false positives generated[30]. This is likely to be even more of a problem for less common disorders. However, depression screening tools can also detect other psychopathology[184].

Assessment and treatment of women in mental health services

Once mental health problems are detected, clear referral pathways should facilitate prompt treatment. The Antenatal and Postnatal Mental Health Guidelines produced by the NICE[2] recommended comprehensive psychosocial assessment by mental health services within two weeks, and treatment within six weeks.

These are challenging targets and mean that generic mental health services would need to fast-track perinatal women and/or specialist perinatal mental health services to be sufficiently resourced to treat women quickly.

The above guidelines also recommended that assessment should include the relationship with the baby, but it is not clear which tool could be used by mental health practitioners to identify women (and partners) needing extra help with this relationship.

Barriers to access

Some groups may need additional outreach to facilitate assessment and treatment. Teenagers and young women under 25 are at particularly high risk of having perinatal mental disorders, particularly anxiety disorders and PTSD[30], yet are groups that may not access timely antenatal care or mental health services. In secondary care, early intervention services have been specifically designed to facilitate access by young people with psychosis, but perinatal mental health services have not yet been designed with a focus on outreach for young people.

Barriers to access for other groups have also been identified across the care pathway – for example, ethnic and socio-economic differences in initial identification by universal services[185], and socio-economic differences in access to inpatient mother and baby units[186]. Qualitative research finds that different professional groups use different languages to communicate risk and have different perspectives of mental illness severity. Organizational barriers to access include unclear thresholds for escalating care and poor infrastructure for sharing information[187].

Qualitative meta-syntheses of studies in women with mental illness report several additional barriers for effective identification and intervention: fear of stigma, fear of custody loss, and anxiety about being prescribed psychotropic medications due to concerns about exposure in the unborn child[157,188].

Community and outpatient perinatal mental health care

Little is known currently about which community service models would best support women with the full range of diagnoses and complex needs. Qualitative research has found that, while women generally appreciate the tailoring of care to their perinatal specific needs, they also highlight that care from specialist teams

can mean disruption of continuity in community care[189].

Trials in US obstetric settings report a significantly greater improvement in depression in pregnancy and postpartum, compared to usual care, where integrative collaborative care includes an engagement session, assessment by a care manager, choice of support with antidepressant medication or a psychotherapy, and outreach for missed appointments[141,190].

Models of collaborative care in psychiatric settings liaising between maternity, primary care, generic community psychiatric care and specialist perinatal mental health care need to be developed and evaluated for women with perinatal mental disorders.

Current specialist perinatal mental health service models often exclude certain groups (e.g., women with comorbid substance misuse problems and/or personality disorder or experiences of child removal by social services)[191]. There has been remarkably little research on how services can best help women with complex mental health needs that are likely to impact on the mother and the child. Women often have themselves a history of developmental trauma, including removal from their own parents who may have been violent and abusive, and other experiences of childhood maltreatment[192].

Similarly, there is relatively little research into services for women with schizophrenia and related disorders, who, despite some evidence of reduced fertility, are likely to be pregnant at some point in their lives[193,194] and, from a human rights perspective, have the right to family life, with support if needed wherever possible, while ensuring safeguarding of children.

In practice, many countries do not have practitioners trained specifically for the perinatal period. Qualitative studies suggest that receiving interventions within generic services can be experienced as unhelpful by women[189,195], partly due to the therapists' failure to understand the potential impact of mental disorders on maternal functioning[195], and poor facilities for infants[169,195], though, as RCTs in LMICs demonstrate, task-shifting is possible if staff are suitably trained[96].

Where specialist community perinatal mental health services are available, the optimal skill mix of such services is not yet known. In the UK, for example, community multidisciplinary perinatal mental health teams now usually include most if not all of the following: psychiatrists, psychologists, mental health nurses, social workers, nursery nurses, an occupational therapist and a specialist pharmacist. Interventions include psychological therapies, medications, support in the relationship with the infant, and care planning including for women with a history of moderate to severe illnesses who may relapse in the postnatal period. Services have also recently expanded their remit to mental health assessment of partners[196]. Research in the effectiveness of these teams is underway. However, as staff in generic services need to address the needs of women of childbearing age, there is a potential risk of such perinatal mental health services deskilling staff in community and generic care.

Further evidence is needed on whether extension of services to the second year after birth is effective and cost-effective. However, quantitative and qualitative evidence supports the idea that the second year after birth is an important time for intervention. There is evidence of care needs after discharge from inpatient care[197], increased symptoms in the years 1-4 postpartum[198], a continued risk period for suicide beyond the first year after birth[45], and the importance of the first 1,001 days of the infants' life (from conception to age 2)[199]. This evidence also highlights the importance of generic psychiatric care, which needs to "think family" after the first two years postpartum.

Inpatient care

The provision of psychiatric inpatient mother and baby units around the world varies considerably[200]. However, these units have been established in several European countries, Australia and more recently Sri Lanka, India, the US, and New Zealand.

Mother and baby units provide mental health care for mothers, alongside care of the infant(s), and aim to treat the mother's mental illness and promote the facilitation of mother-infant interactions[200].

Consensus on the structure and staffing of these units varies internationally, but individual jurisdictions have produced guidance on skill mix and the minimum number of beds needed to retain specialist skills[201,202]. There are differences also in the nature of care for the infant (which varies from care provided by nurses, families providing care also within the unit, to a lack of facilities to admit infants overnight, so that infants are cared for at home other than for a few hours each day on the unit)[203-205].

Before-and-after assessments of the clinical and social care outcomes of patients attending mother and baby units indicate considerable improvements at discharge[203,205]. The extent of improvement is, however, adversely impacted by key clinical and demographic factors, such as a diagnosis of schizophrenia or personality disorder, low social support and low socio-economic status[206].

We have recently completed the first study using a quasi-experimental design to examine the effectiveness and cost-effectiveness of mother and baby units compared with generic acute psychiatric wards or crisis resolution teams (teams available daily providing intensive treatment at home)[207]. Analysis is underway to examine the effectiveness of mother and baby units in reducing readmission rates and other outcomes, including improving quality of mother-infant interactions one month after discharge.

RESEARCH IMPLICATIONS

Perinatal mental health research is increasingly seen as critical to public mental health, but evidence gaps mean that there is a need for:

- large RCTs on effectiveness and cost-effectiveness of interventions for the full range of disorders, including complex PTSD, eating disorders, anxiety disorders, autism and psychosis, in pregnancy and after birth;
- intervention studies in women with perinatal mental disorders that have adverse obstetric/pregnancy outcomes – obstet-

ric research (e.g., smoking cessation in pregnancy RCTs) should include better measures of perinatal mental health (to investigate whether this affects treatment efficacy and safety), and RCTs of obstetric interventions modified for this population (in particular, complex interventions that address multi-morbidity) should be conducted;
- research into how to support parenting difficulties, including support for women who experience custody loss;
- research on how to improve access to treatment for women with difficulties due to factors such as poverty, racism, stigma, interpersonal violence;
- research into public health interventions to fight stigma and to address the underlying causes of perinatal mental disorders;
- structured approaches in evaluating large-scale implementation programs, addressing not only maintenance of fidelity of interventions, but also how to facilitate system change with local contextual solutions.

Methodological work needed includes:

- improved measurement (adapting use of current instruments and/or developing new instruments, where needed, for the perinatal period, with robust evaluation of their psychometric properties);
- development of one or more core outcome sets, with the participation of women with lived experience of disorders;
- development of methods so that outcomes related to infant physical and mental health can be included in cost-effectiveness analyses of interventions for perinatal mental disorders[208];
- more systematic use of tools when designing and evaluating studies in systematic reviews (e.g., ROBINS-I[209] for observational studies of medication outcomes in pregnancy; TIDieR[210] for trials of psychosocial interventions);
- use of individual participant data meta-analysis, wherever possible, to facilitate systematic adjustment for known confounders and increase precision of estimates.

CONCLUSIONS

Generic psychiatric services will always care for women of childbearing age, many of whom will become pregnant, sometimes planned and sometimes unplanned, and have children. Therefore, mental health professionals in generic services need to be trained to "think family", so that they can deliver care with a life course lens, having pregnancies and families in mind.

Effective co-designed specialist perinatal mental health care, where available, is likely to impact on psychological morbidity in women and their children, but there is remarkably little known about how best to deliver this care.

Preconception and public health strategies may have the greatest impact on population health, but investment into perinatal mental health services, particularly when underpinned by a larger evidence base on interventions, is likely to reduce suffering for women and positively impact on their families.

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Advances in virtual care for perinatal mental disorders

In their excellent review, Howard and Khalifeh[1] ably outline the extent and burden of perinatal mental disorders internationally on women, children and families, and highlight the evidence-based treatments that can address these disorders. A key point in the review is the ever-consistent evidence that the vast majority of these disorders remain untreated or undertreated, in high, middle and low income countries alike. It is estimated globally that as few as one in every five women affected by a perinatal mental disorder receives the required treatment to achieve remission[2]. With 130 million births per year worldwide, and an estimated 20% of women affected annually, this means that about 2 million women each year will experience untreated or undertreated perinatal mental illness, with its substantial impact across generations.

The reasons why perinatal mental disorders are undertreated are multiple, complex and often inter-related. Some women are not offered, or do not seek, treatment due to lack of awareness about their condition, or due to shame, stigma, or family and community-related beliefs and pressures about mental illness around the time of pregnancy[3].

Evidence-based psychotherapies are a highly effective treatment option for common conditions such as depression, anxiety, obsessive-compulsive disorder, and trauma and stressor-related disorders, and preferred by most women. Yet, pregnant women may be unable to take time off work for regular in-person sessions while putting in hours prior to a parental leave. Postpartum, some women may not be able to travel initially after caesarean sections, and unpredictable infant schedules may make it difficult – if not impossible – to attend regular in-person appointments. In more severe illnesses, women and providers are often reluctant to initiate medications and/or increase dosages to adequate levels, especially when specialist support is unavailable to help determine whether potential benefits outweigh evidence around safety concerns[4]. Limitations in access to and uptake of treatment are compounded by a lack of specialized psychological and psychiatric support in many jurisdictions, especially outside of high income urban settings, and by the cost of services, transportation to reach them, and childcare during treatment sessions.

Virtual care – defined as any interaction occurring remotely between patients or members of their circle of care that uses communication or information technology to facilitate or maximize quality and effectiveness of patient care[5] – is a very attractive solution to these important and long-standing barriers to treatment of perinatal mental disorders.

Virtual care interventions may range from self-guided patient-facing applications, to asynchronous patient-provider or provider-provider communications, to live interactions over telephone or video that allow for care at a distance, or combinations of these. Models of care that leverage mobile applications are particularly accessible, sustainable, and provide low-cost scalable opportunities. Mobile technology has spread rapidly around the globe. Today, it is estimated that more than five billion people have mobile devices, and over half of these connections are smartphones, making virtual care a viable option for many. As such, virtual care has great potential to address some of the urgent challenges in ensuring timely and equitable access to effective health services for women with perinatal mental disorders across the globe.

Before we uptake these novel interventions, important questions need to be addressed. What types of virtual care interventions have been introduced in the treatment of perinatal mental disorders, and for what vulnerable sub-populations? Are these interventions reaching women who otherwise would not receive treatment? Are they as effective as in-person care? Do they need to be as effective as in-person care, if it means that some people who would otherwise receive no care at all are now receiving at least some evidence-based treatment?

Multiple interventions are being developed and evaluated, with many showing substantial promise for addressing the unique treatment barriers for perinatal mental disorders. A meta-synthesis of five qualitative studies reported that online peer-moderated discussion groups might reduce stigma and increase help-seeking. The beneficial effect may be related to helping women reconceptualize what it means to be a "good mother" and separate the stigma of experiencing mental illness from that of their maternal identity.

A recent meta-analytic review (including five randomized controlled trials) found that therapist-assisted web-based psychological interventions may also be an effective option for the treatment of perinatal depressive and anxiety symptoms, with medium-sized effects[6]. This is a highly attractive model clinically, as this type of intervention is more efficient than 1:1 live interactions, in that one clinician may be able to support more women in a specified time period, and women can work on their exercises during their own time, thus reducing the challenge of finding specific times for therapy on a continual basis.

In terms of "live" virtual care interventions, a recent trial of nurse-delivered telephone interpersonal therapy (IPT) for postpartum depression conducted by one of us (N=241) found that women receiving IPT were 4.5 less likely to be clinically depressed at 12 weeks post-randomization compared to those who received standard available care[7]. Some smaller "pilot" studies have started to make comparisons of video-based to in-person care, showing that, while women like in-person care when available, video- and telephone-based treatments provide more convenience, related to needing time off work and unpredictable child schedules[8].

Virtual care is also being leveraged to support women and health care providers when access to specialized advice is not immediately available in their jurisdictions. In the US, the Massachusetts Child Psychiatry Access Program (MCPAP) for Moms allows rapid telephonic access to perinatal psychiatric consultation for obstetrical providers, so that women can be

treated in their antenatal and postnatal care settings.

In the first 3.5 years, MCPAP for Moms enrolled 145 obstetric practices, conducted 145 trainings for 1,174 health care providers, and served 3,699 women, suggesting excellent utilization, with growing evidence of effectiveness[9]. In Canada, we found that decisional conflict around whether or not to use antidepressants in pregnancy was significantly reduced for preconception and postpartum women after using an online interactive patient decision aid, specifically among those who had no ready access to specialized reproductive psychiatric care[10].

One notable learning in the virtual care research is that not all interventions are one and the same. Even subtle differences in intervention design, application and dosage can impact acceptability, adherence and efficacy. For example, there is evidence to suggest that therapist-facilitated web-based psychological treatment is associated with high attrition when low-intensity online coaching is provided, but retention rates improve significantly when modified to telephone-based coaching[6].

Future research should target virtual care initiatives that improve access and reach among socio-economically vulnerable populations, including those with limited access to web or telephone, or those who have difficulty finding a private safe space to engage (e.g., in the setting of intimate partner violence). Further, effectiveness across cultures is important to determine whether standard interventions require modification.

Given the flexibility of digital technology in modern health systems, virtual care is a promising and exciting area to examine in order to address the undertreatment of women with perinatal mental disorders and improve access, uptake and reach. Rigorously designed trials and protocols to address unanswered questions are critical to ensuring that we make the most of this unprecedented opportunity.

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Pregnant women are still therapeutic orphans

"The pregnant woman is perhaps the last true therapeutic orphan. Because of the ethical, medicolegal and foetal safety concerns regarding pregnant women, few pharmacokinetic, pharmacodynamic or clinical trials are conducted during pregnancy." Stika and Frederiksen[1] made this observation about the lack of research on drug safety and efficacy in pregnant women in 2001.

In 2010, the US National Institutes of Health (NIH) published a report including this insightful comment: "There is so much we still do not know about how to treat pregnant women with health problems effectively and safely and how to prevent poor pregnancy outcomes. Clinical research could help provide that information. Yet, there remains a literally unhealthy reluctance to include pregnant women in clinical trials."[2]

Regrettably, these statements remain true today. In the US, a trans-governmental task force was charged with reviewing the gaps in knowledge about safe and effective therapies for pregnant and lactating women. The task force considered ethical issues raised by their enrolment in clinical research, reviewed existing investigations, produced recommendations to develop therapies, and considered effective communication strategies with health care professionals and the public. A striking statement in this document bears emphasizing: "A central theme resonated throughout the recommendations – the need to alter cultural assumptions that have significantly limited scientific knowledge of therapeutic product safety, effectiveness, and dosing for pregnant and lactating women. The cultural shift is necessary to emphasize the importance and public health significance of building a knowledge base to inform medical decision making for these populations."[3]

The societal motivation to protect pregnant women is powerful, but it must be aligned with their health and well-being. Pregnant women would be far better served by changing the conceptual framework from protecting them *from* research to protecting them *through* research. Excluding pregnant women from clinical trials limits medical knowledge for this population, which is discriminatory and dangerous. Allowing pregnant women to participate in research would ultimately contribute to protection of the population of pregnant women in the future.

The majority of pregnant women take at least one medication to treat a maternal condition. The average number of medications (excluding vitamins) used in pregnancy increased from 2.5 in 1976-1978 to 4.2 in 2006-2008, when 93.9% of pregnant women took at least one medication[4]. Despite these facts, evidence to guide effective drug treatment of pregnant women is largely lacking. A limited number of drug labels approved by the US Food and Drug Administration (primarily antiretroviral and anticonvulsant agents) include information about dose changes in pregnancy. However, the frequency and magnitude of plasma concentration changes across pregnancy is unknown for the majority of medications.

The significance of this lack of data was

demonstrated by the recommendation that pregnant women exposed to anthrax via bioterrorism take the antibiotic amoxicillin prophylactically. Subsequent pharmacokinetic studies revealed that plasma concentrations of this antibiotic would have been inadequate to protect pregnant women, because the physiology of pregnancy increases its clearance[5].

Notably, the NIH Adaptive COVID-19 Treatment Trial, a multinational double-blind placebo-controlled trial to evaluate the safety and efficacy of antiviral agents in hospitalized adults, excluded pregnant and lactating women.

The culture shift we need is supported by careful consideration of core health care ethical standards[6]. Non-maleficence is the principle of not causing harm to others. The mantra of "do no harm" is often invoked by practitioners as a rationale for withholding medications from an individual pregnant woman. Discomfort with responsibility for the potential harm to the foetus through drug exposure (the error of commission) is typically greater than for the harm of not prescribing medication to the pregnant woman, on whose health the foetus depends (the error of omission). The justification for not treating pregnant women also includes inadequate data to determine the benefits and harms of treatment, which creates a perpetual cycle of health disadvantage across time.

The principle of beneficence involves conceptualizing harms more broadly: creating knowledge that advances pharmacological care for pregnant women in the future benefits the population of these women. The principle of respect for autonomy implies the prioritization of patient decision-making for health care: who sets the boundary between the pregnant woman deciding for herself about research participation or a governing body that puts limits on the research that may be done with her? The final principle, justice, requires a fair distribution of benefits, risks and costs. Pregnant women unfairly pay for society's concern about harm to their foetuses. Barring these women from research participation violates the spirit of non-discriminatory access to advancing their health care.

Paradoxically, in the US, protectionism appears to end when the umbilical cord is cut. Mothers and newborns become social orphans. Much of our public policy suggests that maternal and infant health is a private matter for women to manage, rather than one of collective importance or governmental concern. The US Centers for Disease Control and Prevention reported that 55% of women of reproductive age in the country live in poverty – a clear adverse exposure.

The US is the only industrialized country that does not allow paid parental leave. Maternity leave is a critical factor in promoting maternal-infant attachment, improving health and behavioral outcomes for the mother-infant pair, and supporting breastfeeding. Paid leave and longer duration of leave (>12 weeks) reduces the adverse impact of early return to work after childbirth and is associated with improved mental health outcomes, especially among mothers working full-time[7]. Once back to work, many mothers do not have sick pay available, and childcare is unaffordable. The implicit message of these policies is that a woman's value is as a unit of business: she is responsible financially for the inconvenience of her absence from revenue-producing work due to childbirth and caring for her infant.

Another needed conceptual shift is optimizing the mental health of pregnant women rather than reducing symptoms of mental disorders. Positive mental health is a distinct construct, separate from the absence of disease, that is associated with improved birth outcomes and parenting practices which support favorable child development[8]. Emotional well-being is an overall positive state of emotional tone, life satisfaction, a sense of meaning and purpose, balance, and ability to pursue personal goals[9].

The quality of the foetal and childhood biopsychosocial milieu during the plastic early development phase is one of the determinants of the risk for diseases through the life cycle. For this reason, mental health of pregnant women and mothers must be optimized. For many of these women, health is optimized with pharmacotherapy.

Mental health professionals must insist on policies that improve the health of our pregnant and mothering patients. Through partnerships with visionary leaders internationally, we must consolidate and share responsibility for advancing treatment research for pregnant women with psychiatric illness and other medical disorders. In doing so, we will honor the extraordinary gift of newborns by caring for the women who create and nurture our next generation. We must adopt our orphaned pregnant women into the mainstream of health care research and practice.

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Prenatal mental health and the effects of stress on the foetus and the child. Should psychiatrists look beyond mental disorders?

Howard and Khalifeh[1] provide a thorough overview of the range of diagnosable mental disorders that can occur in the perinatal period, together with their frequency and methods for treatment. They discuss this in the context of help both for the mother and to prevent possible adverse effects on the child.

However, psychiatrists and other professionals may be able to help even if the pregnant woman does not have a mental disorder. The evidence suggests that there can be an increased risk to the future child if the mother feels stressed, or has experienced early trauma. It is important to think and help beyond diagnosis.

Several different types of prenatal stress for the mother have been shown to increase the risk of emotional, behavioral and cognitive problems for the child, and to play a causal role. Such stress in the mother includes her worry about the outcome of her pregnancy, her exposure to a raised level of daily hassles, to a natural or man-made disaster, and to emotional cruelty or other forms of domestic abuse by her partner[2].

External stressors and the mothers' levels of anxiety and depression are often even higher in low and middle income countries. In these countries, there can be additional stress due to poverty, external situations such as war, higher levels of interpersonal violence, and reasons for worry about the pregnancy outcome because of high infant or maternal mortality[3].

If the mother is stressed during pregnancy, the child is at increased risk of symptoms of anxiety and depression, attention-deficit/hyperactivity disorder, conduct disorder, and of being on the autistic spectrum. There can be other problems, including asthma and preterm delivery. Very severe stress in the first trimester, such as the death of an older child or exposure to an earthquake, increases the risk of later schizophrenia[4]. With the other outcomes, there can be effects throughout pregnancy.

With all these effects of prenatal stress, the evidence shows that there is only an increase in *risk* to the future child. Most children are not affected, and in those who are the degree of the impact is variable. The individual genetic vulnerabilities of the child, and the nature of the postnatal care can also influence outcome.

Early childhood maltreatment of the mother has been found to be associated with altered brain structure in the newborn, with reduced cortical grey matter. This association was independent of the mother's prenatal mood, and of other potential confounding variables[5]. This suggests that such early trauma may affect the mother's biology in a way that in turn alters the development of the brain of her foetus, and may indicate vulnerability to later depression and other problems for the child.

The pathways by which these various types of stress affect the woman's biology and so alter foetal neurodevelopment are not fully known. But some pathways are being uncovered[6]. These particularly involve the hypothalamic-pituitary-adrenal (HPA) axis, and the immune system[7]. The HPA axis and other biological systems respond to a wide range of external stressors, and their response is not associated with specific diagnoses of mental illness.

There is evidence that maternal and foetal cortisol levels are correlated especially in more anxious or depressed mothers. If the mother is anxious or depressed, this can alter the function of the placenta in a way that allows more cortisol to pass through to the foetus. Raised maternal cortisol is associated with altered brain function in the child, including higher internalizing symptoms in girls via alterations in neonatal amygdala connectivity[8]. Possible mediating factors for the effects of early trauma are those associated with the immune system and inflammation.

If we can intervene to help reduce stresses for pregnant women, we may be able to prevent some child neurodevelopmental problems. Psychiatrists are trained to diagnose mental disorders, and diagnosis is certainly important for treatment selection and prognosis. But in some contexts it is important to think beyond terms of specific diagnoses, and stress in pregnancy is one of them.

There have been attempts to think in a new way about mental ill health. One is the development of the Research Domain Criteria. This suggests a new framework to provide empirically based theories about psychological mechanisms that may be targeted in interventions. This approach would be ideal if we had a biological test showing which pregnant women are likely to be affected in a way linked to harming the foetus and later child. We do not yet have such a test. We know too little about which biological changes in the mother mediate the effects on the foetus.

But we may still be able to help. During pregnancy almost all women have contact with health professionals, who have an important role in helping both the woman and her future child. Health systems in different countries vary. But psychiatrists can help set the agenda. A wide range of different types of stress need to be detected and addressed. This is an issue that women themselves find important. In a recent poll, women chose "stress in pregnancy" as the topic most requiring increased attention from researchers, above others such as nutrition or infant attachment, in relation to child development[9], although the authors of this study do warn about the risk of alarming pregnant women about mild to moderate stress.

Thus, it may be appropriate for health professionals caring for pregnant women to explore aspects of their mental well-being which may be a source of stress. How is the relationship with the partner? Did they suffer from early abuse or other adverse childhood experiences? Do they have specific anxiety about the outcome of their pregnancy? Have they been exposed to any other major stresses, such as fire or flood; or major problems with money or housing? These are not questions usually explored and may not lead to a specific diagnosis. But, in taking care of pregnant women and in preventing adverse outcomes for their child, we may need to think in new ways about mental health in pregnancy.

We also may need to offer other support

in addition to drugs and talking therapies. These may include help with the relationship with the partner. The father is often a major source of stress, but can also be a major support. This may involve assisting with practical problems such as housing, or facilitating the provision of a stronger or more supportive social network.

The role of psychiatrists and all those caring for the emotional well-being of women in the perinatal period, and for the future child, is much more than helping with diagnosed psychiatric disorders.

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Supporting psychological well-being around the time of birth: what can we learn from maternity care?

The early identification and management of perinatal mental problems for women without pre-existing mental disorders is largely dependent on health professionals within maternity care and primary care[1]. Despite being willing to offer mental health care, there is evidence that many of these health professionals often do not feel confident and feel ill equipped to identify and support women with mental health problems[2].

While training and clearer care pathways will undoubtedly contribute to improve professional confidence in managing perinatal mental disorders, there are some features of the maternity care context that should be considered when moving forward to optimize perinatal mental health care: a) the overarching focus on health rather than ill health; b) the need to differentiate between manifestations related to pregnancy or childbirth and mental health problems.

A brief look at the history of maternity care in the latter half of the 20th century provides some insights into its overarching focus on health. Hospital births in the UK grew from just over 60% in 1960 to 96% by 1990. Alongside this development there was a change in how women gave birth. Spontaneous childbirth was the norm during the 1960s, with an induction rate of just 8%. Induction rates grew to 39% by 1974[3]. The increasing trend in obstetric interventions was evident internationally and became the driver for change in the 1990s. In 1990, the World Health Organization released *Care in Normal Birth: A Practical Guide*. Changing Childbirth was launched in the UK in 1993 and the Mother Friendly Childbirth Initiative in North America was launched in 1996. Recurring principles in these initiatives were the empowerment of women and autonomy in childbirth process while doing no harm. These remain the corner stone of maternity care today.

These maternity care principles are among the dimensions of psychological well-being outlined by Fava and Guidi[4] in a previous Forum in this journal: environmental mastery, personal growth, purpose in life, autonomy, self-acceptance and positive relations with others. Psychological well-being, that promotes flourishing rather than simply the absence of illness, should find a natural home in maternity care and yet, until recently, it has been relatively understudied[5].

Howard and Khalifeh[1] highlight that women with common mental disorders have adverse pregnancy outcomes such as preterm birth, although the evidence is by no means consistent. Conversely, there is growing evidence that women with high positive affect have higher gestational age and reduced risk of preterm birth than those with low positive affect, even after controlling for the effects of birthweight and psychosocial stress[6]. As with common mental disorders, the evidence is not consistent, with some studies demonstrating effect sizes that are not clinically meaningful[7] or statistically significant[5].

Much more research is needed to understand psychological well-being around the time of birth and its impact on the maternity population as a whole. Incorporating psychological well-being into care would offer an innovative approach to screening, prevention, and the interventions that we offer women. Reframing perinatal mental health to include psychological well-being may also help address stigma associated with diagnosis and treatment of perinatal disorders, that is heightened in the perinatal period due to a sense of shame and guilt related to being perceived as a "bad" mother. Focusing on psychological well-being should in no way detract from the identification and treatment of women with mental disorders. The promotion of euthymia (a state of internal calm and contentment) within general psychiatry has much to offer perinatal mental health care[4].

The second, and related, issue is the need to differentiate between the manifestations of pregnancy or childbirth and mental health problems. Running parallel to changes in maternity care were developments in perinatal mental health research and practice. In the 1960s and 70s, postpartum blues became popularized as a mild disorder that impacted on most women in the days just after childbirth. Postnatal depression also came to the fore in research and practice. By the 1980s there were queries about the legitimacy of such diagnoses. A. Oakley, a British sociologist, noted in her book *Women Confined* that women's accounts of depression in her research

sample reflected exhaustion, sleep deprivation, and feeling ill prepared for the shock of becoming a new parent, rather than being a psychological disorder[8]. Subsequent research indicates that the reality is likely to be much more complicated than either of these positions suggest.

Howard and Khalifeh note that measurement of perinatal mental health is hindered by lack of understanding of the importance of somatic symptoms[1]. Well-validated symptom checklists for depression in the general population, such as the Patient Health Questionnaire, have questions on tiredness and sleep disturbance that can be difficult to interpret, as it is unclear if these somatic symptoms are pregnancy-related or mental health-related. This does not mean that such questions are redundant. Rather, they provide a clear rationale for collaborative research and practice to disentangle the unique features of mental health in the perinatal period and in particular what constitutes ill health.

Yonkers et al[9] conducted an observational study of 838 women which aimed to determine if the rates of behavioral and somatic symptoms in pregnant women vary across trimesters and independently of a possible depressive disorder diagnosis. Women completed the Composite International Diagnostic Interview and the Edinburgh Postnatal Depression Scale before 17 weeks of gestation, at 26-30 weeks of pregnancy and 4-12 weeks postpartum. Pregnant women often experienced somatic symptoms in the first trimester of pregnancy, although depressed women still differed from those who were not depressed. Appetite increase, oversleeping and agitation were not informative symptoms in regard to identifying a major depressive disorder in pregnancy. It is important to explore this complex relationship further, as failure to do so could lead to the over-pathologizing of mental health manifestations on the one hand and on the other failure to identify obstetric complications in women with mental disorders, who are at increased risk for a range of obstetric adverse outcomes[1].

Despite perinatal mental disorders being the commonest complication of childbearing, mental health care continues to languish in the shadow of physical health care in the perinatal period. Throughout all the changes in maternity care, women with mental health problems have struggled to have their voices heard. Howard and Khalifeh have documented the considerable progress that has been made in perinatal mental health care, but many challenges remain. Much can and needs to be done to support the psychological well-being of women and their families. Reframing how we conceptualize perinatal mental health to include well-being approaches that acknowledge the complex relationship between pregnancy and mental health provides an opportunity to find effective solutions, so that more women and their families flourish.

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Perinatal mental health and the COVID-19 pandemic

Howard and Khalifeh[1] provide us with an excellent account of the epidemiology of perinatal mental health; the importance of social determinants of mental ill health, such as poverty, racism, and gender-based violence; and the state of current evidence to inform intervention and service delivery models. Their timely and comprehensive review of the current state of evidence identifies critical gaps in knowledge that will be important to address as the COVID-19 pandemic unfolds, particularly with regard to the intersection of individual level and community level interventions.

Once the worst impacts of the COVID-19 pandemic are past, the questions that should concern us are: a) how well prepared were we for an event on this scale; b) what service delivery models and intervention strategies are the most effective in supporting parent mental health when families and communities are faced with such large-scale upheaval; and c) what can be done to guard against events such as COVID-19 further entrenching mental health inequalities, both *within* high income countries, and *between* low, middle and high income countries.

With governments enforcing restrictions on travel, closing schools and workplaces, encouraging people to stay at home and limiting social gatherings, families with young children face a series of multi-faceted and unanticipated challenges. First-time parents are finding themselves caring for a newborn at home with limited or no access to support from extended family and restricted access to primary health care and mental health services. Parents of older children are faced with keeping them occupied at home for an extended (and unknown) period of time, coupled with responsibility for supervision of home schooling.

Millions of people previously employed have lost their jobs, with little chance of finding alternative employment at least in the short term. Those fortunate enough to have ongoing employment are having to navigate ways of maintaining paid work schedules and simultaneously manage the care of children at home. Not surprisingly, by early April 2020, the Australian national helpline for parents experiencing perinatal depression or anxiety (PANDA) had already recorded a 30% increase in calls to its telephone counselling service.

Globally, family violence services are

also gearing up for an escalation of domestic violence in coming months. Governments everywhere are struggling to manage both the economic and social fallout of containment measures, and what this means for citizens. In the past few months, the Australian government has announced an additional $150m for domestic violence services and free child care for working parents with children under five years of age.

These measures are welcome and, in the case of free child care, represent a huge turnaround in Australian government policy. However, other public health measures that normally provide support to families have been drastically curtailed. For example, publicly funded maternal and child health services can no longer provide new mothers groups or home visiting services. Programs specifically designed to provide culturally appropriate care and support to socially disadvantaged populations, such as group pregnancy care for families of refugee background, have also been wound back[2]. In low and middle income countries, evidence suggests there will be even more stark consequences of containment measures for children and families who are already vulnerable[3].

It has long been recognized that perinatal mental ill health has a complex etiology with both biological and social determinants[4]. The contribution of social and environmental factors such as gender-based violence, racism and forced migration is reflected in the higher prevalence of perinatal mental health disorders among women experiencing intimate partner violence and other adverse life circumstances[5,6]. In a longitudinal study of over 1,500 first-time mothers conducted by our group, one in three women experienced depressive symptoms during the first 12 months postpartum, and of these, two fifths (40%) had experienced emotional and/or physical violence by a current or former intimate partner in the first year after childbirth[6].

Gender-based violence, racism and other forms of human rights abuse have their roots in institutions and systems that fail to give all citizens equitable access to social and economic resources. Consideration of these contextual factors in framing service delivery responses is a critical element of high-quality mental health care, clearly articulated in the United Nations Sustainable Development Goals. As Howard and Khalifeh argue, public health interventions are also needed to tackle social determinants of risk for poor perinatal mental health at a systems and community level.

The COVID-19 pandemic necessitates worldwide action to strengthen both public health interventions promoting perinatal mental health and the capacity of mental health care services to support and enable the resilience of families dealing with cumulative social and economic stresses at times of crisis[7]. Howard and Khalifeh identify significant evidence gaps related to treatment efficacy, especially for women facing difficulties related to poverty, racism, stigma and interpersonal violence. They also draw attention to the paucity of evidence regarding large scale community-level interventions tackling system change with local contextual solutions. Strategies that work for particular communities and contexts may not work in others. In the Australian setting, this is most evident in relation to First Nations people, who experience markedly worse perinatal mental health outcomes than non-Indigenous Australians[8].

Mental health clinicians, health services and communities all have important roles to play in the development of rapid responses to limit the escalation and persistence of perinatal and other mental health disorders as a result of the COVID-19 pandemic. It is critical that the opportunity is not lost to ensure that these responses include the development and testing of co-designed strategies that build community-level resilience, foster strengths-based, trauma informed approaches, and tackle the sources of mental health inequalities globally. Better tailoring of individual level responses, taking account of social, economic and cultural contexts and engaging consumers and communities in the co-design of local primary health care and mental health services, is also needed to avoid further entrenchment of health inequalities[9].

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Postpartum psychosis: an important clue to the etiology of mental illness

Howard and Khalifeh[1] masterfully review the epidemiology of perinatal mental health conditions and the evidence base for their management. Here I address a further issue and exciting opportunity: the role that the study of severe perinatal mental illness can play in advancing our understanding of the etiology of mental health conditions.

The close relationship of severe episodes of mental illness to childbirth, episodes labelled postpartum psychosis, has been observed for hundreds, if not thousands, of years, and more recently this link has received support from clinical and ep-

idemiological studies[2]. Despite this long history, we have failed to take advantage of this important clue to the pathophysiology of mental illness.

One reason may be the confusion that remains around classification, with both DSM and ICD not dealing adequately with severe postpartum mental illness. As with many mental health conditions, there may be fuzziness around the boundaries, but there is clarity at the core of the concept of postpartum psychosis, and this concept remains useful and in widespread use by clinicians and women themselves. For example, the main third sector organization supporting women and their families in the UK is called Action on Postpartum Psychosis (app-network.org). Despite this nosological confusion, however, there is no doubt that "we know it when we see it".

What, then, is postpartum psychosis and why is this condition potentially so important in our understanding of the etiology of mental disorders? Postpartum psychosis is a severe episode of mental illness that impacts around 1 in 1,000 women following childbirth[2]. Onset is in the immediate postpartum, most often the first or second postpartum week. The symptoms are most commonly of an affective psychosis, with perplexity common, and often a rapidly and constantly changing ("kaleidoscopic") presentation.

Postpartum psychosis is a true psychiatric emergency, with admission to hospital usually required, but, despite the initial severity and rapidity of presentation, prognosis is good, with most episodes responding well to treatment, predominantly medication in the acute stage. Following the initial psychotic phase, however, women may experience longer episodes of depression, and many of them report that full recovery takes many months. Psychological interventions, including peer support, in the longer term can be very helpful in the recovery process.

Although around 50% of women with postpartum psychosis have not experienced a previous episode of mental illness, there is a clear link to bipolar disorder, especially bipolar I disorder. Women with a previous diagnosis of bipolar disorder are at high risk (around one in five deliveries)[3]. In addition, women who experience postpartum psychosis as a first episode, even if not clearly bipolar at initial presentation, are at high risk of subsequent bipolar illness[4].

The evidence is clear, therefore, that childbirth is a potent trigger of episodes of severe mental illness, and that this risk is not spread evenly across all mental illness, but shows a specific link to bipolar disorder. What are the mechanisms behind this association? Although psychological and social factors clearly play an important role in perinatal mental health conditions in general, and postnatal depression in particular, when it comes to postpartum psychosis biological factors are likely to be primary, with hormonal, immunological, circadian rhythm, and genetic factors all suggested to play a role[2].

There is a dramatic rise in levels of reproductive hormones (oestrogen and progesterone) in pregnancy and a precipitous fall in the immediate postpartum, corresponding to the exact time that sees the peak onset for postpartum psychosis. Periods of hormonal fluctuation, in the menstrual cycle for example, are known to be associated with mood symptoms, and this had led to hormonal factors being considered in the etiology of postpartum psychosis. The evidence base for this assertion remains, however, mostly circumstantial. There have been no consistently demonstrated abnormalities in hormonal levels in women experiencing perinatal mental illness, but it remains possible that women with postpartum episodes are differentially sensitive to the normal hormonal fluctuations associated with pregnancy and childbirth[5].

In recent years, the role that immunological mechanisms and inflammation play in psychiatric disorders has received considerable attention. This, combined with the fact that pregnancy is a major immunological challenge, has led some to hypothesize that immune and neuroinflammatory mechanisms play a role in the etiology of postpartum psychosis. Further support comes from the evidence of increased risk in first pregnancies, a finding shared with other pregnancy-related disorders, such as pre-eclampsia, which are thought to be driven by immunological mechanisms. Studies have found some evidence pointing to the role of immune biomarkers. For example, women with postpartum psychosis in one study did not display the expected T cell elevation following childbirth, but rather presented a monocytosis[6]. In addition, small numbers of women with postpartum psychosis (around 2%) were reported to have antineuronal autoantibodies in one study[7].

A further clue to etiology comes from the known link between circadian rhythm disturbance and the triggering of mood disorder, particularly mania, combined with the almost universal disturbance of sleep patterns that having a baby involves. Although it has not been studied extensively, there is some evidence in support of this hypothesis. For example, one study found that women with bipolar disorder who reported that sleep loss triggered episodes of mania were more than twice as likely to have experienced postpartum psychosis[8].

A further hypothesis receiving attention is the potential involvement of genetic factors. Family and linkage studies suggest a genetic etiology, and a number of linkage and candidate gene studies have been reported, but are yet to yield replicated results[2]. Sample sizes have been limited up to now, but large-scale collaborative efforts are underway to significantly increase the numbers available.

In summary, childbirth is a potent trigger for severe mood disorder, and this link gives us unrivalled opportunities for research into etiology. In no other scenario can we identify individuals, currently well, who are at such a high risk of experiencing a severe episode of mental illness in a defined two-week period. In addition to understanding more about etiology, we also have a significant opportunity for prevention, through the development of predictive models identifying which women are at very high risk[9].

We need, therefore, to take advantage of the vital clue that postpartum psychosis represents. First, we need this condition to be better dealt with by the ICD and DSM classification systems, which currently are of little help in ensuring that these episodes are recorded. Second, we need to build large cohorts of women who have

experienced this condition for international collaborations to look, for example, at its genetic underpinnings. Finally, we need prospective studies of selected populations, for example women with previous episodes of bipolar disorder, applying a range of paradigms, from imaging to other biomarkers, allowing us to better identify subjects at high risk.

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Pregnancy specific anxiety: an under-recognized problem

Howard and Khalifeh[1] discuss the high prevalence of common mental disorders in the perinatal period and emphasize the need for early detection. Overall, research in this area has mostly focused on perinatal depression, and the role of anxiety has been relatively neglected until recently. It is also true, however, that anxiety and depression often co-exist.

A recent systematic review reports the prevalence of any clinically diagnosed anxiety disorder across the three trimesters of pregnancy to be 15.2%. In the first four weeks following childbirth, 17.8% of women experience significant anxiety symptoms. These rates are higher in low- and middle-income countries (LMICs) compared to high-income ones[2].

A form of anxiety which has not received the attention it deserves is pregnancy specific anxiety (PSA), i.e. the condition marked by worries, concerns and fears about pregnancy, childbirth, the health of the infant, and future parenting. This is considered to be distinct from generalized anxiety, as it occurs specifically during pregnancy and the anxiety revolves only around pregnancy-specific issues. PSA shows a different longitudinal course from generalized anxiety, is predictive of birth weight and gestational age at birth, and is more common in nulliparous women.

An overlapping construct is that of pregnancy related anxiety (PRA), which was proposed following a concept analysis of 38 studies[3]. PRA is described as the nervousness and fear about the baby's health, the mother's health and appearance, the experience with the health care system, and social and financial issues in the context of pregnancy, childbirth and parenting.

While the prevalence of PSA is reported to be around 29% in high-income countries[4], studies from LMICs such as India, Iran, Tanzania and China have reported rates up to 55.7%. Most studies report higher rates of PSA in the third trimester of pregnancy[5,6].

The interest in PSA has led to the development of two specific tools: the Perinatal Anxiety Screening Scale (PASS) and the Pregnancy-Related Anxiety Questionnaire - Revised (PRAQ-R). The PASS is a 31-item questionnaire used to screen a broad range of anxiety symptoms in perinatal women, with pregnancy-specific anxiety questions as a separate part[7]. The PRAQ-R is a 10-item questionnaire specifically focusing on symptoms of PSA, such as fear of giving birth, worries about bearing a physically or mentally challenged child, and concern about one's own appearance[8].

The risk factors for PSA are different in LMICs compared to high-income countries. Studies conducted in India and Africa have emphasized that – despite good family support and marital life – perceived stress, active depression and the number of people living in the home predicted PSA[5]. In high-income countries, young age, being unmarried, lower education, lower household income, being nulliparous, and having an undesired pregnancy were associated with a higher risk for PSA[4].

PSA has also been found to be related to pregnancy outcomes. Among Iranian women, PSA in the third trimester was associated with preterm birth. A study from the US found high levels of PSA to be significantly associated with an increased risk for spontaneous preterm birth, even after adjusting for several confounding factors. A cohort study in China found that PSA in the second and third trimesters was associated with small-for-gestational-age infants.

PSA may also play a role in birth preferences, as shown by a multi-ethnic prospective cohort study from Amsterdam, which found that women with PSA were more likely to receive pain relief/sedation and had an increased risk for primary caesarean section.

Another important finding is the relationship of PSA to infant temperament. In a systematic review, Erickson et al[9] found an association between PSA and infant temperament in seven of the nine studies reviewed, three of which included large, representative, population-based samples. In a study of 282 mothers, PSA during second and third trimesters was significantly associated with infant's negative emotional reactivity, mainly fearfulness. PSA emerged as the only significant predictor even after controlling for background factors and for postnatal depressive and general anxiety symptoms[10].

PSA has also been shown to have persisting effects in the postnatal period. Women who had PSA at 32 weeks of gestation exhibited clinically significant anxiety at six months postpartum even after controlling for prenatal generalized anxiety.

The risk for PSA is likely to be particularly high in countries with high maternal and infant mortality rates. In African countries, maternal mortality rates range from 163 to 533 per 100,000. In some African countries, 51 per 1,000 infants may not survive their first year. In addition, pregnant women in these areas may face challenges such as food insecurity and lack of adequate maternity services, which may

contribute to high levels of anxiety about their pregnancy and infant outcomes.

We believe that research in the area of perinatal mental health needs to be context-specific and aim to develop useful screening and assessment methods, in addition to cost-effective interventions and services. The area of PSA may indeed be particularly relevant to LMICs.

PSA needs to be regarded as a distinct entity, which may have a different clinical profile and course compared to generalized anxiety. However, it appears to be an understudied and under-recognized topic in perinatal mental health. Considering its impact on both maternal and foetal outcomes, it needs greater attention from both clinicians and researchers.

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Paternal perinatal mental disorders are inextricably linked to maternal and child morbidity

While women and their offspring disproportionately bear the morbidity and mortality burden of perinatal mental disorders, men should not be forgotten in perinatal health care settings. Yet historically, as emphasized by Howard and Khalifeh[1], they have been overlooked.

Compared with maternal mental disorders, there has been scant investigation of the prevalence, pathogenesis, risk, impact and economic costs of common mental disorders in fathers during the perinatal period, and of targeted interventions that could inform family-focused service delivery models.

Over the past five years, the focus has somewhat shifted, and a stronger lens has been cast on men, especially with respect to perinatal depression and anxiety. This is coupled to the recognition that pregnancy, birth and fatherhood directly influence men's mental health and well-being. Notwithstanding, paternal perinatal depression and anxiety are not recognized as discrete diagnostic entities in the DSM-5. The lack of explicit diagnostic criteria has led to heterogeneity in the way these conditions are defined, and contributed to variability in research findings.

The prenatal, labour and delivery, and postnatal periods are characterized by psychological, emotional, biological, social and role changes that signal the transition to fatherhood. In a substantial proportion of fathers, this transition is also associated with serious and impairing mental health concerns. Perinatal mood and anxiety disorders are common in men and, like in women, can lead to cognitive, developmental and behavioural problems as well as to mood and anxiety disorders in the offspring[2].

Prevalence estimates for depression during pregnancy and up to a year postpartum are 8% in men, nearly twice the rate in the general adult male population. The prevalence averages 16% for any anxiety disorder in the prenatal and postnatal periods, a rate that is comparable with that in the general population[3,4]. However, prevalence rates of anxiety in fathers during the perinatal period are highly variable, ranging from 2.4% to 51%. This reflects, to some extent, cross-study methodological differences in measurement, sampling, eligibility criteria, study setting, and cultural factors[5]. It should be noted that the rates of depression and anxiety in men and fathers are likely to be under-estimates, in view of symptom under-reporting by men.

Although the etiopathogenesis of paternal perinatal depression and anxiety has not been elucidated, it is plausible that a complex interrelationship exists among individual-level biological predisposition (e.g., genetic, epigenetic, neuroendocrine determinants), psychosocial variables, relational stress, and environmental and social factors.

It is notable that maternal and paternal perinatal depression are mutually interdependent. Maternal depression is one of the most common predictors of paternal perinatal depression, while mothers whose partners are depressed are more than four times more likely to have worsened symptoms by six months postpartum[6].

In men, there is also a high coexistence of anxiety and depression, with high anxiety levels during the perinatal period contributing to depression, stress and perceived diminished self-efficacy in coping with the challenges of fatherhood[4,5]. Unfortunately, our understanding of the trajectories of co-occurring depression and anxiety in relation to perinatal stage, and of the precipitating, perpetuating and maintaining factors for depression-anxiety occurrence in the prenatal and postnatal periods, is very limited. Longitudinal studies which prospectively assess mood and anxiety disorders and symptoms in men prior to pregnancy and at repeated intervals throughout the perinatal period, and which include "non-perinatal" male controls, to parse out the prenatal effects of depression and anxiety from normal variation, are needed[4].

Despite the prevalence and impact of paternal perinatal mood and anxiety disorders, family-focused programs that seek to address fathers' well-being are very few. Further, the absence of randomized controlled trials (RCTs) of tailored psychotherapy or pharmacotherapy is striking. The benefits of cognitive behaviour

therapy (CBT)-based treatments, which have proven efficacy in maternal perinatal depression and anxiety, are unknown at this point in time. So too are the benefits of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, which have not been evaluated in RCTs in pregnant mothers on ethical grounds.

Several models of care have been proposed for fathers. First, including fathers as supporting partners to mothers living with perinatal depression treated with individual or group CBT. Second, using a whole family approach by engaging both partners in treatment concurrently (e.g., couples therapy). Third, providing exclusive treatment options for fathers with perinatal mental disorders (e.g., CBT). CBT delivered in a group setting or via the Internet may be viable options, as there is some evidence that they are associated with lower dropout rates in men.

In a systematic review of interventions for paternal perinatal depression, six of the 14 trials found a significant but small reduction in depression scores, while the remaining eight reported no beneficial effects[7]. The interventions were all psychoeducationally oriented and, interestingly, none exclusively targeted paternal mental health. Instead, they addressed paternal well-being indirectly by focusing on the mother, infant or couple relationship.

All this calls for targeted psychological and pharmacological intervention trials in fathers, including trials of transdiagnostic interventions for co-occurring mood, anxiety and substance use disorders, to establish what works. The urgency to provide interventions to men is underscored by findings of an association between depression in fathers during the postnatal period and subsequent depression in daughters at age 18 years[8].

Perinatal mental illness cannot be optimally addressed if men are not included as active partners in the continuum of prenatal and postnatal care. Perinatal mental health services should routinely incorporate comprehensive assessment of paternal psychopathology. The time to act is now.

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Nature and prevalence of combinations of mental disorders and their association with excess mortality in a population-based cohort study

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The nature and prevalence of combinations of mental disorders and their associations with premature mortality have never been reported in a comprehensive way. We describe the most common combinations of mental disorders and estimate excess mortality associated with these combinations. We designed a population-based cohort study including all 7,505,576 persons living in Denmark at some point between January 1, 1995 and December 31, 2016. Information on mental disorders and mortality was obtained from national registers. A total of 546,090 individuals (10.5%) living in Denmark on January 1, 1995 were diagnosed with at least one mental disorder during the 22-year follow-up period. The overall crude rate of diagnosis of mental disorders was 9.28 (95% CI: 9.26-9.30) per 1,000 person-years. The rate of diagnosis of additional mental disorders was 70.01 (95% CI: 69.80-70.26) per 1,000 person-years for individuals with one disorder already diagnosed. At the end of follow-up, two out of five individuals with mental disorders were diagnosed with two or more disorder types. The most prevalent were neurotic/stress-related/somatoform disorders (ICD-10 F40-F48) and mood disorders (ICD-10 F30-F39), which – alone or in combination with other disorders – were present in 64.8% of individuals diagnosed with any mental disorder. Mortality rates were higher for people with mental disorders compared to those without mental disorders. The highest mortality rate ratio was 5.97 (95% CI: 5.52-6.45) for the combination of schizophrenia (ICD-10 F20-F29), neurotic/stress-related/somatoform disorders and substance use disorders (ICD-10 F10-F19). Any combination of mental disorders was associated with a shorter life expectancy compared to the general Danish population, with differences in remaining life expectancy ranging from 5.06 years (95% CI: 5.01-5.11) to 17.46 years (95% CI: 16.86-18.03). The largest excess mortality was observed for combinations that included substance use disorders. This study reports novel estimates related to the "force of comorbidity" and provides new insights into the contribution of substance use disorders to premature mortality in those with comorbid mental disorders.

Key words: Mental disorders, comorbidity, mortality, life expectancy, substance use disorders, mood disorders, neurotic/stress-related/somatoform disorders, schizophrenia

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It has long been recognized that individuals with a mental disorder are at increased risk of subsequently developing other mental disorders[1]. In a recent study based on comprehensive Danish registers, we demonstrated the pervasive nature of comorbidity within mental disorders by showing that individuals with any type of psychiatric diagnosis were at increased risk for subsequently developing all other types of mental disorders[2]. In that study, we restricted the analyses to pairs of disorders. This simplifying assumption made the analyses more tractable, but ignored the fact that some individuals will have three or more types of mental disorders.

While statistical methods have provided insights into the patterns of comorbidity (e.g., internalizing and externalizing disorders as defined by latent class analysis)[3,4], the nature and prevalence of combinations of mental disorders have not previously been described in a comprehensive way. Groups of disorders can be considered in temporally-ordered sets (i.e., permutations) or sets that occurred during a period of observation regardless of temporal order (i.e., combinations). To keep the analysis of comorbidity tractable, we chose to explore combinations of mental disorders regardless of temporal order. Actually, our previous research[2] found that, for pairs of mental disorders with comparable ages of onset (e.g., depression and anxiety disorders)[5], the risk of comorbidity was often symmetrical, regardless of which disorder came first.

It is clear that mental disorders are associated with premature mortality[6-8]. However, mortality-related metrics such as mortality rate ratios are usually shown for single types of mental disorders[9,10], or broad categories of mental disorders[7]. While it is useful to compare these estimates across mental disorders, and some models adjust for prior mental disorders[11], such studies have not captured the complex nature of comorbidity and its potential impact on mortality.

Based on the types of mental disorders included in the Global Burden of Disease study, we have recently demonstrated that those with two or more types of mental disorders have a shorter life expectancy (i.e., more life-years lost) compared to those with one type of mental disorder[12]. There is a need to more precisely map the associations between specific combinations of mental disorders and excess mortality.

We had the opportunity to explore the above-mentioned research questions using high quality Danish registers. The aims of the current study were to: a) describe the rate of accumulation of mental disorders over time; b) explore the prevalence and demographic correlates of combinations of mental disorders; c)

estimate the mortality rate ratio for these combinations; and d) estimate the reduction in life expectancy for each mental disorder set.

Based on our previous observations that common disorders such as mood disorders, neurotic/stress-related/somatoform disorders and substance use disorders were each associated with appreciable risks of developing a range of other disorders[2], we predicted that these disorders would be found in many common combinations. Furthermore, since we estimated that substance use disorders were strongly associated with premature mortality (when looking both at mortality rates and life expectancy)[7], and that life expectancy was shorter for those with two or more types of mental disorders[12], we predicted that combinations including substance use disorders or a larger number of disorders would be associated with greater risk of premature mortality.

METHODS

Study population

We defined two population-based cohorts – one dynamic and one fixed – in order to optimize the analyses of the key research questions in this study.

The dynamic cohort included all 7,505,576 persons younger than 95 years living in Denmark at some point between January 1, 1995 and December 31, 2016. Each individual in the study was followed from birth, immigration to Denmark, or January 1, 1995 (whichever happened last) until death, emigration from Denmark, 95th birthday, or December 31, 2016 (whichever happened first).

The fixed cohort comprised a subset of the dynamic cohort. More specifically, it included all 5,205,859 individuals living in Denmark on January 1, 1995 (thus, it did not include those born in or immigrating to Denmark after that date).

All data were obtained from the Danish Civil Registration System[13], which has maintained information on all residents since 1968, including sex, date of birth, continuously updated information on vital status, and a unique personal identification number that can be used to link information from various national registries.

Assessment of mental disorders

Information on mental disorders was obtained from the Danish Psychiatric Central Research Register[14], which contains data on all admissions to psychiatric inpatient facilities since 1969 and all visits to outpatient psychiatric departments and emergency departments since 1995.

The diagnostic system used was the Danish modification of the ICD-8 from 1969 to 1993, and of the ICD-10 from 1994 onwards. In order to make the analyses tractable, and to avoid identified comorbidity within broad domains (e.g., several types of anxiety disorders or substance use disorders), we used the ICD-10 subchapter categories considered in previous publications based on Danish registers[2,3]: organic, including symptomatic, mental disorders (F00-F09); mental and behavioral disorders due to psychoactive substance use (substance use disorders) (F10-F19); schizophrenia and related disorders (F20-F29); mood disorders (F30-F39); neurotic, stress-related and somatoform disorders (F40-F48); eating disorders (F50); personality disorders (F60); intellectual disabilities (F70-F79); pervasive developmental disorders (F84); and behavioral and emotional disorders with onset usually occurring in childhood and adolescence (here abbreviated as "behavioral disorders") (F90-F98).

For each individual in the study, the date of onset for each disorder was defined as the date of first contact with the psychiatric care system.

Statistical analysis

Prevalence estimates and demographic correlates of all combinations of mental disorders were calculated using the fixed cohort of individuals living in Denmark on January 1, 1995, who had 22 years of follow-up (unless censored due to death or emigration). This was done to allow for accumulation of comorbidity over time, and measurement of demographic correlates on the same date (which would not have been possible with the dynamic cohort).

We described the rate and number of different mental disorders diagnosed during the 22-year period according to sex, country of birth (Denmark or others) and several baseline characteristics (each measured on January 1, 1995): age, gross yearly income, highest education achieved, and labour market affiliation[15]. *Post-hoc* analyses compared the rate of diagnoses between different categories using Wald tests.

Results on mortality were based on the dynamic cohort (the fixed cohort of individuals living in Denmark on January 1, 1995 plus those born in or immigrating to Denmark between 1995 and 2016). We used the dynamic cohort to estimate mortality because time-to-event analyses can easily deal with dynamic cohorts, and the larger sample provided us with more precise estimates.

Each person was classified as experiencing a specific combination of mental disorders, with all disorders modelled as time-varying variables[16]. Date of onset for a given combination of disorders was based on the date of diagnosis of the last of the disorders.

Mortality rate ratios (MRRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models, with age as the underlying time scale, and adjusting for sex and calendar time. Sex-specific estimates were obtained by including an interaction term in the models.

In keeping with previous studies[7,8,10], remaining life expectancy after onset of a combination of disorders compared to the general population of same sex and age was estimated as excess life-years lost. The technical development of this method has recently been published[8,17], and a detailed account of how to implement it is available[18]. CIs for these estimates were obtained using non-parametric bootstrap with 1,000 iterations.

All analyses were performed using R version 3.5.2. The Danish Data Protection Agency, Statistics Denmark, and the Danish Health Data Authority approved this study.

Table 1 Diagnoses of mental disorders according to baseline characteristics of the fixed cohort (those living in Denmark on January 1, 1995)

			Follow-up (millions of person-years)	Rate of mental disorders per 1,000 person-years		Number (%) of people receiving diagnoses of mental disorders in 1995-2016				
	N	%		Rate (95% CI)	p	No diagnosis	Exactly one	Exactly two	Exactly three	Four or more
All persons	5,205,859	100.0	96.2	9.28 (9.26-9.30)	-	4,659,769 (89.5)	322,715 (6.2)	137,992 (2.7)	57,052 (1.1)	28,331 (0.5)
Gender										
Females	2,636,186	50.6	48.8	10.22 (10.19-10.24)	Ref.	2,329,457 (88.4)	183,055 (6.9)	76,453 (2.9)	31,496 (1.2)	15,725 (0.6)
Males	2,569,673	49.4	47.4	8.32 (8.29-8.34)	<0.001	2,330,312 (90.7)	139,660 (5.4)	61,539 (2.4)	25,556 (1.0)	12,606 (0.5)
Age in years										
0-24	1,601,184	30.8	32.4	11.16 (11.13-11.20)	Ref.	1,400,078 (87.4)	104,258 (6.5)	54,490 (3.4)	26,783 (1.7)	15,575 (1.0)
25-44	1,546,373	29.7	31.7	8.15 (8.12-8.18)	<0.001	1,397,201 (90.4)	79,074 (5.1)	42,451 (2.7)	18,652 1.2)	8,995 (0.6)
45-64	1,264,591	24.3	23.9	6.48 (6.45-6.51)	<0.001	1,163,068 (92.0)	64,262 (5.1)	25,163 (2.0)	8,834 (0.7)	3,264 (0.3)
65-84	710,330	13.6	7.8	14.24 (14.15-14.32)	<0.001	621,377 (87.5)	70,455 (9.9)	15,270 (2.1)	2,739 (0.4)	489 (0.1)
85+	83,381	1.6	0.3	19.97 (19.47-20.48)	<0.001	78,045 (93.6)	4,666 (5.6)	618 (0.7)	44 (0.1)	8 (0.0)
Country of birth										
Denmark	4,909,089	94.3	91.2	9.14 (9.12-9.16)	Ref.	4,398,470 (89.6)	302,871 (6.2)	128,048 (2.6)	53,284 (1.1)	26,416 (0.5)
Other	279,953	5.4	4.8	11.96 (11.86-12.06)	<0.001	246,092 (87.9)	18,739 (6.7)	9,563 (3.4)	3,676 (1.3)	1,883 (0.7)
Unknown	16,817	0.3	0.2	9.45 (9.07-9.85)	0.109	15,207 (90.4)	1,105 (6.6)	381 (2.3)	92 (0.5)	32 (0.2)
Gross annual income										
First tertile	1,729,421	33.2	26.7	14.85 (14.80-14.90)	Ref.	1,482,786 (85.7)	149,100 (8.6)	61,036 (3.5)	24,141 (1.4)	12,358 (0.7)
Second tertile	1,729,404	33.2	34.5	8.65 (8.62-8.68)	<0.001	1,551,023 (89.7)	101,624 (5.9)	46,463 (2.7)	20,268 (1.2)	10,026 (0.6)
Third tertile	1,729,407	33.2	34.6	5.58 (5.55-5.60)	<0.001	1,610,373 (93.1)	70,879 (4.1)	29,868 (1.7)	12,441 (0.7)	5,846 (0.3)
No information	17,627	0.30	0.2	14.00 (13.54-14.48)	0.001	15,587 (88.4)	1,112 (6.3)	625 (3.5)	202 (1.1)	101 (0.6)
Highest education achieved										
Primary school	1,501,845	28.8	27.9	11.63 (11.59-11.67)	Ref.	1,306,090 (87.0)	113,138 (7.5)	50,673 (3.4)	21,054 (1.4)	10,890 (0.7)
High school / vocational training	2,044,183	39.3	40.9	8.10 (8.07-8.13)	<0.001	1,846,787 (90.3)	112,270 (5.5)	51,436 (2.5)	22,566 (1.1)	11,124 (0.5)
Higher education	1,161,094	22.3	22.9	7.20 (7.16-7.23)	<0.001	1,062,171 (91.5)	56,650 (4.9)	25,734 (2.2)	11,076 (1.0)	5,463 (0.5)
No information	498,737	9.6	4.4	16.12 (16.00-16.24)	<0.001	444,721 (89.2)	40,657 (8.2)	10,149 (2.0)	2,356 (0.5)	854 (0.2)
Labour market affiliation										
Employed	3,197,123	61.4	65.2	6.41 (6.39-6.43)	Ref.	2,944,905 (92.1)	145,423 (4.5)	65,480 (2.0)	28,088 (0.9)	13,227 (0.4)
Unemployed	324,286	6.2	6.5	12.80 (12.71-12.88)	<0.001	277,111 (85.5)	24,699 (7.6)	13,152 (4.1)	6,178 (1.9)	3,146 (1.0)
Outside workforce for other reasons	1,587,885	30.5	24.2	15.95 (15.90-16.00)	<0.001	1,345,347 (84.7)	149,862 (9.4)	58,372 (3.7)	22,492 (1.4)	11,812 (0.7)
No information	96,565	1.9	0.3	18.25 (17.80-18.71)	<0.001	92,406 (95.7)	2,731 (2.8)	988 (1.0)	294 (0.3)	146 (0.2)

Table 2 Mental disorders diagnosed in 1995-2016 by type and count

	At least one (N=546,090; 10.5%)			Exactly one (N=322,715; 6.2%)		Exactly two (N=137,992; 2.6%)		Exactly three (N=57,052; 1.1%)		Four or more (N=28,331; 0.5%)	
	Diagnoses	% of total population	% of 1+ disorders	Diagnoses	% of 1 disorder	Diagnoses	% of 2 disorders	Diagnoses	% of 3 disorders	Diagnoses	% of 4+ disorders
Organic disorders	111,575	2.1%	20.4%	76,503	23.7%	22,694	16.4%	7,694	13.5%	4,684	16.5%
Substance use disorders	109,264	2.1%	20.0%	27,639	8.6%	36,562	26.5%	25,828	45.3%	19,235	67.9%
Schizophrenia	73,131	1.4%	13.4%	19,884	6.2%	22,852	16.6%	15,654	27.4%	14,741	52.0%
Mood disorders	199,701	3.8%	36.6%	67,267	20.8%	71,825	52.1%	38,356	67.2%	22,253	78.5%
Neurotic/stress-related/ somatoform disorders	237,277	4.6%	43.5%	96,478	29.9%	73,057	52.9%	42,513	74.5%	25,229	89.1%
Eating disorders	17,613	0.3%	3.2%	6,525	2.0%	4,444	3.2%	3,208	5.6%	3,436	12.1%
Personality disorders	80,160	1.5%	14.7%	10,604	3.3%	24,760	17.9%	24,572	43.1%	20,224	71.4%
Intellectual disabilities	15,387	0.3%	2.8%	3,200	1.0%	5,963	4.3%	3,352	5.9%	2,872	10.1%
Developmental disorders	11,004	0.2%	2.0%	2,863	0.9%	3,787	2.7%	2,390	4.2%	1,964	6.9%
Behavioral disorders	37,337	0.7%	6.8%	11,752	3.6%	10,040	7.3%	7,589	13.3%	7,956	28.1%
Total person-diagnoses	892,449			322,715		275,984		171,156		122,594	

"Behavioral disorders" is an abbreviation for "behavioral and emotional disorders with onset usually occurring in childhood and adolescence"

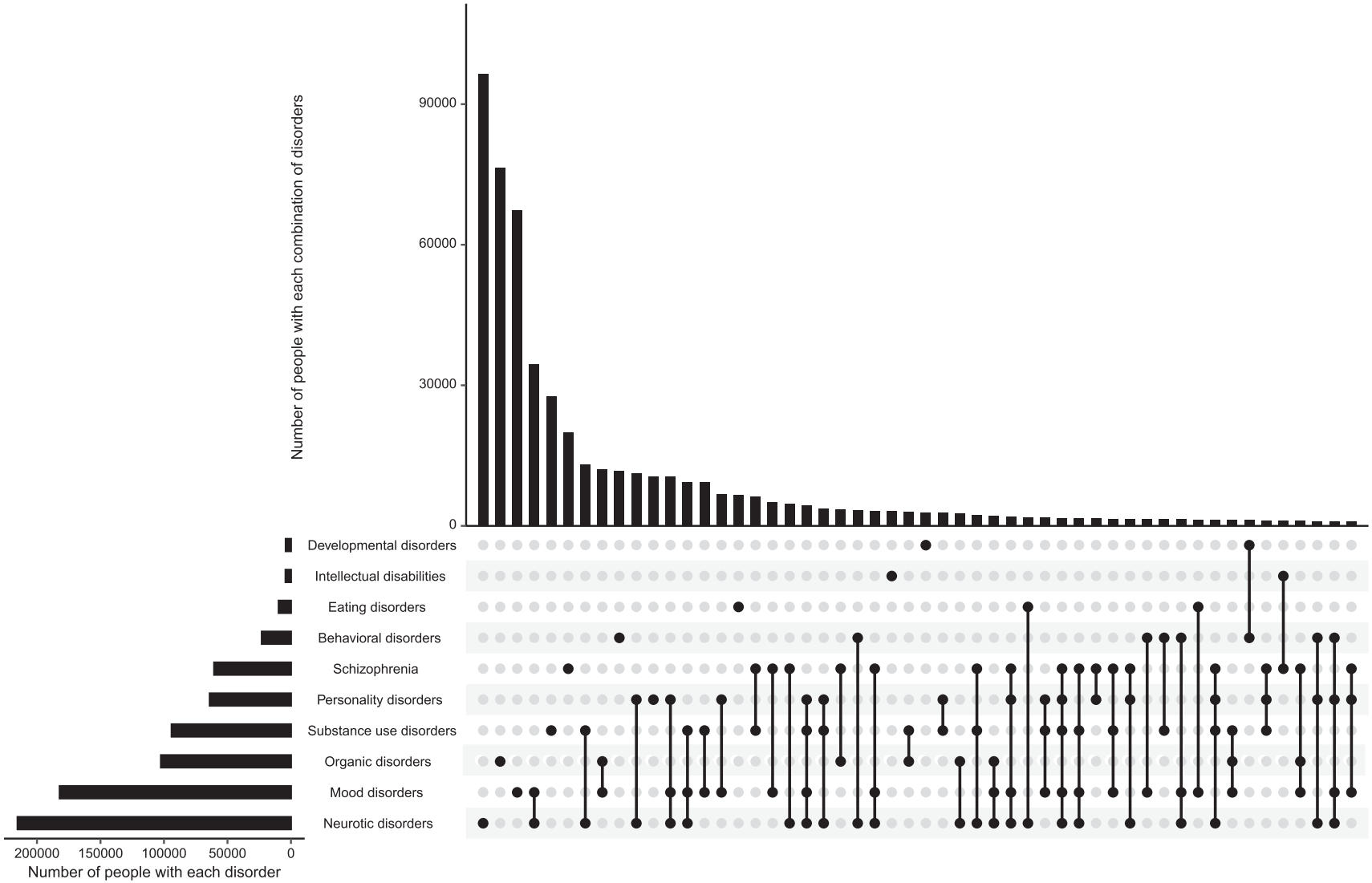

Figure 1 Combinations of mental disorders (with at least 1,000 people) diagnosed during the follow-up period (1995-2016); number of people diagnosed with each single disorder (horizontal bars); and number of people diagnosed with each combination of disorders (vertical bars). "Behavioral disorders" is an abbreviation for "behavioral and emotional disorders with onset usually occurring in childhood and adolescence". "Neurotic disorders" is an abbreviation for "neurotic, stress-related and somatoform disorders".

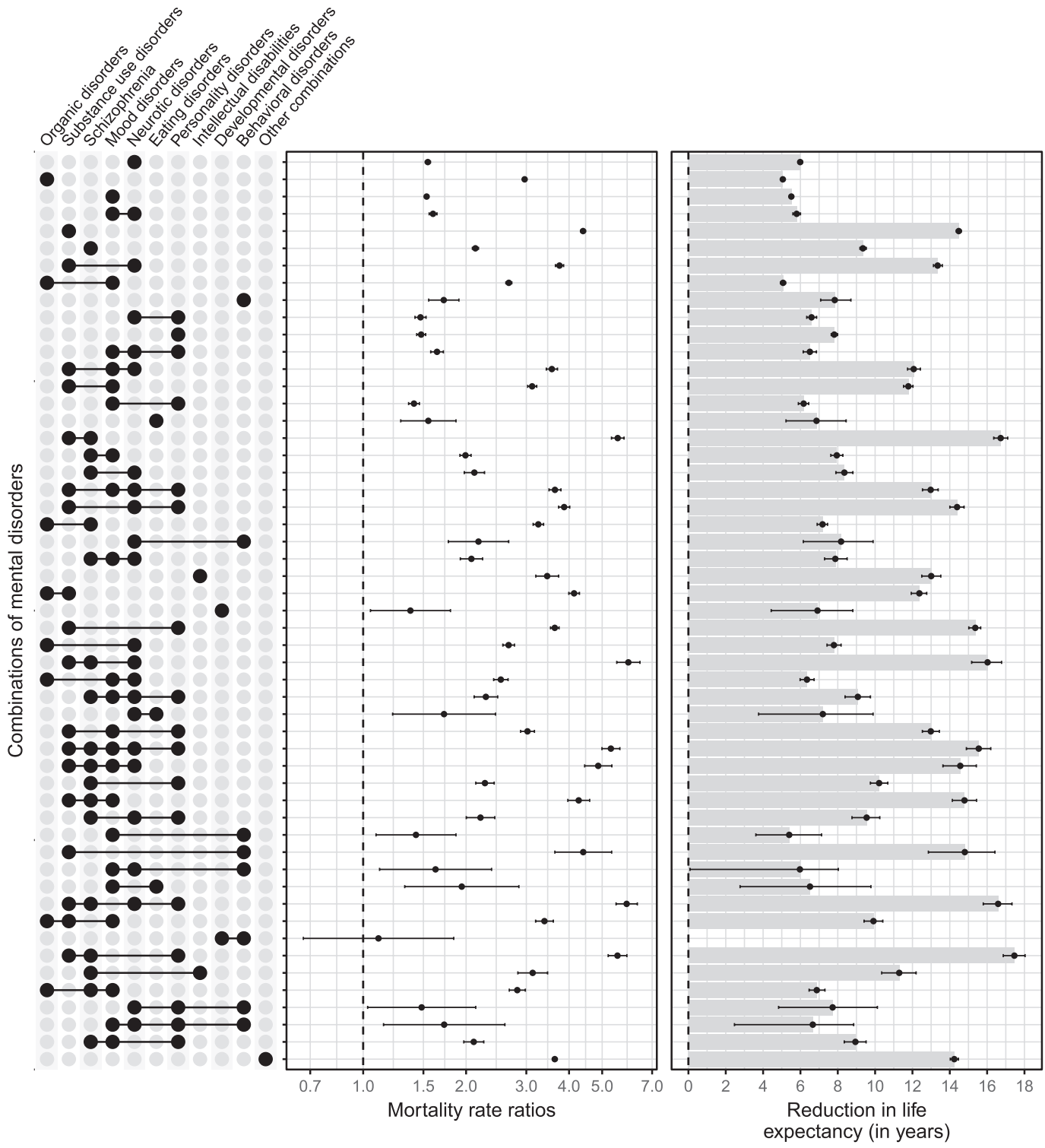

Figure 2 Mortality rate ratios comparing individuals experiencing each combination of mental disorders with individuals without any diagnosed disorder, adjusted for sex, age and calendar time; and reduction in life expectancy (in years) for individuals experiencing each combination of mental disorders compared to the general population of the same sex and age. The dashed line represents no excess mortality. "Behavioral disorders" is an abbreviation for "behavioral and emotional disorders with onset usually occurring in childhood and adolescence". "Neurotic disorders" is an abbreviation for "neurotic, stress-related and somatoform disorders".

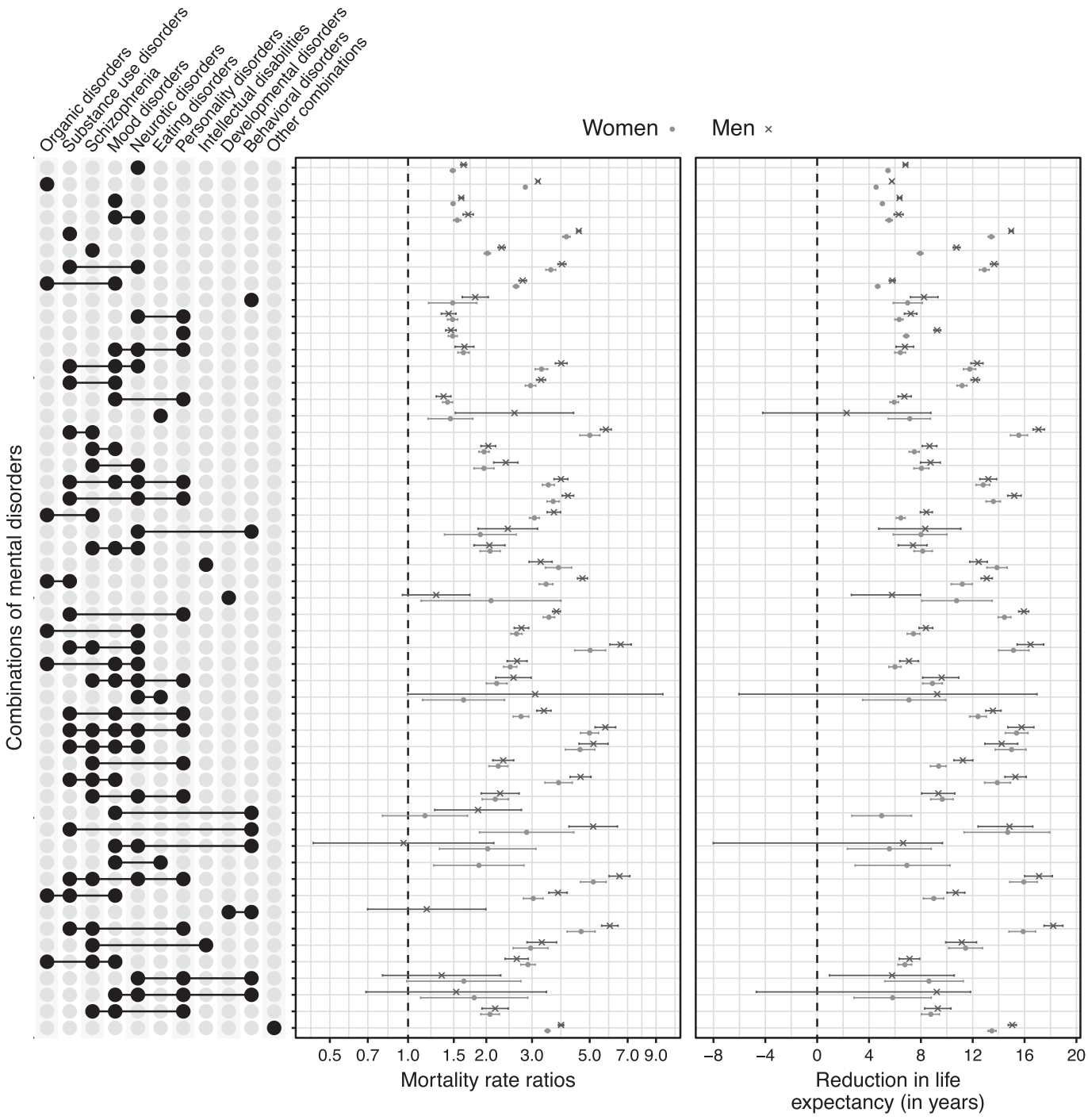

Figure 3 Sex-specific mortality rate ratios comparing individuals experiencing each combination of mental disorders with individuals without any diagnosed disorder, adjusted for age and calendar time; and reduction in life expectancy (in years) for individuals experiencing each combination of mental disorders compared to the general population of the same sex and age. The dashed line represents no excess mortality. "Behavioral disorders" is an abbreviation for "behavioral and emotional disorders with onset usually occurring in childhood and adolescence". "Neurotic disorders" is an abbreviation for "neurotic, stress-related and somatoform disorders".

RESULTS

The fixed cohort of 5,205,859 Danish residents on January 1, 1995 (2,569,673 males and 2,636,186 females) was followed for 96.2 million person-years, and the longest individual follow-up period was 22 years (1995-2016). Overall, 75% of persons were followed for at least 17.7 years.

During the follow-up period, 546,090 persons (10.5%) were diagnosed with at least one mental disorder. The overall crude rate of diagnosis of mental disorders was 9.28 (95% CI: 9.26-9.30)

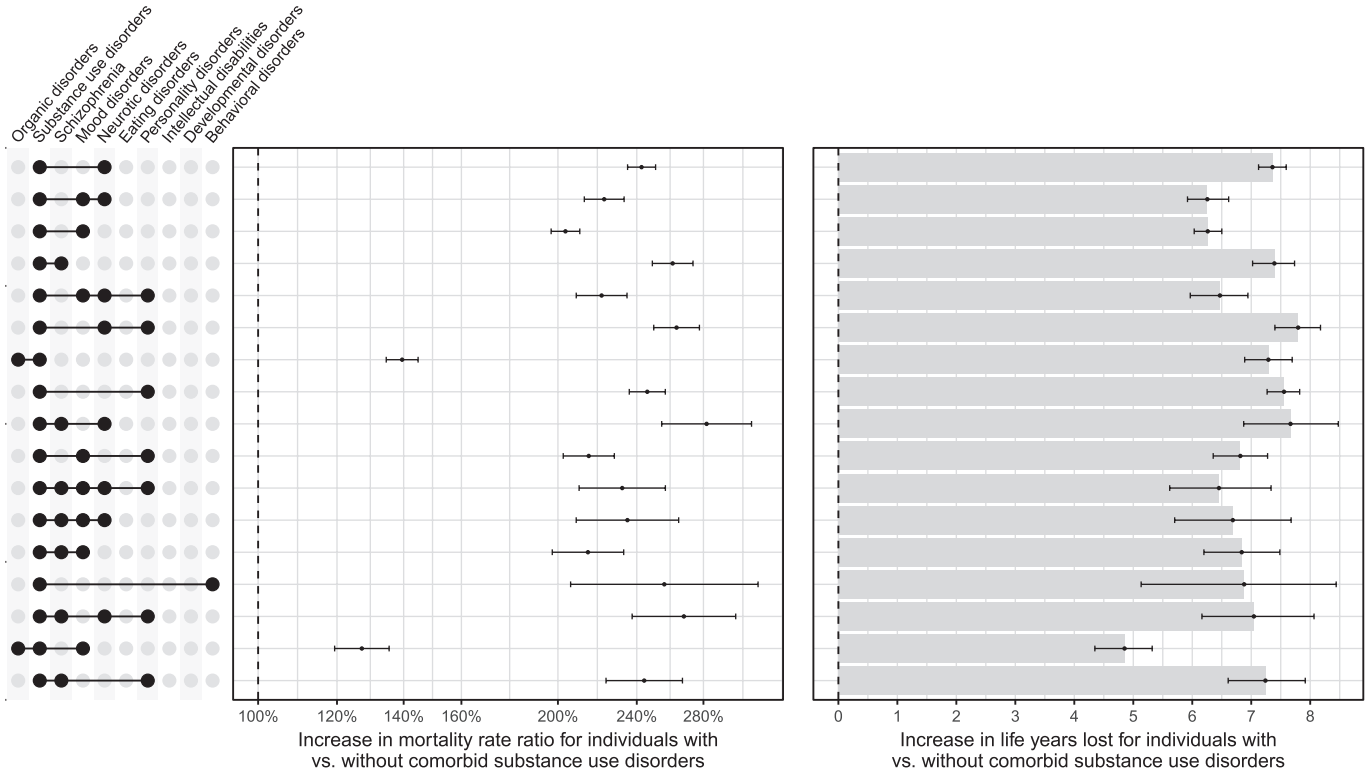

Figure 4 Increase in mortality rate ratio for individuals experiencing each combination of mental disorders with vs. without substance use disorders, adjusted for sex, age and calendar time; and increase in life years lost for individuals experiencing each combination of mental disorders with vs. without substance use disorders. The dashed line represents no excess mortality associated with the addition of substance use disorders to each combination of disorders. "Behavioral disorders" is an abbreviation for "behavioral and emotional disorders with onset usually occurring in childhood and adolescence". "Neurotic disorders" is an abbreviation for "neurotic, stress-related and somatoform disorders".

per 1,000 person-years. The rate of mental disorders was lower among males compared to females, among individuals 45-64 years old compared to other age groups, among those born in Denmark compared to those born elsewhere, among higher income vs. lower income and higher education vs. lower education groups, and among those employed vs. unemployed or otherwise outside the workforce ($p<0.001$ for all comparisons, see Table 1).

The rate of diagnosis of additional mental disorders was 70.01 (95% CI: 69.80-70.26) per 1,000 person-years for individuals with one disorder already diagnosed. In those with two disorders, the rate of additional disorders was 63.70 (95% CI: 63.35-64.06) per 1,000 person-years. The rates of additional disorders dropped slightly to 55.33 (95% CI: 54.77-55.89) and 45.48 (95% CI: 44.57-46.42) for individuals diagnosed with three, or four or more disorders, respectively.

Mental disorders by count and type

During the 22-year follow-up period, the 546,090 persons with at least one disorder received in total 892,449 mental disorder diagnoses. At the end of follow-up, there were 332,715 persons (6.2%) with exactly one disorder, 137,992 (2.7%) with exactly two, 57,052 (1.1%) with exactly three, and 28,331 (0.5%) with four or more mental disorders (see Table 1).

The 22-year prevalence for all disorders is presented in Table 2 and Figure 1. The most prevalent mental disorders were neurotic/stress-related/somatoform disorders (4.6% of the total population) and mood disorders (3.8% of the total population). Among individuals with at least one mental disorder, 43.5% had a neurotic/stress-related/somatoform disorder and 36.6% had a mood disorder.

Most common sets of mental disorders

We observed 616 out of 1,024 possible sets of disorders (2^{10} combinations of disorders without considering time ordering). The 52 most common sets (with at least 1,000 individuals each), representing 92.8% of all persons with diagnosed mental disorders, are shown in Figure 1.

The three most common sets were composed of one disorder type (exactly-one-count sets): neurotic/stress-related/somatoform disorders (N=96,478; 17.7% of the total 546,090 individuals with at least one diagnosis), organic disorders (N=76,503; 14.0%), and mood disorders (N=67,267; 12.3%).

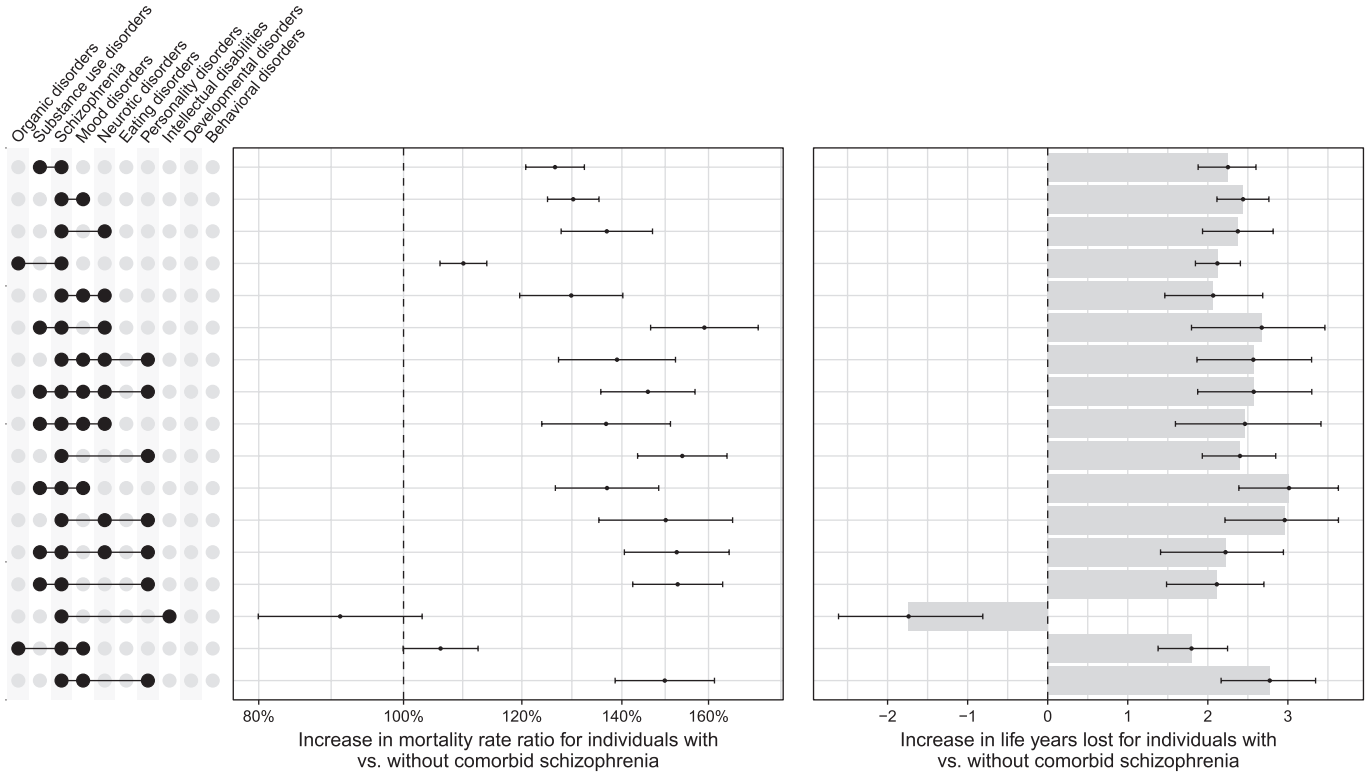

Figure 5 Increase in mortality rate ratio for individuals experiencing each combination of mental disorders with vs. without schizophrenia, adjusted for sex, age and calendar time; and increase in life years lost for individuals experiencing each combination of mental disorders with vs. without schizophrenia. The dashed line represents no excess mortality associated with the addition of schizophrenia to each combination of disorders. "Behavioral disorders" is an abbreviation for "behavioral and emotional disorders with onset usually occurring in childhood and adolescence". "Neurotic disorders" is an abbreviation for "neurotic, stress-related and somatoform disorders".

The fourth most common set was comorbid mood and neurotic/stress-related/somatoform disorders (which was also the most prevalent exactly-two-count set; N=34,504; 6.3%). The most common exactly-three-count set consisted of mood, neurotic/stress-related/somatoform, and personality disorders (N=10,592; 1.9%). These three disorder types, in combination with substance use disorders, comprised the most common exactly-four-count set (N=4,414; 0.8%).

Indeed, mood and/or neurotic/stress-related/somatoform disorders, alone or in combination with other disorders, were present in 64.8% of individuals diagnosed with any mental disorder. This percentage increased to 80.0% among individuals with exactly two disorders, 91.6% among those with three disorders, and 97.7% among those with four or more disorders.

Excess mortality associated with combinations of mental disorders

The dynamic cohort consisted of all 5,205,859 people from the fixed cohort along with an additional 2,299,717 people born in or immigrating to Denmark after January 1, 1995, resulting in a total of 7,505,576 individuals (3,742,852 males and 3,762,724 females) and 116.5 million person-years of follow-up.

Overall, 1,171,035 people (589,337 males and 581,698 females) died during the 22-year observation period (15.6% of all males and females). Mortality rates were higher for people with any of the 52 most common combinations of mental disorders compared to those without mental disorders, except for those experiencing the combination of behavioral and pervasive developmental disorders (MRR 1.11, 95% CI: 0.67-1.84). The highest MRR was 5.97 (95% CI: 5.52-6.45) for the three-disorder combination of schizophrenia, neurotic/stress-related/somatoform disorders and substance use disorders (Figure 2).

Each of the 52 combinations of mental disorders was associated with shorter life expectancy compared with the general population. The smallest difference in remaining life expectancy was observed for organic disorders: 5.06 years (95% CI: 5.01-5.11). The largest difference in life expectancy was observed for those diagnosed with the three-disorder combination of schizophrenia, personality disorders and substance use disorders: 17.46 years (95% CI: 16.86-18.03) (see Figure 2).

Males had higher mortality rates and a larger reduction in life expectancy than females for several disorders (e.g., schizophrenia, mood disorders, neurotic/stress-related/somatoform disorders, substance use disorders) and combinations of disorders (e.g., mood and neurotic/stress-related/somatoform disorders; substance use and neurotic/stress-related/somatoform

disorders; mood and substance use disorders). Females did not have significantly higher mortality rates for any combination of disorders compared to males. However, among persons with pervasive developmental disorders alone, females had a larger reduction in life expectancy (see Figure 3).

The addition of comorbid schizophrenia and, especially, substance use disorders to any diagnosis or set of diagnoses was associated with increased mortality rates and reduced life expectancy across all combinations (see Figures 4 and 5). For example, individuals diagnosed with mood disorders alone experienced 1.5 times higher mortality rates than individuals without any diagnosis (MRR 1.53, 95% CI: 1.51-1.55), while individuals diagnosed with mood and substance use disorders experienced three times higher mortality rates (MRR 3.12, 95% CI: 3.03-3.22).

DISCUSSION

In this study we describe the fine-grained details of patterns of comorbidities within mental disorders, as well as the associations between these sets of mental disorders and subsequent mortality rates and life expectancy.

Overall, one in every 10 individuals received a diagnosis of at least one mental disorder during the 22-year follow-up period. Among those with mental disorders, about two out of five were diagnosed with two or more types. In keeping with prior studies based on latent class analyses[4,5], mood and neurotic/stress-related/ somatoform disorders commonly co-occurred, and contributed to many different sets of comorbid mental disorders.

Results regarding the accumulation of mental disorders showed that the rate of additional diagnoses after an initial diagnosis was higher than the overall rate of any diagnosis, demonstrating the "force of comorbidity". The rates of additional diagnoses after two or more disorders was slightly lower, but still higher than the overall rate of any diagnosis.

Our study is the first to provide mortality estimates related to combinations of a comprehensive range of mental disorders. The associations between mental disorders and mortality highlight the prominent role of comorbid substance use disorders with respect to both elevated mortality rates and reduced life expectancy. These findings are in line with previous research[9,19-21] that observed higher mortality rates in patients with attention deficit/ hyperactivity and other behavioral disorders, schizophrenia, bipolar disorder or depression, if they additionally experienced a comorbid substance use disorder.

Substance use disorders are relatively common[3,6], and we observed that these disorders often feature in combinations of mental disorders. Our previous research found that the risk of being diagnosed with substance use disorders was higher for those with other prior mental disorders[2]. For example, those diagnosed with a mood or neurotic/stress-related/somatoform disorder were 10 and 12 times more likely to be subsequently diagnosed with substance use disorders, respectively; such that 13% were diagnosed with substance use disorders within 15 years after the first diagnosis of the mood or neurotic/stress-related/somatoform disorder. In light of our new findings pointing to the substantial contribution of substance use also to premature mortality in those with mental disorders, efforts related to the prevention[22] and the early detection and prompt treatment[23] of this type of comorbidity warrant added emphasis.

Our study has several key strengths, the most important one being the use of population-based registers, which allowed for the inclusion of the entire population with prospectively collected data. This design and analysis greatly reduce the potential for selection and/or immortal time biases (i.e., when some individuals cannot experience death during follow-up because of the design of the study). Moreover, health care is free in Denmark, reducing the potential inequalities in access to care between people with different socio-economic background. Additionally, as date of death was obtained from registers and is thought to be accurate[24], mortality estimates were not affected by potential misclassification.

However, there are some limitations of the study that need to be taken into consideration. First, in order to make the analyses tractable and allow comparisons to related publications[2,3,7], we considered broad diagnostic categories, rather than specific disorders. Second, we relied on clinical diagnoses rather than direct structured diagnostic interviews to identify mental disorders; however, several studies have confirmed that many register-based mental disorder diagnoses have good validity[25-29].

Third, although the study included the entire population, diagnosed individuals included only those with mental disorders registered in secondary care – individuals with untreated mental disorders, or treated solely by a general practitioner, were misclassified as having not experienced the mental disorder. While it is reasonable to assume that the most severe disorders will eventually be registered in secondary care, the identification of milder disorders could be underestimated[30,31]. In addition, we did not identify remission through registers; the group of individuals with a mental disorder can therefore be interpreted as persons who have had a diagnosis of a mental disorder, irrespective of their potential subsequent recovery.

Fourth, the study period used to identify combinations of disorders comprised 22 years (from 1995 until 2016). While this is a long period to identify the most common sets of disorders, the estimates cannot be interpreted as lifetime prevalences of these combinations. With access to longer follow-up times, we might have seen patterns of comorbidity linking disorders with early onset to those with late onset. Finally, patterns of mental disorders and their associated excess mortality in the Danish population may not generalize to other countries.

To the best of our knowledge, this study is the largest and most detailed to quantify the frequency of combinations of comorbid mental disorders to date. We report novel estimates related to the "force of comorbidity". In addition, we provide new insights into the contribution of substance use disorders to the premature mortality in those with comorbid mental disorders. We hope that this research will motivate clinical research designed to identify ways to prevent the development of comorbidity within mental disorders, as well as early detection and prompt treatment.

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Testing structural models of psychopathology at the genomic level

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Genome-wide association studies (GWAS) have revealed hundreds of genetic loci associated with the vulnerability to major psychiatric disorders, and post-GWAS analyses have shown substantial genetic correlations among these disorders. This evidence supports the existence of a higher-order structure of psychopathology at both the genetic and phenotypic levels. Despite recent efforts by collaborative consortia such as the Hierarchical Taxonomy of Psychopathology (HiTOP), this structure remains unclear. In this study, we tested multiple alternative structural models of psychopathology at the genomic level, using the genetic correlations among fourteen psychiatric disorders and related psychological traits estimated from GWAS summary statistics. The best-fitting model included four correlated higher-order factors – externalizing, internalizing, thought problems, and neurodevelopmental disorders – which showed distinct patterns of genetic correlations with external validity variables and accounted for substantial genetic variance in their constituent disorders. A bifactor model including a general factor of psychopathology as well as the four specific factors fit worse than the above model. Several model modifications were tested to explore the placement of some disorders – such as bipolar disorder, obsessive-compulsive disorder, and eating disorders – within the broader psychopathology structure. The best-fitting model indicated that eating disorders and obsessive-compulsive disorder, on the one hand, and bipolar disorder and schizophrenia, on the other, load together on the same thought problems factor. These findings provide support for several of the HiTOP higher-order dimensions and suggest a similar structure of psychopathology at the genomic and phenotypic levels.

Key words: Genome-wide association studies (GWAS), Hierarchical Taxonomy of Psychopathology (HiTOP), psychiatric disorders, psychological traits, externalizing, internalizing, thought problems, neurodevelopmental disorders

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Over the past several years, genome-wide association studies (GWAS) have shed considerable light on the genetic underpinnings of major psychiatric disorders, including schizophrenia, bipolar disorder, and depression[1-3]. In addition to revealing replicable genetic loci associated with these disorders, various post-GWAS analyses have identified the amount of trait variation that is due to genetic factors – i.e., the single nucleotide polymorphism (SNP)-based heritability[4,5] – as well as the genetic correlations between traits[6]. Recent studies have shown substantial genetic correlations among various psychiatric disorders[6,7], mirroring phenotypic correlations, and suggesting a shared genetic vulnerability which reflects a higher-order structure of psychopathology[8-10].

Various models of the underlying phenotypic structure of psychopathology, which capture the substantial correlations among psychiatric disorders, have been advanced in the literature, including a two-factor model comprising externalizing and internalizing dimensions[11], a three-factor model that distinguishes distress from fears within internalizing[12], and models that include a thought problems factor[13].

One theoretical conceptualization of the structure of psychopathology, the Hierarchical Taxonomy of Psychopathology (HiTOP)[8], posits that the risk for psychopathology is captured by a general factor (p factor), which in turn influences specific spectra of psychopathology (e.g., internalizing, thought disorder), which in turn influence more specific dimensions or subfactors (e.g., fears and distress pathology) and disorders (e.g., major depressive disorder).

A bifactor model, including a general factor onto which all disorders load and specific factors that capture the remaining covariance related to groups of disorders (e.g., externalizing and internalizing), has shown a sharp rise in popularity among psychopathology researchers. Nonetheless, statisticians have pointed out difficulties in distinguishing between bifactor and correlated factor models[14,15] and the tendency for model fit indices to be biased in favor of the bifactor model[16-18].

Some researchers argue that genetic and psychobiological levels of analysis enhance investigation of the structure of psychopathology and augment what is learned through pure statistical comparisons[14]. Given this, and the moderate-to-high genetic correlations observed among psychiatric disorders and related psychological traits, examination of the higher-order structure of psychopathology at the genomic level is warranted.

Two recent studies have examined the factor structure of psychopathology and related traits at the genomic level. Grotzinger et al[19] fit a model containing a single common factor of psychopathology using GWAS summary statistics for schizophrenia, bipolar disorder, major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and anxiety disorders. Their results indicated that each disorder had a moderate-to-high loading on the common factor, revealing that genetic covariation among psychiatric disorders can be captured using factor analysis. Lee et al[20] used an exploratory approach to examine the genetic covariance among eight psychiatric disorders using GWAS summary statistics, and found evidence for a three-factor model which included factors representing compulsive behaviors, mood and psychotic disorders, and neurodevelopmental disorders.

In the present study, we capitalized on the fourteen largest GWAS of psychiatric disorders and related psychological traits to obtain estimates of genetic correlations and test alternative structural models of psychopathology at the genomic level. We included more disorders and traits and tested more alternative

models of psychopathology than in previous studies[19,20], guided by both the phenotypic literature and previously estimated genetic correlations. We also evaluated the construct validity of our best-fitting model by estimating genetic correlations between the higher-order factors and external criterion variables, such as educational attainment and personality characteristics.

METHODS

GWAS summary statistics

We conducted a systematic search of repositories of publicly available GWAS summary statistics for psychiatric disorders and relevant external criterion variables.

The summary statistics for attention-deficit/hyperactivity disorder (ADHD)[21], autism spectrum disorder (ASD)[22], bipolar disorder[3], anorexia nervosa[23], MDD[1], schizophrenia[2], PTSD[24], obsessive-compulsive disorder (OCD)[25], tobacco use[26], and anxiety disorders[27] were downloaded from the Psychiatric Genomics Consortium (PGC) repository. Some of these samples were augmented by samples from other consortia, such as the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) for ADHD, ASD and MDD; the Anxiety NeuroGenetics Study (ANGST) for anxiety disorders; the International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS) for OCD; and the Tobacco and Genetics Consortium (TGC) for tobacco use. The summary statistics for antisocial behavior[28] were obtained from the Broad Antisocial Behavior Consortium (BroadABC), and those for aggression[29] from the Early Genetics and Lifecourse Epidemiology (EAGLE) consortium (Table 1).

The summary statistics for age at first birth and number of children[30], neuroticism, subjective well-being, depression symptoms[31], and educational attainment[32] were downloaded from the Social Science Genetic Association Consortium (SSGAC) repository; those for extraversion[33], openness to experience, agreeableness, and conscientiousness[34] from the Genetics of Personality Consortium (GPC) repository; those for loneliness[35] from the PGC; and those for body mass index[36] were obtained from the Genetic Investigation of Anthropometric Traits (GIANT) consortium repository and the UK Biobank (Table 2).

When summary statistics for an existing GWAS could not be found online, the authors of the relevant publications were contacted via email and asked to provide those statistics, as was the case for alcohol dependence[37] and cannabis dependence[38]. When results from more than one GWAS of the same disorder were available, the most recent and largest GWAS was chosen. With the exception of schizophrenia and loneliness, for which only GWAS from admixed populations were available, we used summary statistics from European ancestry individuals.

Tobacco use, antisocial behavior, aggression, and all of the external criterion variables were assessed using a continuous

Table 1 Characteristics of studies of disorders and traits included in the analyses

Phenotype	Study	Year	Data source	Sample size (cases/controls)	Study design	Effect size	Ancestry
ADHD	DeMontis et al[21]	2017	PGC, iPSYCH	20,183/35,191	Case-control	OR	European
Alcohol dependence	Walters et al[37]	2018	PGC	10,206/28,480	Case-control	OR	European
Cannabis dependence	Agrawal et al[38]	2018	PGC	3,757/9,931	Case-control	Beta	European
Tobacco use	Furberg et al[26]	2010	PGC, TGC	73,853	Continuous	Beta	European
Aggression	Pappa et al[30]	2016	EAGLE	18,988	Continuous	Beta	European
Antisocial behavior	Tielbeek et al[28]	2017	BroadABC	16,400	Continuous	Beta	European
Eating disorders	Duncan et al[24]	2017	PGC	3,495/10,982	Case-control	OR	European
Anxiety disorders	Otowa et al[27]	2016	PGC, ANGST	7,016/14,745	Case-control	Beta	European
PTSD	Duncan et al[24]	2017	PGC	2,424/7,113	Case-control	OR	European
MDD	Wray et al[1]	2018	PGC, iPSYCH	59,851/113,154	Case-control	OR	European
OCD	Arnold et al[25]	2017	PGC, IOCDF-GC, OCGAS	2,688/7,037	Case-control	OR	European
Schizophrenia	Ripke et al[2]	2014	PGC	36,989/113,075	Case-control	OR	Admixed
Bipolar disorder	Stahl et al[3]	2019	PGC	20,352/31,358	Case-control	OR	European
ASD	Grove et al[22]	2019	PGC, iPSYCH	18,382/27,969	Case-control	OR	European

ADHD – attention-deficit/hyperactivity disorder, PTSD – post-traumatic stress disorder, MDD – major depressive disorder, OCD – obsessive-compulsive disorder, ASD – autism spectrum disorder, PGC – Psychiatric Genetics Consortium, iPsych – Lundbeck Foundation Initiative for Integrative Psychiatric Research, EAGLE – Early Genetics and Lifecourse Epidemiology, BroadABC – Broad Antisocial Behavior Consortium, ANGST – Anxiety NeuroGenetics Study, IOCDF-GC – International Obsessive Compulsive Disorder Foundation Genetics Collaborative, OCGAS – OCD Collaborative Genetics Association Studies, TGC – Tobacco and Genetics Consortium, OR – odds ratio, beta – standardized regression coefficient

Table 2 Characteristics of external criterion variables

Phenotype	Study	Year	Data source	Sample size	Study design	Effect size	Ancestry
Neuroticism	Okbay et al[31]	2016	SSGAC	298,420	Continuous	Beta	European
Depression symptoms	Okbay et al[31]	2016	SSGAC	161,460	Continuous	Beta	European
Subjective well-being	Okbay et al[31]	2016	SSGAC	298,420	Continuous	Beta	European
Extraversion	Van Den Berg et al[33]	2015	GPC	170,910	Continuous	Beta	European
Agreeableness	De Moor et al[34]	2012	GPC	20,669	Continuous	Beta	European
Conscientiousness	De Moor et al[34]	2012	GPC	20,669	Continuous	Beta	European
Openness	De Moor et al[34]	2012	GPC	20,669	Continuous	Beta	European
Educational attainment	Lee et al[32]	2018	SSGAC	766,345	Continuous	Beta	European
Loneliness	Gao et al[35]	2016	PGC	10,760	Continuous	Beta	Admixed
Body mass index	Yengo et al[36]	2018	GIANT + UK Biobank	681,275	Continuous	Beta	European
Number of children	Barban et al[30]	2016	SSGAC	333,702	Continuous	Beta	European
Age at first birth	Barban et al[30]	2016	SSGAC	237,516	Continuous	Beta	European

SSGAC – Social Science Genetic Association Consortium, GPC – Genetics of Personality Consortium, PGC – Psychiatric Genetics Consortium, GIANT – Genetic Investigation of Anthropometric Traits consortium, beta – standardized regression coefficient

variable study design, whereas GWAS for all other psychiatric disorders used a case-control design. The total sample size included in analyses consisted of 658,640 participants.

Statistical analysis

All analyses were conducted using the recently developed Genomic Structural Equation Modeling (SEM) R package[19]. Genomic SEM employs a novel extension of the widely used LD-score regression method[4] that calculates the genetic covariance among traits using GWAS summary statistics from multiple studies. Potential sample overlap across studies (e.g., shared control samples) is accounted for by the regression.

Genomic SEM first estimates a *p x p* genetic covariance matrix S containing SNP-based heritabilities for each of the *p* disorders or traits on the diagonal and genetic covariances among the *p* disorders and traits in the off-diagonal elements. The estimation uncertainty of S that is required for accurate model estimation is captured in a matrix V, which contains squared standard errors of the estimates in S on the diagonal, and the covariance between each pair of elements of S in the off-diagonal. These off-diagonal terms capture the potential sample overlap across traits.

After GWAS summary statistics were identified for the fourteen psychiatric disorders and traits of interest, the publicly-available files were formatted for Genomic SEM pre-processing. Next, the genetic covariance matrix was calculated using LD weights for populations of European ethnicity provided by the Broad Institute and the LD-score regression function of the Genomic SEM R package. The estimated genetic covariance matrix S and its associated sampling matrix V were then used for model fitting analyses.

Pre-specified structural models were fitted and evaluated using the weighted least squares (WLS) discrepancy function. WLS directly incorporates the V matrix, and is also recommended over maximum likelihood estimation by the creators of Genomic SEM[19].

The alternative *a priori* hypothesized structural models were fitted and compared utilizing confirmatory factor analysis (CFA). To evaluate the fit of each model, we used the comparative fit index (CFI) and the Bayesian information criterion (BIC). The fit of each model was evaluated using the combination of CFI and BIC, as each individual fit index has its strengths and limitations and a consensus has not been reached to use a single index to evaluate the adequacy of model fit[39].

The CFI is an absolute index of model fit where values >0.90 indicate good fit[40,41], whereas the BIC is a relative index of model fit that can be used to adjudicate among alternative models[39,42]. The model with the lowest value for BIC is considered the best fitting model, and it has been shown that differences of BIC >10 represent very strong evidence in favor of the model with the lower BIC[43]. Models were considered untenable if they contained factor loadings that were out of bounds, not significantly different from zero, or had very large standard errors.

User-defined models were provided to the Genomic SEM software in the lavaan syntax[44]. Six CFA models with increasing complexity were specified *a priori* to evaluate and contrast different hypotheses regarding the latent factor structure of psychopathology. The alternative models were defined as specified below.

Model 1 included a single common factor on which all disorders and traits loaded. Model 2 was characterized by three correlated psychopathology factors (externalizing, internalizing, and thought problems). Externalizing was indicated by ADHD, aggression, alcohol dependence, cannabis dependence, tobacco use, and antisocial behavior; internalizing was indicated by MDD, PTSD, anxiety disorders, and eating disorders; and

thought problems was indicated by schizophrenia, bipolar disorder, OCD and ASD.

Model 3 included four correlated factors representing externalizing, internalizing, thought problems, and substance use disorders. Model 4 posited a four-factor structure extending Model 2, in which neurodevelopmental disorders – i.e., ADHD, ASD and aggression – loaded onto a unique factor. In this model, the neurodevelopmental disorders were specified with what are known as cross-loadings: they were indicators of the same factors from the previous three-factor model as well as of the new unique factor, which was uncorrelated with the other three factors. Model 5 was similar to model 4, except that ADHD, ASD and aggression loaded only on the neurodevelopmental disorders factor, which was correlated with all the other factors.

Model 6 specified a bifactor model with a general psychopathology factor and four uncorrelated specific factors (externalizing, internalizing, thought problems, and neurodevelopmental disorders). In this model, all disorders loaded on a general factor as well as on their respective specific factors, which were orthogonal to the general factor and to each other. This structure implies that the correlations among all disorders and traits across psychopathology domains are only due to the general factor, whereas the correlations among disorders and traits within psychopathology domains are also due to the domain-specific factors.

Several exploratory models were also tested (Models 5a-5h), due to conflicting evidence in the literature regarding the placement of individual disorders (bipolar disorder, OCD, MDD and eating disorders) within the larger multivariate psychopathology structure. All exploratory models were tested as variations of Model 5.

Finally, we estimated genetic correlations of the higher-order psychopathology factors with several external criterion variables. These genetic correlations were estimated within the measurement model such that disorders' loadings on their respective factors as well as the higher-order factors' correlations with external criterion variables were simultaneously estimated in Genomic SEM.

RESULTS

Genetic correlations among the fourteen psychiatric disorders and related traits are shown in Table 3. Correlations among disorders are strongest within each psychopathology domain (externalizing, internalizing, thought problems, and neurodevelopmental disorders). However, correlations among disorders across psychopathology domains are non-negligible and in some cases of moderate magnitude.

Fit statistics of the alternative models reflecting the underlying structure of psychopathology are presented in Table 4. We first contrasted a model with a single common factor (Model 1) with a three-factor model that comprised externalizing, internalizing, and thought problems dimensions (Model 2). Model 2 had significantly better fit than Model 1, based on a CFI closer to 0.90 and a much smaller BIC. Next we tested Models 3, 4 and 5, all of which included four factors. Model 3 (including externalizing, internalizing, thought problems, and substance use disorders) resulted in a larger BIC value than Model 2, indicating that the addition of the substance use disorders factor resulted in a worse-fitting model. In contrast, Model 4 (specifying a neurode-

Table 3 Genetic correlations among the fourteen psychiatric disorders and related traits

	AGG	ADHD	ASD	CIGS	CAN	ALC	ASB	ANX	MDD	PTSD	BIP	OCD	SCZ	ED
AGG	1													
ADHD	0.77	1												
ASD	0.49	0.37	1											
CIGS	0.52	0.41	0.07	1										
CAN	0.81	0.42	0.03	0.12	1									
ALC	0.12	0.41	0.02	0.33	0.12	1								
ASB	0.24	0.52	0.21	0.20	0.41	0.59	1							
ANX	0.67	0.30	0.28	0.09	0.35	0.54	0.42	1						
MDD	0.46	0.56	0.44	0.16	0.23	0.44	0.55	0.89	1					
PTSD	0.40	0.52	0.24	0.44	0.41	0.33	0.36	0.09	0.49	1				
BIP	0.11	0.12	0.13	0.20	0.34	0.24	0.11	0.18	0.33	0.07	1			
OCD	0.38	–0.16	0.12	–0.05	0.25	–0.27	–0.05	0.30	0.30	0.42	0.32	1		
SCZ	0.04	0.12	0.21	0.11	0.07	0.09	0.09	0.26	0.37	0.18	0.68	0.33	1	
ED	–0.20	–0.26	–0.08	–0.12	0.04	–0.10	–0.10	0.09	0.20	–0.02	0.18	0.50	0.23	1

AGG – aggression, ADHD – attention-deficit/hyperactivity disorder, ASD – autism spectrum disorder, CIGS – number of cigarettes smoked per day, CAN – cannabis dependence, ALC – alcohol dependence, ASB – antisocial behavior, ANX – anxiety disorders, MDD – major depressive disorder, PTSD – post-traumatic stress disorders, BIP – bipolar disorder, OCD – obsessive-compulsive disorder, SCZ – schizophrenia, ED – eating disorders. Borders denote correlations among disorders within each higher-order dimension.

Table 4 Models and model fit statistics

	χ^2	df	CFI	BIC	Model compared to	ΔBIC
1. One common factor	1052	77	0.71	1427.0		
2. Three correlated factors (EXT, INT and TP)	554	74	0.86	969.3	1	457.7
3. Four correlated factors (EXT, INT, TP and SUD)	548	71	0.86	1003.5	2	+34.2
4. Four factor model (EXT, INT, TP and uncorrelated NDD)	419	71	0.90	874.5	2	94.8
5. Four correlated factors (EXT, INT, TP and NDD; ED on INT)	385	71	0.91	840.5	4	34.0
6. Bifactor model, with four uncorrelated specific factors (ED on INT only)	400	63	0.90	962.7	5	+122.2
Modified four correlated factors models						
5a. Four correlated factors, BIP on TP and EXT	384	70	0.91	852.9	5	12.4
5b. Four correlated factors, BIP on TP and INT	383	70	0.91	851.9	5	11.4
5c. Four correlated factors, OCD on TP and INT	385	70	0.91	853.9	5	13.4
5d. Four correlated factors, OCD on INT only	402	71	0.90	857.5	5	17.0
5e. Four correlated factors, MDD on INT and TP	382	70	0.91	850.9	5	10.4
5f. Four correlated factors, ED on INT and EXT		model would not run				
5g. Four correlated factors, ED on INT and TP	341	70	0.92	809.9	5	30.6
5h. Four correlated factors, ED on TP only	**341**	**71**	**0.92**	**796.5**	**5**	**44.0**
5i. Bifactor model, with four uncorrelated specific factors (ED on TP only)	366	63	0.91	928.7	5h	+132.2

CFI – comparative fit index, BIC – Bayesian information criterion, EXT – externalizing factor, INT – internalizing factor, TP – thought problems factor, SUD – substance use disorders factor, NDD – neurodevelopmental disorders factor, BIP – bipolar disorder, OCD – obsessive-compulsive disorder, MDD – major depressive disorder, ED – eating disorders. The model in bold is the best-fitting model based on a BIC difference >10. ΔBICs that have plus signs indicate that the more parsimonious models have better fit than the more complex models.

velopmental disorders factor uncorrelated with externalizing, internalizing, and thought problems factors) fit better than the three correlated factor model, based on a large reduction in BIC. Model 5, in which the neurodevelopmental disorders factor was correlated with the other factors, resulted in a CFI above 0.90 and another substantial reduction in BIC. Finally, Model 6 (a bifactor model that comprised a general factor as well the four specific externalizing, internalizing, thought problems, and neurodevelopmental disorders factors, all of which were uncorrelated) fit worse than Model 5.

Models in which bipolar disorder loaded on thought problems and externalizing (Model 5a) or thought problems and internalizing (Model 5b) were rejected, as they fit worse than Model 5, and due to bipolar disorder's small and negative factor loadings on the externalizing and internalizing factors (i.e., –.01, SE=.10 and –.05, SE=.10, respectively).

A model in which OCD loaded on thought problems and internalizing (Model 5c) was rejected because it fit worse than Model 5, and due to OCD's small and non-significant loading on internalizing (i.e., .06, SE=.09). Similarly, a model in which OCD loaded only on internalizing (Model 5d) fit worse than a model in which it loaded only on thought problems.

A model in which MDD loaded on internalizing and thought problems (Model 5e) was rejected because it fit worse than Model 5, and because MDD had a negative loading on thought problems (–.10, SE=.15) and its loading on internalizing was out of bounds (1.05, SE=.17).

Models in which eating disorders loaded on internalizing and externalizing (Model 5f) or internalizing and thought problems (Model 5g) were rejected either because they would not run (Model 5f) or due to a negative loading on internalizing (Model 5g: –.27, SE=.08). However, a model in which eating disorders loaded only on thought problems (Model 5h) had a better fit than Model 5, and eating disorders loaded most strongly in this model compared to any other model tested.

We also tested a bifactor version of this model (Model 5i), which fit worse than Model 5 and had problematic model characteristics. Specifically, all of the disorders' loadings on the externalizing and internalizing specific factors became non-significant and some loadings became negative (cannabis and PTSD) after accounting for their loading on the general factor, while the loading of eating disorders on the general factor was negative and non-significant. In addition, many of the factor loadings' standard errors were much larger than in the four correlated factors model.

Our results thus suggest that the best-fitting model comprises four moderately correlated factors of externalizing, internalizing, thought problems, and neurodevelopmental disorders, in which eating disorders load only on thought problems (Model 5h). As shown in Figure 1 and Table 5, all factor loadings and correlations were significant, as they were greater than twice their

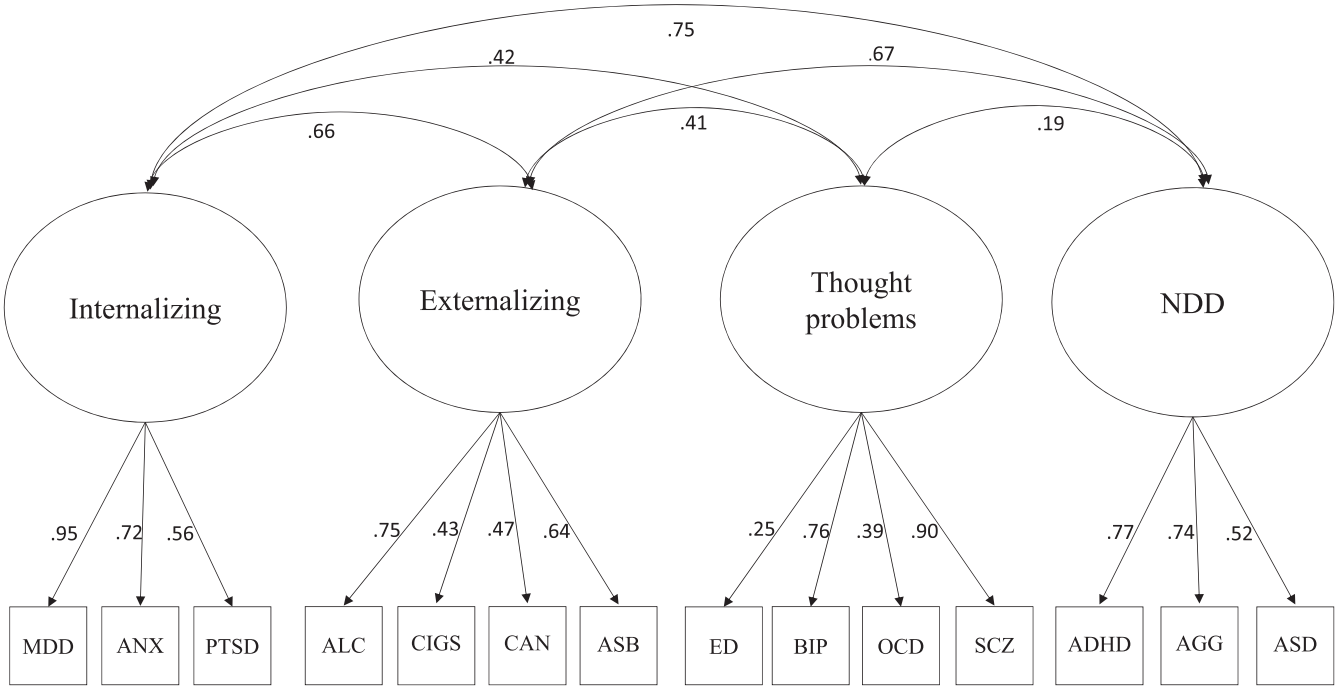

Figure 1 Best-fitting confirmatory factor analysis model. NDD – neurodevelopmental disorders, SCZ – schizophrenia, OCD – obsessive-compulsive disorder, BIP – bipolar disorder, ASD – autism spectrum disorder, PTSD – post-traumatic stress disorder, MDD – major depressive disorder, ANX – anxiety disorders, ED – eating disorders, ASB – antisocial behavior, ALC – alcohol dependence, CAN – cannabis dependence, CIGS – number of cigarettes smoked per day, ADHD – attention-deficit/hyperactivity disorder, AGG – aggression.

standard errors, and were moderate to high. The exception to this was eating disorders, which had a small but significant loading on thought problems. The average of the disorders' and traits' genetic variance accounted for by the factors was substantial (internalizing = .54, externalizing = .33, thought problems = .38, and neurodevelopmental disorders = .49).

The externalizing and internalizing factors were positively and moderately correlated with all other factors and with each other, while thought problems and neurodevelopmental disorders were only weakly correlated. As shown in Figure 1, the neurodevelopmental disorders factor was moderately to highly genetically correlated with the externalizing and internalizing factors (.67 and .75, respectively), suggesting that the genes that predispose to neurodevelopmental disorders in early childhood also predispose to externalizing and internalizing disorders later in childhood and into adolescence and adulthood.

Figure 2 presents the differential genetic correlations between the higher-order psychopathology dimensions from Model 5h and the external criterion variables listed in Table 2. The externalizing factor was more strongly correlated with extraversion, age at first birth (negative), and educational attainment (negative) than were the internalizing and neurodevelopmental disorders factors. The thought problems dimension had the weakest correlations with these external variables. The externalizing and neurodevelopmental disorders dimensions were more strongly correlated with total number of children born than were the internalizing or thought problems dimensions.

In contrast, the internalizing factor was strongly related to loneliness, depression symptoms, subjective well-being (negative), and neuroticism. The externalizing and neurodevelopmental disorders factors were more strongly associated with these criteria than thought problems. Externalizing, internalizing, and neurodevelopmental disorders had similar negative associations with conscientiousness, agreeableness, and body mass index. Finally, thought problems was positively correlated with openness to experience and educational attainment, whereas the other factors were either unrelated or negatively related.

Most crucially, the direction of associations between the four higher-order psychopathology factors and the external criteria were in the expected direction, and the relative magnitude of the four factors' genetic correlations with the external criteria also matched theoretical expectations. For example, all psychopathology dimensions had some association with loneliness, depression symptoms, and subjective well-being, but the internalizing factor displayed the largest associations. These different patterns of genetic correlations provide evidence for the external validity of the higher-order psychopathology factors.

DISCUSSION

In this study, factor analyses of GWAS summary statistics for fourteen psychiatric disorders and related traits revealed four moderately correlated factors – externalizing, internalizing, thought

Table 5 Standardized factor loadings and factor correlations from Model 5h (standardized regression coefficient with standard error)

	EXT	INT	TP	NDD
Antisocial behavior	.64 (.14)***			
Tobacco use	.43 (.09)***			
Alcohol dependence	.75 (.13)***			
Cannabis dependence	.47 (.16)**			
PTSD		.56 (.09)***		
MDD		.95 (.10)***		
Anxiety disorders		.72 (.09)***		
Eating disorders			.25 (.05)***	
Schizophrenia			.90 (.05)***	
Bipolar disorder			.76 (.04)***	
OCD			.39 (.05)***	
ASD				.52 (.05)***
Aggression				.74 (.12)***
ADHD				.77 (.06)***
EXT	–			
INT	.66 (.14)***	–		
TP	.41 (.08)***	.42 (.05)***	–	
NDD	.67 (.15)***	.75 (.09)***	.19 (.04)***	–

ADHD – attention-deficit/hyperactivity disorder, ASD – autism spectrum disorder, MDD – major depressive disorder, PTSD – post-traumatic stress disorders, OCD – obsessive-compulsive disorder, EXT – externalizing factor, INT – internalizing factor, TP – thought problems factor, NDD – neurodevelopmental disorders factor
*p<0.05, **p<0.01, ***p< 0.001

problems, and neurodevelopmental disorders – which showed distinct patterns of genetic correlations with external validity variables. A bifactor model comprising a general factor of psychopathology did not fit as well as the corresponding best-fitting correlated factors model and yielded problematic model characteristics, suggestive of overfitting.

Given that our analyses used GWAS summary statistics from fourteen different studies, it is noteworthy that our best-fitting model mirrored features found in many phenotypic factor analyses, such as moderate-to-high factor loadings and moderate factor correlations. Indeed, these features and the four factors in our best-fitting model mirror crucial aspects of the HiTOP model of psychopathology.

In addition, each GWAS comprises meta-analyses of distinct cohorts, rather than a single cohort in which participants reported on all disorders simultaneously. Our analyses are thus unaffected by issues such as shared measurement error, response biases, common method variance, and small sample size, that can affect phenotypic studies.

It is worth noting that many of the models we tested fell short of conventional standards for good model fit, likely due to the limitations of extant GWAS summary statistics. However, the best fitting model did surpass standards for good fit (i.e., CFI >0.90). The four factors were also differentially associated with external criterion variables, suggesting that they represent meaningfully distinct dimensions of psychopathology. The direction and magnitude of these correlations is consistent with previous phenotypic[45,46] and genetic studies[31,47-49] of higher-order dimensions of psychopathology.

Finally, the neurodevelopmental disorders factor was moderately-to-highly genetically correlated with the externalizing and internalizing factors, suggesting that the genes that predispose to neurodevelopmental disorders in early childhood also predispose to externalizing and internalizing disorders later in childhood and into adolescence and adulthood. This suggests an etiological basis for the association of ADHD or ASD in childhood with antisocial behavior, substance use disorders, anxiety, and depression in adolescence and adulthood.

Two previous studies have modeled the structure of psychopathology using GWAS summary statistics[19,20], and our results strengthen the main conclusion of those studies that factor analysis can be used to model genetic covariation among psychopathological disorders. The current study adds to this literature by including a greater number of psychiatric disorders and related psychological traits in the analyses and testing a greater number of alternative models of psychopathology.

The best-fitting model in the current study indicated that eating disorders and OCD, on the one hand, and bipolar disorder and schizophrenia, on the other, load together on the same thought problems factor, which mirrors findings from a previous study[19]. We also replicated the finding that ASD and ADHD load together on a separate neurodevelopmental disorders factor[20].

Nevertheless, our results differ from those two previous studies in a number of important ways. First, using CFA, we found that the fourteen disorders and related traits included in our study were best represented by four correlated factors, including a thought problems factor onto which bipolar disorder, schizophrenia, OCD, and eating disorders loaded. Second, our findings suggest that MDD loads together with other internalizing disorders rather than with bipolar disorder and schizophrenia. These differences across studies illustrate how the inclusion or exclusion of particular disorders or traits, as well as the use of different statistical methods, can yield different results.

For disorders whose placement in the multivariate higher-order structure of psychopathology is still open to debate, we tested alternative models in which the disorder loaded on multiple factors. The most notable such modification is the placement of eating disorders, which ultimately loaded on the thought problems factor. Recently, structural models of psychopathology suggested that eating disorders can be placed within the internalizing framework[50,51], although some models suggest it is a separate dimension[8]. Our finding that these disorders loaded most strongly on the thought problems factor seems to suggest that this factor

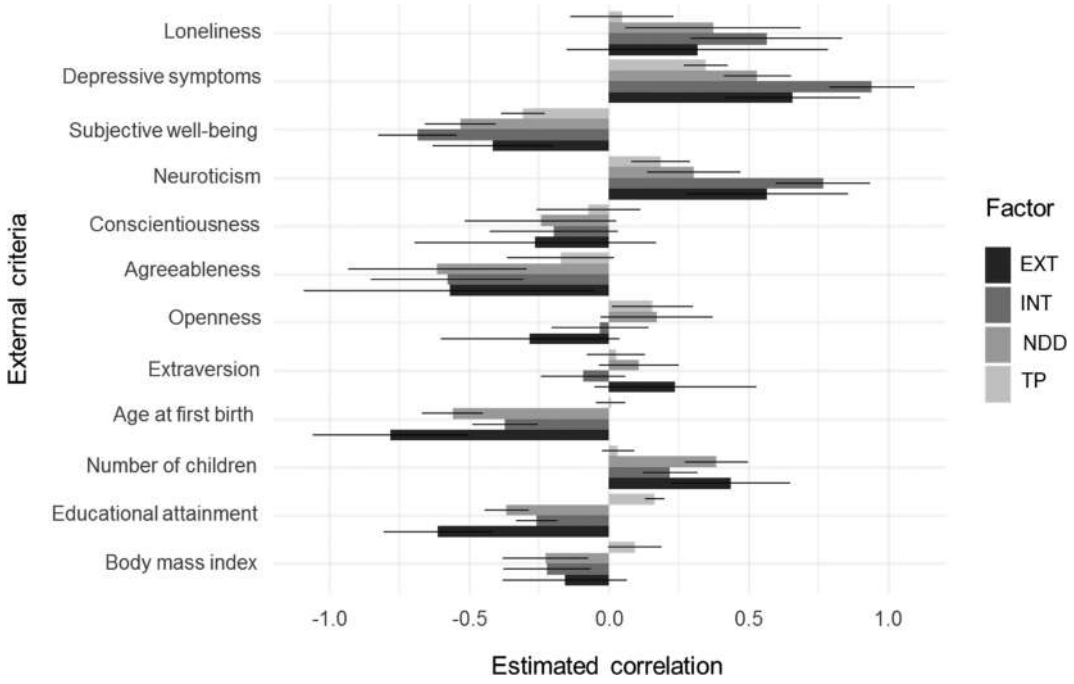

Figure 2 Genetic correlations of the external criterion variables with the four higher-order psychopathology factors. EXT – externalizing higher-order factor, INT – internalizing higher-order factor, TP – thought problems higher-order factor, NDD – neurodevelopmental disorders higher-order factor. Bars indicate 95% confidence intervals.

is characterized by disturbed cognitions found across disparate psychopathological disorders. The placement of eating disorders on this factor is consistent with previous studies that have found substantial covariation between eating disorders and OCD[52,53], which also loaded on the thought problems factor in the current study.

Our findings can also be contextualized within the current literature on the phenotypic structure of psychopathology. The HiTOP model includes most forms of psychopathology, several of which have not been studied in a GWAS and were thus not included in the current analyses. However, comparison of our results with the HiTOP model yields some interesting points. First, the HiTOP model, and indeed other phenotypic models of psychopathology[54,55], distinguish between disinhibited (e.g., substance use) and antagonistic (e.g., antisocial personality and other personality disorders) forms of externalizing. In our analyses, however, a model that distinguished substance use pathology from other externalizing disorders did not perform well.

Second, in the HiTOP framework, eating disorders and OCD are clustered within internalizing psychopathology, whereas they were best characterized within the thought problems factor in the current study. Finally, the HiTOP model tentatively posits that mania can be captured within both internalizing and thought disorder factors. Our inability to distinguish between mania and depression within bipolar disorder precluded a test of this model. Rather, bipolar disorder loaded with other thought disorders, perhaps reflecting the strong genetic relationship between more severe mania and schizophrenia[3].

As GWAS summary statistics become available on more fine-grained dimensions of psychopathology, we will be able to test more detailed models posited within the HiTOP framework, such as distinguishing between fears and distress pathology within internalizing, and modeling dimensions of detachment and somatoform psychopathology.

Modeling higher-order psychopathology dimensions may have several advantages for genetic studies over studying individual diagnoses one at a time. These include a more parsimonious and accurate representation of psychopathology[8,56], higher heritability, capitalization on pleiotropy to increase genetic associations[57,58], greater genetic correlations with external variables, greater statistical power to detect genetic associations due to more information contained in latent continuous versus observed categorical phenotypes[54,55], and elimination of measurement error.

These advantages, as well as GWAS of more fine-grained phenotypes (e.g., of distinct anxiety disorders), should increase the genetic signal and consequently the number of genome-wide significant associations found in GWAS[59]. The resolving power of such factor analyses should increase as individual GWAS meta-analyses become larger and better powered statistically, and as continuous psychopathology dimensions are included as phenotypes in GWAS, both of which should result in higher GWAS-based heritabilities and greater genetic signal to model.

Future research using GWAS of continuous psychopathology dimensions in large samples should attempt to replicate the higher-order structure of psychopathology presented in this study.

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A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders

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There is increasing academic and clinical interest in how "lifestyle factors" traditionally associated with physical health may also relate to mental health and psychological well-being. In response, international and national health bodies are producing guidelines to address health behaviors in the prevention and treatment of mental illness. However, the current evidence for the causal role of lifestyle factors in the onset and prognosis of mental disorders is unclear. We performed a systematic meta-review of the top-tier evidence examining how physical activity, sleep, dietary patterns and tobacco smoking impact on the risk and treatment outcomes across a range of mental disorders. Results from 29 meta-analyses of prospective/cohort studies, 12 Mendelian randomization studies, two meta-reviews, and two meta-analyses of randomized controlled trials were synthesized to generate overviews of the evidence for targeting each of the specific lifestyle factors in the prevention and treatment of depression, anxiety and stress-related disorders, schizophrenia, bipolar disorder, and attention-deficit/hyperactivity disorder. Standout findings include: a) convergent evidence indicating the use of physical activity in primary prevention and clinical treatment across a spectrum of mental disorders; b) emerging evidence implicating tobacco smoking as a causal factor in onset of both common and severe mental illness; c) the need to clearly establish causal relations between dietary patterns and risk of mental illness, and how diet should be best addressed within mental health care; and d) poor sleep as a risk factor for mental illness, although with further research required to understand the complex, bidirectional relations and the benefits of non-pharmacological sleep-focused interventions. The potentially shared neurobiological pathways between multiple lifestyle factors and mental health are discussed, along with directions for future research, and recommendations for the implementation of these findings at public health and clinical service levels.

Key words: Lifestyle factors, mental disorders, psychological well-being, physical activity, sedentary behavior, tobacco smoking, dietary patterns, sleep, depression, anxiety disorders, bipolar disorder, schizophrenia

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Mental disorders affect almost 30% of individuals across the lifespan[1], and are among the largest contributors to the global burden of disease, accounting for 32% of all years lived with disability, and 13% of disability-adjusted life years[2].

Despite many advances in psychotherapies and pharmacological treatments for a range of psychiatric conditions, there remains a substantial proportion of individuals who do not achieve full remission from standard treatment[3,4]. Additionally, a large portion of the global population do not have access to traditional mental health care, due to the scarcity of psychiatric services available, particularly in many low- and middle-income countries[3,5].

There has also been little improvement in primary prevention of mental illness, with clear gaps in both the evidence and implementation for such interventions[6]. Indeed, rates of common mental disorders (i.e., depression and anxiety) appear to even be increasing among the younger generations[7].

Thus, new approaches towards the prevention and treatment of mental illness, which can be delivered alongside or in the absence of traditional mental health care, are needed to reduce the global and growing burden of these conditions.

An emerging body of research has linked both the onset and symptoms of various mental disorders to "lifestyle factors", a term referring to health behaviors such as physical activity, diet, tobacco smoking and sleep[8].

For instance, a mass of cross-sectional evidence[9] shows that a range of psychiatric conditions (including schizophrenia, bipolar disorder, depression, and anxiety and stress-related disorders) are associated with adverse health behaviors, such as poorer dietary and sleeping patterns, low levels of physical activity, and higher rates of tobacco smoking, compared to healthy controls. Additionally, recent findings from population-scale studies document that the relationships between many of these lifestyle risk factors and mental illness also persist in low- and middle-income countries[10-12].

Although useful, this expansive body of cross-sectional research does not uncover the causality of the observed relation-

ships. Therefore, the evidence for which lifestyle factors should be addressed when aiming to prevent the onset of mental illness, or reduce symptoms in those with established conditions, is currently very limited.

Nonetheless, a number of national health policy documents and clinical guidelines are now beginning to address the role of specific lifestyle factors in the prevention and treatment of mental illness. For instance, both the US Physical Activity Guidelines for Americans[13] and the UK Chief Medical Officers' Physical Activity Guidelines[14] recommend attaining at least 150 min of moderate-to-vigorous physical activity per week for reducing the risk of depression (including postnatal depression) (see Table 1).

In order to preserve both overall mental health and cognitive functioning, both Canada's[15] and Australia's[16] 24-Hour Movement Guidelines have adopted a "whole day time-use" paradigm for young people, recommending that each day should include at least 60 min of moderate-to-vigorous exercise, several hours of light physical activity, no more than two hours of sedentary leisure activities, and 8-11 hours of uninterrupted sleep. The UK Royal College of Psychiatrist's position statement on public mental health[6] also describes how the clustering of health-risk behaviors (which include smoking, lack of exercise, and unhealthy eating) increases lifetime risk of mental illness.

Along with this surge of recognition from public health perspectives, the role of behavioral factors is also becoming a topic of increasing interest in psychiatric research and mental health services. Notably, the European Psychiatric Association's guidelines on physical activity in mental illness[17] put forth that there is sufficient evidence to recommend structured exercise training as an effective first-line treatment option for moderate depression, and as an adjunctive intervention for improving symptomatic recovery in severe mental illness. Additionally, the Royal Australian and New Zealand College of Psychiatrists' clinical practice guidelines for mood disorders[18] list exercise, smoking, diet and sleep as "step zero" targets, to be addressed before implementation of pharmacotherapy and/or psychotherapy (see Table 2).

There are a large number of individual clinical trials, epidemiological studies, and meta-analyses investigating the impact of other health behaviors in various psychiatric conditions. However, existing guidelines predominantly focus on physical activity, and typically only in relation to depression or schizophrenia. The broader role of lifestyle factors, across the spectrum of mental disorders, has yet to be established.

This meta-review aimed to establish the current evidence on causal relations between key modifiable health behaviors (physical activity, dietary food intake, tobacco smoking, and sleep) and the incidence and outcomes of major mental disorders, including depression, anxiety and stress-related disorders, attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, schizophrenia and related psychotic disorders. We sought to present an empirical overview of the field of lifestyle medicine for mental illness, and produce evidence-based recommendations for targeting modifiable health behavior factors in the prevention and treatment of these conditions, while also identifying key evidential gaps to inform future research.

METHODS

This meta-review aimed to systematically aggregate the most recent, top-tier evidence for the role of "lifestyle factors" in the prevention and treatment of mental disorders, following the PRISMA statement to ensure comprehensive and transparent reporting[19]. Systematic searches were conducted on February 3, 2020 of the following databases: Allied and Complementary Medicine (AMED), PsycINFO, Ovid MEDLINE, Health Management Information Consortium, EMBASE and the NHS Economic Evaluation and Health Technology Assessment databases.

The following PICOS search algorithm was used: Participants ['mental health or psychological well-being or psychological outcomes or mental well-being or psychiat* or mental illness* or mental disorder* or depress* or mood disorder* or affective disorder* or anxi* or panic or obsessive compulsive or OCD or ADHD or attention deficit or attentional deficit or phobi* or bipolar type or bipolar disorder* or psychosis or psychotic or schizophr* or schizoaffective or antipsychotic* or post traumatic* or personality disorder* or stress disorder* or dissociative disorder or antidepress* or antipsychotic*.ti]; Interventions/Exposures [physical activity or exercis* or sport* or walking or intensity activity or resistance training or muscle or sedentary or screen time or screentime or aerobic or fitness or diet* or nutri* or food* or vegan or vege* or meat or carbohy* or fibre or sugar* or adipos* or vitamin* or fruit* or sleep* or insomn* or circad* or smoke* or smoking or tobacco or nicotine or healthy or obes* or weight or bodyweight or body mass or BMI or health behav* or behavior change or behavior change or lifestyle*.ti]; Outcomes ['meta-analy* or metaanaly* or meta reg* or metareg* or systematic review* or Mendel* or meta-review or reviews or umbrella review or updated review*.ti]; Study design ['prospective or protect* or inciden* or onset or prevent* or cohort or predict* or risk or longitudinal or randomized or randomised or mendel* or bidirectional or controlled or trial* or causal'].

Separate searches of the Cochrane Database of Systematic Reviews and Google Scholar were also conducted to identify additional articles.

Eligibility criteria

The lifestyle factors examined were those pertaining to physical activity, diet, sleep and smoking.

"Physical activity" was considered in the broadest sense, including overall physical activity levels, structured exercise training interventions, and also studies examining the absence of physical activity, i.e. sedentary behavior. "Diet" focused on dietary food intake/interventions, and did not include studies evaluating specific nutrient treatments (as these have been already reviewed extensively in this journal[20]) or those examining blood levels of individual vitamins/minerals/fatty acids (as blood levels of these nutrients are influenced by many genetic and environmental factors, independent from dietary intake[21,22]). "Sleep" was examined as general sleep patterns, quality or quantity,

along with studies examining either the impact of sleep disorders (i.e., insomnia) on risk of mental illnesses, or the efficacy of non-pharmacological interventions directly targeting sleep to improve psychiatric symptoms. The term "smoking" was used only in reference to tobacco consumption, from personal usage or passive exposure, rather than illicit drugs, as the known psychoactive effects of these latter substances have been reviewed extensively in this journal[23].

Mental disorders eligible to be included in this meta-review were mood disorders (moderate or severe depression and bipolar disorder), psychotic disorders (including schizophrenia and related conditions), anxiety and stress-related disorders, dissociative disorders, personality disorders, and ADHD. We excluded psychiatric conditions which are directly characterized by adverse health behaviors (i.e., eating disorders and alcohol or substance use disorders) along with other neurodevelopmental disorders (e.g., autism, intellectual disability) and neurodegenerative disorders (e.g., dementia), as these were considered beyond the scope of this review.

Protective factors were examined using two sources of data. First, we searched for meta-analyses of longitudinal data that examined relationships between the various lifestyle factors and prospective risk/onset of mental illness. Eligible meta-analyses were those presenting suitable quantitative data – as adjusted or raw odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs) – on how baseline status of behavioral variables influences the prospective risk of mental illness, including diagnosed psychiatric conditions and clinically significant symptoms (using established cutoffs on validated screening instruments, or based on percentile cutoffs of psychiatric symptom scores).

The second source of data used for examining protective factors were any Mendelian randomization (MR) studies of the link between lifestyle factors and mental illness. Briefly, MR is a causal inference method that can be used to estimate the effect of an exposure (X) on an outcome (Y) whilst minimizing bias from confounding and reverse causation[24,25]. Suitable genetic instruments (usually single nucleotide polymorphisms, SNPs) are identified through genome-wide association studies (GWAS). Individuals carrying the effect allele of the variant have higher (or lower) levels of X on average than those without the effect alleles. Following Mendel's laws of segregation and independent assortment, the genetic variants are inherited randomly at conception, and are inherited independently of confounding lifestyle factors[26]. Therefore, MR can be considered somewhat analogous to a randomized controlled trial (RCT) of behavioral factors in the prevention of mental illness, as genetic variants randomly predispose individuals to experience different levels of these factors[26]. As genes also remain unchanged throughout the life course, they are also not altered by the outcome of interest, thus reducing bias from reverse causation[26]. Therefore, while meta-analyses of prospective cohort studies are useful for identifying the overall strength and directionality of associations, the MR analyses were used to further infer the causal nature of the observed relationships.

The evidence for lifestyle interventions in the treatment of people with diagnosed mental disorders was examined using two different sources of data, but both based on meta-analyses of RCTs (typically considered the top-tier of evidence in health intervention research). First, we searched for existing meta-reviews of meta-analyses of RCTs published in the last five years, for each lifestyle factor, providing quantitative effects of physical activity, diet, smoking cessation or non-pharmacological sleep interventions on psychiatric symptoms in people with mental illness. Second, for the lifestyle factors that were not covered within the existing meta-reviews, we sought out meta-analyses of RCTs examining their impact (using the search strategy above), and synthesized the evidence from the meta-analyses using a methodology derived from a previous meta-review[20]. For meta-analyses with mixed samples, only those in which at least 75% of the sample examined the eligible mental illnesses (as described above) were included.

Data extraction

A systematic tool was applied to each eligible meta-analysis/MR study to extract the relevant data on the association of lifestyle factors with risk of mental illness, or the effects of lifestyle interventions on psychiatric outcomes. Results of eligible meta-reviews were extracted narratively, summarized from their respective articles.

For meta-analyses of longitudinal studies, the strength and direction of the prospective associations between lifestyle factors and mental illness were quantified categorically, and thus extracted as ORs, HRs or RRs, with 95% confidence intervals (CIs).

For meta-analyses of RCTs of lifestyle interventions in mental illness, effect size data were quantified as a continuous variable (i.e., magnitude of effect on psychiatric symptoms) and thus extracted as standardized mean differences (SMDs), Cohen's d or Hedges' g. These were then classified as small (<0.4), moderate (0.4-0.8), or large (>0.8).

For all meta-analyses, data on the degree of between-study heterogeneity (quantified as I^2 values) were also extracted, where reported.

In cases where multiple eligible meta-analyses examined a specific lifestyle factor in the risk/treatment of the same mental disorder, the most recent was used preferentially. Where older meta-analyses featured >25% more studies than the newer versions and contained important, novel findings from unique analyses not captured in the most recent versions, these were also extracted and presented alongside the newer findings. In cases where two MR studies had examined the same lifestyle factor for the same mental health outcome, both studies (regardless of recency or sample size) were included and reviewed.

We also extracted relevant study characteristics where reported, including number of pooled comparisons within meta-analyses (n), sample size (N), details on the specifics of lifestyle exposure or intervention examined, and sample features. The results of key subgroup/sensitivity analyses showing how different age groups, illnesses or outcomes examined, or different types of exposure/interventions modified the effect of the specific life-

style factor were extracted as well. For the purposes of providing a concise summary of the literature, only the findings from secondary analyses which provided important, unique insights into the evidence were extracted.

Quality assessment of included studies

The National Institutes of Health (NIH)'s Quality Assessment Tool for Systematic Reviews and Meta-Analyses was used to assess the quality of the included meta-analyses. This tool evaluates the quality of meta-analyses rating them for adequacy of the search question, specification of inclusion and exclusion criteria, systematic search, screening of papers, quality assessment and summaries of included studies, and tests for publication bias and heterogeneity. In accordance with previous meta-reviews using the NIH tool[27], the quality of included meta-analyses was categorized as "good" (7 or 8), "fair" (4-6), or "poor" (0-3).

As no consensus tool exists for determining the quality of MR and meta-review studies, these were omitted from formal quality assessment.

RESULTS

Systematic search

The main search returned a total of 1,811 results, which were reduced to 834 after duplicates were excluded. A total of 92 full text papers were retrieved, from which 41 met full inclusion criteria. Of note, one seemingly eligible study[28] was excluded for invalid findings due to inconsistent coding of effect directionality. Four additional studies were identified from the supplementary searches, and thus 45 studies were included in total. Across the different lifestyle factors, 11 of the eligible papers focused on physical activity/exercise, 15 were on smoking, 12 examined diet, and 10 considered sleep. Some papers covered multiple factors.

The results below synthesize the findings of 29 meta-analyses of prospective/cohort studies, 12 Mendelian randomization studies, two meta-reviews, and two meta-analyses of RCTs. Individual details for the prospective meta-analyses and MR studies examining lifestyle risk factors for mental disorders are provided in Tables 1-8.

Lifestyle factors in the prevention of mental disorders

Physical activity and risk of depression

A meta-analysis of 36 prospective comparisons[29] found that higher levels of physical activity significantly reduced the subsequent risk of incident depression over a mean follow-up time of 7.4 years (OR=0.837, 95% CI: 0.794-0.883), with low heterogeneity between included studies (I^2=0%). Although there was indication of publication bias, adjusting for this did not alter overall findings (OR=0.85, 95% CI: 0.81-0.89). Subgroup analyses found similar results for protective effects of physical activity in studies measuring incidence of depressive symptoms (n=28, OR=0.844, 95% CI: 0.798-0.892) or major depressive disorder (n=10, OR=0.862, 95% CI: 0.757-0.981), and in children/adolescents (n=3, OR=0.907, 95% CI: 0.836-0.985), adults (n=16, OR=0.787, 95% CI: 0.707-0.877) or older adults (n=16, OR=0.794, 95% CI: 0.726-0.868). Adjusting for baseline depressive symptoms, body mass index, smoking status, age, gender and other confounds did not alter the findings.

Prospective associations between sedentary behavior and depression were examined in three meta-analyses[30-32]. The largest analysis examining overall sedentary behavior found that more sedentary individuals were at significantly increased risk of depression over time (determined via diagnostic records or clinical interviews) compared to less sedentary counterparts (n=11, RR=1.14, 95% CI: 1.06-1.21, I^2=0%)[32]. However, subsequent meta-analyses examining sedentary behavior specifically as "screen time" found only very small associations with prospective risk of depressive symptoms in all available samples[30], and no association in children and adolescents samples only[31] (see Table 1).

Two MR studies examined the causal relations between physical activity and depression[33,34]. Choi et al[34] applied a factor-wide design to Wray et al's GWAS[35], corrected for multiple testing and adjusted for potential confounders, to identify a broad spectrum of modifiable risk factors potentially implicated in major depression. MR analysis of the available variables related to physical activity found some evidence that self-reported cycling or swimming may causally decrease depression risk, although only at a nominal level of significance (which did not survive correction for multiple testing). Other self-report variables concerning specific types of physical activity (such as self-reported "part of a gym or club", "walking for pleasure" or "heavy do-it-yourself, DIY") had no evidence of causal relations with depression.

A second study conducted a bi-directional two-sample MR to investigate risk of major depression in relation to both self-reported moderate-vigorous physical activity and objectively measured physical activity (with accelerometer data, using mean acceleration over 72 hours)[33]. Major depression summary data were from Wray et al's GWAS[35]. Initial analyses found no clear evidence that either form of activity causally influenced risk of major depression. However, as these initial analyses identified only two SNPs associated with overall objectively measured activity, a relaxed p value threshold of $p<1\times10^{-7}$ was used, which instead identified 10 SNPs. Using this genetic instrument, there was strong evidence for objectively measured overall physical activity as a protective factor for major depression: IVW (inverse-variance weighted) OR=0.74, 95% CI: 0.59-0.92, p=0.006. This was consistent across multiple sensitivity analyses to test for pleiotropy (see Table 2).

Physical activity and risk of anxiety and stress-related disorders

The relationship between physical activity and incident anx-

Table 1 Physical activity and prospective risk of mental disorders in meta-analyses

	Outcome	n	Exposure	Main results	Summary
Schuch et al[29] (NIH=7)	Clinical depression or depressive symptoms	36	Higher physical activity levels	OR=0.837, 95% CI: 0.794-0.883 I^2=0.00%	Good quality review indicating that high levels of physical activity reduce the risk of depression. Effects persisted across age groups and geographic regions. Although there was evidence of significant publication bias, correcting for this did not alter the indicated protective effects.
Wang et al[30] (NIH=5)	Clinical depression or depressive symptoms	7	Screen time-based sedentary behavior	OR=1.02, 95% CI: 1.01-1.04 I^2=3.0%	Fair quality review which found only a very small association between screen time-based sedentary behavior and prospective risk of depression, with low heterogeneity.
Liu et al[31] (NIH=5)	Depressive symptoms	4	Screen time in children and adolescents	OR=0.88, 95% CI: 0.67-1.14 I^2=90.4%	Fair quality review finding no prospective associations between screen time and depression. However, there was a lack of large-scale longitudinal studies to determine this.
Zhai et al[32] (NIH=6)	Clinical depression or depressive symptoms	11	Sedentary behavior	RR=1.14, 95% CI: 1.06-1.21 I^2=0.00%	Fair quality review showing that higher sedentary behavior (of all types) at baseline was associated with increased risk of depression at follow-up.
Schuch et al[36] (NIH=7)	Incident anxiety	11	Higher physical activity levels	OR=0.748, 95% CI: 0.629-0.889 I^2=23.96%	Good quality review indicating that self-reported physical activity reduces the risk of anxiety. There was evidence of significant publication bias, and correcting for this slightly reduced the protective effects. Subgroup analyses found that physical activity reduces risk of agoraphobia and post-traumatic stress.
McDowell et al[37] (NIH=7)	Anxiety symptoms	9	Higher physical activity levels	OR=0.874, 95% CI: 0.77-0.99 I^2=48.7%	Good quality review showing that physical activity is associated with reduced risk of anxiety symptoms and anxiety disorders. The moderate degree of heterogeneity between studies and the limited number of studies using diagnosis outcomes prevent firm conclusions.
	Any anxiety disorder	3		OR=0.663, 95% CI: 0.53-0.82 I^2=62.3%	
	Diagnosed GAD	3		OR=0.544, 95% CI: 0.32-0.92 I^2=0.00%	
Brokmeier et al[38] (NIH=6)	Psychotic disorders	5	Higher physical activity levels	OR=0.728, 95% CI: 0.532-0.995 I^2=36.9%	Fair quality review showing that higher levels of physical activity are associated with significantly reduced prospective risk of psychosis. However, significant associations were not observed in the two studies that sufficiently adjusted for confounding factors, although this may be due to the limited sample size of this subgroup underpowering the analysis.

n – number of comparisons, OR – odds ratio, RR – risk ratio, NIH – quality of the study evaluated by the National Institutes of Health's Quality Assessment Tool for Systematic Reviews and Meta-Analyses (good: 7 or 8; fair: 4-6; poor: 0-3), GAD – generalized anxiety disorder

iety was examined across 11 cohorts with a total of 69,037 participants[36]. Over the average follow-up period of 3.5 years, higher levels of physical activity significantly reduced incident anxiety (OR=0.748, 95% CI: 0.629-0.889), with low heterogeneity (I^2=23.96%). There was some indication of publication bias, although significant positive effects of physical activity remained when adjusting for this (OR=0.86, 95% CI: 0.69-0.99). Examination of specific anxiety disorders indicated risk reduction from physical activity for agoraphobia (n=2, OR=0.43, 95% CI: 0.19-0.99) and post-traumatic stress disorder (n=2, OR=0.58, 95% CI: 0.39-0.86), with no significant effects observed for other disorders. It should be noted, however, that only small samples were available for these subgroup analyses.

A subsequent meta-analysis[37] examining the longitudinal relations of physical activity with different measures of anxiety indicated protective benefits from high levels of physical activity for each measure, including elevated anxiety symptoms (n=9, OR=0.874, 95% CI: 0.77-0.99, I^2=48.7%), anxiety disorder diagnosis (n=3, OR=0.663, 95% CI: 0.53-0.82, I^2=62.3%), and generalized anxiety disorder (n=3, OR=0.544, 95% CI: 0.32-0.92, I^2=0%), although limitations concerning the low number of studies and the considerable heterogeneity were again noted[37] (see Table 1).

No MR studies examined the relationship between physical activity and the risk of anxiety.

Physical activity and risk of psychotic and bipolar disorders

One meta-analysis examined prospective associations of physical activity with schizophrenia and related psychotic disorders[38]. Across five prospective comparisons, with 4-32 years of follow-up, higher levels of physical activity significantly reduced risk of incident psychosis (OR=0.728, 95% CI: 0.532-0.995, I^2=36.9%). However, in the two studies (N=10,583) that adjusted for confounding factors, overall reductions in psychosis incidence from physical activity were non-significant (OR=0.59, 95% CI: 0.253-1.383, I^2=54.7%) (see Table 1).

Table 2 Causal relations of physical activity and mental disorders in Mendelian randomization studies

	Outcome	Sample	Exposure	Main results	Summary
Choi et al[33]	Major depression	N=143,265 from Wray et al's GWAS[35]	Self-reported moderate-vigorous physical activity (9 SNPs) Objective accelerometer activity (10 SNPs)	Self-reported: IVW OR=1.28, 95% CI: 0.57-3.37, p=0.48 Objective: IVW OR=0.74, 95% CI: 0.59-0.92, p=0.006	This bi-directional analysis found evidence that accelerometer-measured physical activity was protective for depression. Evidence was consistent across multiple pleiotropy robust methods. There was no clear evidence to suggest that depression risk decreased physical activity. Equally, there was no clear evidence that self-reported physical activity was protective for major depression. The analysis was run with a relaxed p value threshold of $p<1\times10^{-7}$.
Choi et al[34]	Major depression	N=431,394 from Wray et al's GWAS[35]	Self-reported: part of a gym/club; usual walking pace; walking for pleasure; transport by walking; frequency of walking; heavy do-it-yourself (DIY); other exercise (including swimming and cycling)	Gym/club member: IVW OR=0.91, 95% CI: 0.784-1.057, p=0.217 Walking pace: IVW OR=1.038, 95% CI: 0.877-1.228, p=0.666 Walking for pleasure: IVW OR=1.02, 95% CI: 0.918-1.123, p=0.765 Transport by walking: IVW OR=0.983, 95% CI: 0.870-1.111, p=0.782 Frequency of walking: IVW OR=1.024, 95% CI: 0.849-1.234, p=0.807 DIY: IVW OR=0.995, 95% CI: 0.889-1.114, p=0.931 Other: IVW OR=0.90, 95% CI: 0.82-0.99, p=0.033	There was no clear evidence for any of the examined factors being causal. There was a nominal association with other exercise (e.g., swimming and cycling), but this did not survive Bonferroni correction. When testing the effects of depression on these outcomes, none was significant after Bonferroni adjustment.
Sun et al[39]	Bipolar disorder	N=20,352 cases and 31,358 controls from Stahl et al's GWAS[40]	Device-measured: overall activity (5 SNPs); sedentary time (5 SNPs); moderate activity (1 SNP)	Overall activity: IVW OR=0.491, 95% CI: 0.314-0.767, p=0.002 Sedentary time: IVW OR=0.702, 95% CI: 0.366-1.345, p=0.287 Moderate activity: IVW OR=0.726, 95% CI: 0.255-2.068, p=0.549	Overall physical activity was protective for bipolar disorder and this result was consistent across the more pleiotropy robust methods. No evidence was found for the reverse direction (i.e., bipolar disorder risk did not influence physical activity). There was no evidence for an effect of overall activity on schizophrenia, nor evidence that sedentary behavior or moderate intensity activity were protective for either disorder.
	Schizophrenia	N=33,426 cases and 32,541 controls from Ruderfer et al's GWAS[41]		Overall activity: IVW OR=1.133, 95% CI: 0.636-2.020, p=0.672 Sedentary time: IVW OR=0.707, 95% CI: 0.430-1.161, p=0.170 Moderate activity: IVW OR=0.657, 95% CI: 0.378-2.026, p=0.379	

GWAS – genome-wide association study, SNP – single nucleotide polymorphism, IVW OR – inverse-variance weighted odds ratio

The risk of schizophrenia and bipolar disorder in relation to overall physical activity, moderate-intensity activity, and sedentary time was examined in one MR study[39], using SNPs associated with device-measured physical activity over 72 hours along with Stahl et al's[40] and Ruderfer et al's[41] GWAS. There was no strong evidence of causal relations with schizophrenia. However, the two-sample MR did find indication of causal relations between increased overall physical activity and decreased risk for bipolar disorder, equating to a 51% lower risk per 8 milligravity increase in mean acceleration (IVW OR=0.491, 95% CI: 0.314-0.767, p=0.002). This estimate was consistent across multiple sensitivity analyses to test for pleiotropy. Associations with specific domains of sedentary behavior or moderate intensity activity were non-significant (see Table 2).

Smoking and risk of common mental disorders

Longitudinal associations between smoking exposure and subsequent risk of depression were examined in four meta-analyses of 19 studies with a total of 79,729 participants. Among 52,568 adults, from seven studies with 1-6 year follow-ups, smoking significantly increased the prospective risk of depression, measured as either diagnosed depressive disorders or clinically-relevant depressive symptoms on validated scales (OR=1.62, 95% CI: 1.1-2.4)[42].

A meta-analysis of six studies including 15,333 adolescents aged 13-19 showed that smokers were significantly more likely to develop depression than non-smokers over 1-6 year follow-up (OR=1.73, 95% CI: 1.32-2.4)[43]. There was notable heterogeneity

Table 3 Smoking and prospective risk of mental disorders in meta-analyses

	Outcome	n	Exposure	Main results	Summary
Luger et al[42] (NIH=3)	Major depressive disorder and depressive symptoms	7	Smokers vs. never smokers	OR=1.62, 95% CI: 1.1-2.4, I^2=NA	Smoking was strongly associated with risk of depression, with effects of 1.5-2 times the risk of non-smoking from a variety of designs, measurements and populations. However, review quality scored low, and the impact of publication bias and study heterogeneity was not determined.
Chaiton et al[43] (NIH=4)	Adolescent depression (diagnosis or clinical symptoms)	6	Smoking	OR=1.73, 95% CI: 1.32-2.4 I^2=NA	Fair quality review showing that smoking in adolescence is associated with increased risk of future depression. However, clinical measures of depression were more likely to report a bidirectional effect (i.e., depression also predicting smoking).
Han et al[44] (NIH=6)	Incident depressive symptoms in children	2	Early life second-hand smoking	OR=1.51, 95% CI: 0.93-2.09, I^2=NA	Fair quality review showing that exposure to second-hand smoking in early life was associated with increased odds of depressive symptoms in cross-sectional studies. However, the effects in the two prospective cohort studies was non-significant.
Chen et al[45] (NIH=6)	Postpartum depression	4	Prenatal smoking	OR=2.88, 95% CI: 0.99-8.39, I^2=89.3%	Fair quality review showing that prenatal smoking was strongly associated with postpartum depression in the overall analysis (including retrospective and longitudinal studies), with no indication of publication bias. However, in the subgroup analysis of longitudinal studies, the effect size was similarly large, but fell short of statistical significance.
Hunter et al[52] (NIH=7)	Incident schizophrenia	6	Personal active smoking	RR=1.99, 95% CI: 1.1-3.61, I^2=97%	Good quality review showing that smokers had an approximately doubled risk of developing schizophrenia relative to non-smokers. Smaller, but still significant, effects were found for prenatal smoking (although this analysis was based on retrospective reports of prenatal smoking exposure).
Gurillo at al[53] (NIH=4)	Psychotic disorders	6	Smoking	RR=2.18, 95% CI: 1.23-3.85, I^2=97.7%	Fair quality review showing that daily tobacco use was associated with a doubled risk of psychosis. Significant risk of publication bias was indicated, and heterogeneity was high.
Huang et al[57] (NIH=5)	ADHD	15	Prenatal exposure to maternal smoking	OR=1.35, 95% CI: 1.2-1.52, I^2=59.5	Fair quality review showing that maternal smoking during pregnancy was associated with increased risk of ADHD in offspring. However, familial and genetic factors were not adequately controlled for, and impact of publication bias was not established.

n – number of comparisons, OR – odds ratio, RR – risk ratio, NIH – quality of the study evaluated by the National Institutes of Health's Quality Assessment Tool for Systematic Reviews and Meta-Analyses (good: 7 or 8; fair: 4-6; poor: 0-3), NA – not available, ADHD – attention-deficit/hyperactivity disorder

among studies (Q test p value=0.08).

The impact of "second-hand smoking" in childhood on prospective risk of depression was examined across two cohort studies of 8,092 individuals[44]. Those exposed to second-hand smoking were at non-significantly higher risk of subsequent depressive symptoms (OR=1.51, 95% CI: 0.93-2.09). Additionally, four prospective studies of 3,736 pregnant women found that prenatal smoking was associated with an almost three-fold increased risk of postpartum depression (OR=2.88, 95% CI: 0.99-8.39), although with high heterogeneity (I^2=89.3%) and effects breaching the threshold for statistical significance (p=0.052)[45] (see Table 3).

No meta-analyses examined the longitudinal relations between smoking and anxiety.

Four MR studies examined smoking as a risk factor for depression or anxiety[46-49]. They assessed relations with individual SNPs located in the nicotine acetylcholine receptor gene cluster (rs16969968 or rs1051730 in CHRNA5-CHRNA3-CHRNB4 on chromosome 15), a gene cluster closely related with smoking behavior, to the extent that each risk allele increase is associated with smoking an additional cigarette each day (on average)[50]. Using this genetic instrument, analyses in the Norwegian HUNT study (N=53,601)[46] and the Copenhagen General Population Study and City Heart Study (N=63,296)[47] found no evidence for a causal association between smoking and primary depression or anxiety. No evidence for smoking increasing risk of antenatal depression was found in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (N=6,294)[48]. A study of the CARTA Consortium applied the same genetic instrument for smoking heaviness and found no causal effects on depression or anxiety (N=127,632)[49].

However, these studies lacked statistical power, due to the use of single genetic variants in the MR analyses. More recently, Wootton et al[51] identified a genetic instrument for "lifetime smoking behavior", consisting of 126 independent SNPs. This instrument captured smoking duration, heaviness and cessation in both smokers and non-smokers. The results provided evidence that lifetime smoking was causally associated with around a two-fold heightened risk of major depression (IVW OR=1.99, 95% CI: 1.71-2.32, p<0.001). Additionally, there was some, although weaker, evidence that genetic risk for major depression was causally associated with smoking (B=0.091, 95% CI: 0.027-0.155, p=0.005). Similarly, smoking initiation increased risk of

Table 4 Causal relations of smoking and mental disorders in Mendelian randomization studies

	Outcome	Sample	Exposure	Main results	Summary
Wootton et al[51]	Major depression	N=135,458 cases and 344,901 controls from Wray et al's GWAS[35]	Lifetime smoking (126 SNPs for combined smoking initiation, duration, heaviness and cessation) Smoking initiation (378 SNPs)	Lifetime smoking: IVW OR=1.99, 95% CI: 1.71-2.32, p<0.001 Smoking initiation: IVW OR=1.54, 95% CI: 1.44-1.64, p<0.01	Strong evidence to suggest causal effects of smoking on risk of both depression and schizophrenia. Results were highly consistent across sensitivity analyses testing for pleiotropy. Bi-directional analyses also showed some evidence for depression and schizophrenia causally increasing odds of smoking behavior. Again this was consistent across more pleiotropy robust methods.
	Schizophrenia	N=36,989 cases and 113,075 controls from Psychiatric Genomics Consortium (PGC)		Lifetime smoking: IVW OR: 2.27, 95% CI: 1.67-3.08, p<0.001 Smoking initiation: IVW OR=1.53, 95% CI: 1.35-1.74, p<0.01	
Vermeulen et al[56]	Bipolar disorder	N=20,129 cases and 21,524 controls from Stahl et al's GWAS[40]	Smoking initiation (378 SNPs) Lifetime smoking (126 SNPs)	Smoking initiation: IVW OR=1.46, 95% CI: 1.28-1.66, p<0.001 Lifetime smoking: IVW OR=1.72, 95% CI: 1.29-2.28, p<0.001	Evidence to suggest that smoking is a causal factor in increased risk for bipolar disorder. This effect was consistent across multiple sensitivity analyses for pleiotropy. The bi-directional effects were tested, but there was no evidence to suggest that bipolar disorder risk increased smoking initiation, heaviness, cessation or lifetime smoking.
Treur et al[58]	ADHD	N=15,548 cases diagnosed >18 years from Demontis et al's GWAS[59]	Smoking initiation (378 SNPs)	OR=3.72, 95% CI: 3.10-4.44, p<0.001	Evidence to suggest that smoking initiation causally increased risk of ADHD. This was consistent across several more pleiotropy robust methods. However, Steiger filtering did also suggest some reverse causation. Furthermore, smoking initiation also predicted ADHD before age 13 years, when a biological causal effect of own smoking is implausible. This result, along with the Steiger filtering, suggests the instrument could be capturing wider risk-taking and impulsivity. Bi-directional analyses suggested that liability to ADHD increased likelihood of smoking initiation and cigarettes per day.
Gage et al[55]	Schizophrenia	N=36,989 cases and 113,075 controls from PGC	Smoking initiation (4 SNPs)	Genome-wide significant SNPs: IVW OR=1.73, 95% CI: 1.30-2.25, p<0.001 Relaxed p value threshold: IVW OR=1.03, 95% CI: 0.97-1.09, p=0.32	There were very few SNPs associated with smoking initiation at the time when this GWAS was conducted, and resultantly the four SNPs used were all in the same gene. With a relaxed p value threshold, there was no evidence for an effect of smoking on schizophrenia. Similarly, no evidence was found for schizophrenia causally increasing smoking.
Wium-Anderson et al[47]	Major depression Lifetime prescription of antidepressants	Danish Population Registry (N=63,296) comprising the Copenhagen General Population Study (CGPS) and the Copenhagen City Heart Study (CCHS)	Smoking heaviness (ever vs. never smokers) from rs1051730 genotype	Depression: OR=0.85, 95% CI: 0.66-1.10 Antidepressants: OR=1.02, 95% CI: 0.93-1.13 (for TT allele compared to CC allele in smokers only) No evidence for an interaction	Evidence that smoking heaviness may be causally associated with antipsychotic use and could causally influence psychotic conditions. A negative control analysis in never smokers found no effect, suggesting that results were not biased by pleiotropy. There was no evidence for a causal effect of smoking heaviness on depression. However, analysis of the Danish registry was underpowered for schizophrenia (due to a low number of cases) and replication analysis conducted using PGC data was unable to separate smokers and non-smokers (thus failing to test for pleiotropy).
	Schizophrenia Lifetime use of antipsychotics			Schizophrenia: OR=1.60, 95% CI: 0.74-3.47 Antipsychotics: OR=1.16, 95% CI: 1.02-1.31 (for TT allele compared to CC allele in smokers only) No evidence for an interaction	

Table 4 Causal relations of smoking and mental disorders in Mendelian randomization studies (*continued*)

	Outcome	Sample	Exposure	Main results	Summary
Taylor et al[49]	Depression, anxiety and psychological distress assessed by clinical interview, symptom scales or self-reported recall of clinician diagnosis	N=127,632 from CARTA Consortium, comprising 25 studies of European ancestry aged ≥16 years	Smoking heaviness in ever vs. current vs. former vs. never smokers from rs1051730 /rs16969968 genotype	In current smokers (OR per T allele): Depression: OR=1.00, 95% CI: 0.95-1.05 Anxiety: OR=1.02, 95% CI: 0.97-1.07 Psychological distress: OR=1.02, 95% CI: 0.98-1.06	There was no evidence for an effect of rs1051730 /rs16969968 genotype on depression, anxiety or psychological stress.
Bjørngaard et al[46]	Depression and anxiety measured on the Hospital Anxiety and Depression Scale (HADS)	N=53,601 from Norwegian HUNT study	Smoking heaviness in current vs. former vs. never smokers from rs1051730 genotype	In smokers only (OR per T allele): Anxiety: OR=1.03, 95% CI: 0.97-1.09 Depression: OR=1.02, 95% CI: 0.95-1.09	There was evidence for an effect of rs1051730 genotype on anxiety when combining smokers and non-smokers, but this was not the case in current and former smokers, thus suggesting that smoking is not a cause of anxiety and depression.
Lewis et al[48]	Depressed mood at 18 weeks of pregnancy measured by the Edinburgh Postnatal Depression Scale (EPDS)	N=6,294 from Avon Longitudinal Study of Parents and Children (ALSPAC) cohort	Smoking status before and during pregnancy from rs1051730 genotype Smoking heaviness stratified by pre-pregnancy smoking status from rs1051730 genotype	For TT compared to CC in smokers: Prenatal depression: OR=0.56, 95% CI: 0.37-0.84 Weak evidence for an interaction (p=0.07)	The rs1051730 genotype predicts smoking heaviness during pregnancy and mothers being less likely to quit. However, there was no clear evidence for a causal effect of smoking on prenatal depression, as the results of genotype given continued smoking during pregnancy were consistent with a reduced risk of reporting depressed mood per effect allele rather than an increased risk.

GWAS – genome-wide association study, SNP – single nucleotide polymorphism, IVW OR – inverse-variance weighted odds ratio, OR – odds ratio, ADHD – attention-deficit/hyperactivity disorder

major depression (IVW OR=1.54, 95% CI: 1.44-1.64, p<0.01), and major depression influenced smoking initiation (B=0.083, 95% CI: 0.039-0.127). The results were consistent across several more pleiotropy robust methods (see Table 4).

Smoking and risk of psychotic disorders and bipolar disorder

The prospective risk for incident psychotic disorders in those who engaged in regular tobacco use compared to non-smokers were calculated in two meta-analyses, both using data from over 1.7 million individuals[52,53]. These meta-analyses consistently found a significantly heightened prospective risk of psychotic disorders, of around two-fold for smokers vs. non-smokers, in terms of daily tobacco use (n=6, RR=2.18, 95% CI: 1.23-3.85, I^2=97.7%)[53] and "personal active smoking" (n=6, RR=1.99, 95% CI: 1.1-3.61, I^2=97%)[52]. However, significant publication bias was indicated and high levels of statistical heterogeneity were found[52,53] (see Table 3).

Three MR studies investigated the causal influence of smoking on schizophrenia. First, the same SNP in the CHRNA3 gene cluster used in the above studies on depression (rs1051730) was used to examine effects on schizophrenia in a Danish general population sample and the international Psychiatric Genomics Consortium (PGC)[47]. Significant causal effects of smoking in increasing the risk of schizophrenia was found in the PGC (OR=1.60, 95% CI: 0.74-3.47). Although the relationship between smoking and diagnosed schizophrenia in the Danish population fell short of statistical significance (OR=1.22, 95% CI: 0.84-1.79), this could have been due to the small number of cases with schizophrenia in the sample (N=57), as further analyses examining smoking and odds of lifetime antipsychotic medication use in this sample (N=2,795 cases) found evidence for a significant causal relationship (OR=1.16, 95% CI: 1.02-1.31).

Second, a two-sample MR analysis[55] used a genetic instrument for "smoking initiation" (i.e., ever having smoked, without taking into account heaviness, duration or cessation) identified in the Tobacco and Genetics Consortium, and used it to predict schizophrenia in the PGC. They found no consistent evidence for causal relations between initiation of smoking and schizophrenia diagnosis, in either direction.

Third, the same genetic instrument used for lifetime smoking (capturing lifetime duration, heaviness and cessation of smoking) in the aforementioned MR study of smoking and depression[51] found that lifetime smoking significantly increased the

Table 5 Diet and prospective risk of mental disorders in meta-analyses

	Outcome	n	Exposure	Main results	Summary
Nicolaou et al[62] (NIH=3)	High depressive symptoms	3	Mediterranean diet	OR=0.88, 95% CI: 0.80-0.96, I^2=15.4%	This meta-analysis of harmonized studies found that adults following a healthy dietary pattern have significantly lower risk of depressive symptoms overtime, even when controlling for depressive symptoms at baseline. Small but significant positive effects were indicated from adherence to a Mediterranean or DASH diet, whereas the AHEI index was non-significant. Scores were low on review quality, probably due to this study being a meta-analysis of specific studies (not a full systematic review).
			Alternative Healthy Eating Index (AHEI)	OR=0.95, 95% CI: 0.84-1.06, I^2=35%	
			Dietary approaches to stop hypertension (DASH)	OR=0.90, 95% CI: 0.84-0.97, I^2=0%	
Lassale et al[61] (NIH=7)	Clinical depression or depressive symptoms	5	Mediterranean diet	OR=0.67, 95% CI: 0.55-0.82, I^2=33.1	Good quality review of multiple dietary patterns which found that adhering to a Mediterranean diet or low inflammatory diet is associated with reduced depression risk in prospective studies. It should be noted that there was heterogeneity in all analyses, and few studies used diagnosis of depression as the outcome.
		4	Healthy Eating Index/ Alternative Healthy Eating Index (AHEI)	OR=0.76, 95% CI: 0.57-1.02, I^2=80.7	
		4	Dietary approaches to stop hypertension (DASH)	OR=0.89, 95% CI: 0.6-1.31, I^2=68.0	
		7	Low dietary inflammatory index	OR=0.76, 95% CI: 0.63-0.92, I^2=55.3	
Tolkien et al[63] (NIH=5)	Clinical depression or depressive symptoms	10	Pro-inflammatory diet	OR=1.31, 95% CI: 1.2-1.44, I^2=5.1%	Fair quality review showing that pro-inflammatory diets are associated with significantly increased risk of depression/depressive symptoms, with low heterogeneity between studies.
Molendijk et al[60] (NIH=7)	Clinical depression or depressive symptoms	17	Healthy dietary patterns	OR=0.77, 95% CI: 0.69-0.84, I^2=88.3	Good quality review showing that healthy dietary patterns and healthy food groups were associated with a lower prospective risk of depressive symptoms. However, there was no evidence for unhealthy diet patterns or unhealthy food groups increasing depression risk. Additionally, no significant associations between diet and depression were found in subgroup analyses of the few studies which controlled for baseline depression severity, or used diagnosis of depression as the outcome. Subgroup analyses further examined various individual food groups, finding mixed results.
		18	Healthy food groups	OR=0.89, 95% CI: 0.83-0.95, I^2=71.3	
		10	Unhealthy dietary patterns	OR=1.05, 95% CI: 0.99-1.12, I^2=45.2	
		7	Unhealthy food groups	OR=1.09, 95% CI: 1.00-1.19, I^2=26.2	
		7	Neutral food groups	OR=0.91, 95% CI: 0.84-1.00, I^2=42.8	
Salari-Moghaddam et al[69] (NIH=7)	Clinical depression or depressive symptoms	2	High dietary glycaemic index	HR=1.05, 95% CI: 0.76-1.44, I^2=86.1%	Good quality review which failed to find prospective relationships between dietary glycaemic index and depression in random effect models. However, this was only examined in two longitudinal studies (for which fixed-effects analyses did observe a significant positive relationship). Thus, the findings overall can neither confirm or rule-out relationships between dietary glycaemic index and depression.
Hu et al[68] (NIH=6)	Clinical depression or depressive symptoms	4	Sugar-sweetened beverage consumption	RR=1.30, 95% CI: 1.19-1.41, I^2=0.00%	Fair quality review showing that regular consumption of sugar-sweetened beverages is associated with greater risk of depression. However, there was a low number of prospective studies assessing this association, which also did not adequately control for broader dietary factors.
Saghafian et al[64] (NIH=5)	Clinical depression or depressive symptoms	6	Fruit intake	RR=0.83, 95% CI: 0.71-0.98, I^2=84.5%	Fair quality review showing that fruit and vegetable intake is prospectively associated with reduced risk of depression. There was significant heterogeneity among studies. However, the observed associations between fruit and depression are inconsistent with other meta-analyses[60].
		7	Vegetable intake	RR=0.86, 95% CI: 0.75-0.98, I^2=68.1%	

Table 5 Diet and prospective risk of mental disorders in meta-analyses (*continued*)

	Outcome	n	Exposure	Main results	Summary
Zhang et al[67] (NIH=6)	Clinical depression or depressive symptoms	3	High meat consumption	RR=1.13, 95% CI: 1.03-1.24, I^2=19.4%	Fair quality review showing that those with highest levels of meat consumption are at higher risk of depression. However, there was a small number of studies in the pooled analysis, which combined odds ratios from "never vs. any" comparisons of meat consumption with studies of high vs. low levels of meat consumption. A larger analysis from subgroups within another review found no associations for meat and depression[60].
Li et al[66] (NIH=6)	Clinical depression or depressive symptoms	3	High dietary zinc intake	RR=0.73, 95% CI: 0.6-0.9, I^2=0.00%	Fair quality review indicating an inverse association between dietary zinc intake and future risk of depression. However, there was a low number of prospective studies assessing this association, which also did not control for other dietary factors.
Grosso et al[65] (NIH=4)	Clinical depression or depressive symptoms	7	Dietary n-3 PUFA consumption	RR=0.85, 95% CI: 0.73-1.00, I^2=19%	Fair quality review supporting the hypothesis that dietary PUFA may lower risk of depression. Fish intake was also associated with reduced risk of depression, which is consistent with a subsequent larger analysis[60].
		4	Dietary EPA + DHA consumption	RR=0.74, 95% CI: 0.61-0.89, I^2=0.00%	

n – number of comparisons, OR – odds ratio, RR – risk ratio, HR – hazard ratio, NIH – quality of the study evaluated by the National Institutes of Health's Quality Assessment Tool for Systematic Reviews and Meta-Analyses (good: 7 or 8; fair: 4-6; poor: 0-3), NA – not available, ADHD – attention-deficit/hyperactivity disorder, PUFA – polyunsaturated fatty acid, EPA – eicosapentaenoic acid, DHA – docosahexaenoic acid

risk for schizophrenia (OR=2.27, 95% CI: 1.67-3.08, p<0.001). There was also an indication of schizophrenia increasing lifetime smoking (B=0.022, 95% CI: 0.005-0.038, p=0.009).

This MR study[51] also updated the earlier two-sample MR analysis of smoking initiation[55], using the more recent GSCAN GWAS instrument (comprising 378 genome-wide significant independent SNPs), and found evidence for an effect of smoking initiation on risk of schizophrenia (IVW OR=1.53, 95% CI: 1.35-1.74, p<0.01), but less clear evidence for an effect of schizophrenia on smoking initiation (B=0.010, 95% CI: 0.000-0.021, p=0.04). The effects of smoking on schizophrenia were consistent across multiple sensitivity methods more robust to pleiotropy (see Table 4).

Concerning the relationship between smoking and bipolar disorder, no prospective meta-analysis examined relative odds in smokers vs. non-smokers. However, a two-sample MR study[56] assessed the impact of both smoking initiation and total lifetime smoking (using the same genetic instruments as those described above[51]) on risk of bipolar disorder across 41,653 individuals from the PGC (including 20,129 cases and 21,524 controls), using summary level data. These analyses found evidence suggesting that smoking was a causal risk factor for bipolar disorder (IVW OR=1.46 for smoking initiation, 95% CI: 1.28-1.66, p<0.001, and IVW OR=1.72 for lifetime smoking, 95% CI: 1.29-2.28, p<0.001), consistently across pleiotropy robust sensitivity methods. On the other hand, there was no clear evidence that the diagnosis of bipolar disorder causally affected the risk of smoking-related outcomes[56] (see Table 4).

Smoking and risk of ADHD

The link between smoking and the incidence of ADHD was examined in one meta-analysis[57] and one MR analysis[58].

A large-scale meta-analysis of 15 cohort studies including 2,965,933 individuals compared the incidence of ADHD diagnoses in the offspring of smoking vs. non-smoking mothers[57]. Pooled analyses of ORs adjusted for a range of confounding maternal factors (e.g., mother's age, education and socio-demographic status) and offspring variables (i.e., child's gender and gestational age) showed that maternal smoking significantly heightened the risk of ADHD (OR=1.35, 95% CI: 1.2-1.52, I^2=59.5%). There was non-significant indication of publication bias, and results were robust even when adjusting for this (see Table 3).

The MR study applied a two-sample MR approach using the most recent GWAS of smoking initiation[58] from the GSCAN consortium and ADHD diagnoses after age 18 years[59]. Bi-directional analyses found that smoking initiation significantly increased risk of ADHD (OR=3.72, 95% CI: 3.10-4.44, p<0.001), while ADHD also affected smoking initiation (B=0.07, p<0.001). However, smoking initiation also predicted ADHD diagnosis before age 13 years, leading the authors to conclude that results could be due to pleiotropy (see Table 4).

Diet and risk of depression

The association between dietary patterns and longitudinal risk for depression (defined as clinical depression or depressive symptoms) was examined in ten eligible meta-analyses (see Table 5).

A meta-analysis pooling all "healthy dietary patterns" from 17 comparisons (total N=127,973) found that these patterns were associated with significantly reduced prospective risk of depression (OR=0.77, 95% CI: 0.69-0.84, I^2=88.3%)[60]. Similar effects were observed in a pooled analysis of "healthy food groups" such

Table 6 Causal relations of diet and mental disorders in Mendelian randomization studies

	Outcome	Sample	Exposure	Main results	Summary
Choi et al[34]	Major depression	N=431,394 from Wray et al's GWAS[35]	Multivitamin supplements, tea intake, salt intake, lamb intake, inconsistent diet, cereal intake, vitamin B supplements	Multivitamin: OR=1.28, 95% CI: 1.11-1.47, p=0.0006 Tea intake: OR=0.95, 95% CI: 0.91-0.99, p=0.02 Salt intake: OR=1.10, 95% CI: 1.01-1.19, p=0.03 Lamb intake: OR=1.17, 95% CI: 0.95-1.44, p=0.14 Inconsistent diet: OR=1.15, 95% CI: 0.87-1.53, p=0.34 Cereal intake: OR=0.98, 95% CI: 0.94-1.02, p=0.42 Vitamin B: OR=1.002, 95% CI: 0.95-1.05, p=0.93	There was evidence to suggest that multivitamin intake causally increased risk of major depression at follow-up. This result survived Bonferroni correction for multiple testing. There was also nominal evidence for salt intake as a causal factor for depression (non-significant after correction for multiple testing). The only diet-related factor indicated as causally reducing depression risk was tea drinking. However, this association was non-significant after correcting for multiple testing.

OR – odds ratio, GWAS – genome-wide association study

as fish, vegetables and fruits (n=18, N=147,011, OR=0.89, 95% CI: 0.83-0.95, I^2=71.3%)[60]. However, pooled analyses for all "unhealthy dietary patterns", "unhealthy food groups" and "neutral food groups" found that none of these categories were significantly associated with the risk of depression[60].

In a more recent meta-analysis examining specific whole-of-diet patterns, the risk of depression was decreased for those with a high Mediterranean diet score (n=5, N=36,556, OR=0.67, 95% CI: 0.55-0.82, I^2=33.1%), with low heterogeneity between studies. Prospective associations with the DASH diet score (OR=0.89, 95% CI: 0.6-1.31, I^2=68.0%) and Healthy Eating Index/Alternative Healthy Eating Index (AHEI) scores (OR=0.76, 95% CI: 0.57-1.02, I^2=80.7%) had greater heterogeneity and were non-significant[61]. The Mediterranean diet score is typically based on nine items: five regarded as beneficial (fruit, vegetables, legumes, cereals, fish), two as detrimental (meat, dairy), one component on fat, and one on moderate alcohol intake. The DASH (dietary approaches to stop hypertension) diet score considers eight components (negative: sweet beverages, meat, sodium; positive: fruit, vegetables, legumes and nuts, wholegrain, low-fat dairy). The AHEI includes 11 components (vegetables, fruit, nut and soy protein, ratio of white to red meat, cereal fiber, trans fat, polyunsaturated-to-saturated fat ratio, duration of multivitamin use, and alcohol).

A subsequent but smaller meta-analysis of three harmonized datasets, controlling for depressive symptoms at baseline, found significantly reduced risk of depressive symptoms among those with high Mediterranean diet score (OR=0.88, 95% CI: 0.80-0.96, I^2=15.4%) or DASH score (OR=0.90, 95% CI: 0.84-0.97, I^2=0%), with little or zero heterogeneity[62]. Prospective associations with the AHEI were non-significant[62].

A lower Dietary Inflammatory Index (an index that quantifies the inflammatory potential of a diet based on up to 45 food parameters) was also found to be associated with reduced risk of depression (n=7, N=32,908, OR=0.76, 95% CI: 0.63-0.92, I^2=55.3%)[61]. Confirming this, a separate meta-analysis examining the opposite direction of effect found that individuals with pro-inflammatory diets at baseline were at significantly greater risk of depression, with low heterogeneity between studies (n=10, N=77,420, OR=1.31, 95% CI: 1.2-1.44, I^2=5.1%), with equally large risk observed in studies using >10 year or <10 year follow-up periods[63].

Of note, however, the results of the above meta-analyses were based mostly on self-reported depressive symptoms. Small subgroup analyses of studies which used clinical diagnosis of depression as the outcome did not find significant associations with dietary patterns[60].

Eligible data on various individual dietary aspects were presented in seven meta-analyses. Prospective risk of depression (including self-reported depressive symptoms) was significantly lower for those with greater intakes of vegetables (n=7, RR=0.86, 95% CI: 0.75-0.98, I^2=68.1%)[64], dietary zinc (n=3, RR=0.73, 95% CI: 0.6-0.9, I^2=0%)[66], fish (n=16, 0.86, 95% CI: 0.78-0.95, I^2=68.4%)[60], and dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (n=4, RR=0.74, 95% CI: 0.61-0.89, I^2=0)[65], while associations with dietary omega-3 fatty acids also approached significance (n=7, RR=0.85, 95% CI: 0.73-1.00, I^2=19%)[65].

The prospective risk of depression was significantly higher for those with greater consumption of sugar-sweetened beverages (n=4, RR=1.30, 95% CI: 1.19-1.41, I^2=0%)[68]. Although greater fruit intake was prospectively associated with reduced risk (n=6, RR=0.83, 95% CI: 0.71-0.98, I^2=84.5%)[64] and meat consumption was associated with heightened risk (n=3, RR=1.13, 95% CI: 1.03-1.24, I^2=19.4%)[67] for depression in meta-analyses focusing specifically on these foods, subgroup analyses within a broader meta-analysis found no significant associations for depression with either fruit intake or meat intake[60].

Non-significant prospective associations with depression were found for dietary glycaemic index (n=2, HR=1.05, 95% CI: 0.76-1.44, I^2=86.1%)[69], legumes/pulses (n=4, OR=0.93, 95% CI: 0.79-1.10, I^2=43.1%)[60], and nuts/seeds/soy (n=2, OR=0.92, 95% CI: 0.84-1.02, I^2=0.1%)[60]. It should also be noted that the strength of the findings for individual dietary aspects is reduced by the high levels of heterogeneity, limited comparisons within the meta-analyses, lack of clinical diagnostic outcomes, and inadequate control for how the individual dietary components related to other dietary factors.

Table 7 Sleep and prospective risk of mental disorders in meta-analyses

	Outcome	n	Exposure	Main results	Summary
Bao et al[70] (NIH=5)	Clinical depression or depressive symptoms	11	Sleep disturbances	RR=1.92, 95% CI: 1.60-2.30, I^2=10.2%	Fair quality review finding that individuals with "sleep disturbances" (including insomnia, complaints of sleeping difficulties and general poor sleep quality) are at significantly heightened risk of developing depression, with low heterogeneity between studies. Sensitivity analyses found associations between depression and sleep disturbances applied to both major depressive disorders and depressive symptoms.
		4	Persistent sleep disturbances	RR=3.90, 95% CI: 2.77-5.48, I^2=27.1%	
Zhai et al[74] (NIH=6)	Clinical depression or depressive symptoms	7	Short sleep duration	RR=1.31, 95% CI: 1.04-1.64, I^2=0%	Fair quality review indicating that both shorter and longer than average sleep durations are equally associated with significantly increased risk of depression in adults, with no indication of heterogeneity influencing the findings.
		5	Long sleep duration	RR=1.42, 95% CI: 1.04-1.92, I^2=0%	
Lee et al[75] (NIH=8)	ADHD or clinically significant ADHD symptoms	3	Short sleep duration	RR=2.61, 95% CI: 1.36-5.00, I^2=83.0%	Good quality review finding that short sleep duration is associated with significantly greater risk of ADHD overtime, in children and adults. However, there was a low number of total studies/participants and significant heterogeneity among prospective studies.
Li et al[72] (NIH=7)	Clinical depression or depressive symptoms	34	Insomnia (night-time symptoms)	RR=2.27, 95% CI: 1.89-2.71, I^2=92.6%	Good quality review showing that insomnia (although primarily identified by night-time symptoms) significantly increases the risk of depression, although with high heterogeneity between studies. There was some indication of publication bias, but adjusting for this did not alter the overall findings.
Hertenstein et al[73] (NIH=7)	All psychiatric disorders	19	Insomnia disorders	OR=2.60, 95% CI: 1.70-3.97, I^2=96.2%	Good quality review of studies with at least 12 months of follow-up reporting that individuals with insomnia (including presence of both day-time and night-time symptoms) are at greatly increased risk of developing psychiatric disorders. Subgroup analyses found that insomnia increased the risk of depression or anxiety disorders by around 3-fold, whereas effects on psychosis risk were weaker (n=1 only, data not shown). There was a substantial degree of heterogeneity between studies, and publication bias may have influenced effect estimates.
	Clinical depression or depressive symptoms	10		OR=2.83, 95% CI: 1.55-5.17, I^2=93.67%	
	Anxiety disorders	6		OR=3.23, 95% CI: 1.52-6.85, I^2=96.37%	

n – number of comparisons, OR – odds ratio, RR – risk ratio, NIH – quality of the study evaluated by the National Institutes of Health's Quality Assessment Tool for Systematic Reviews and Meta-Analyses (good: 7 or 8; fair: 4-6; poor: 0-3), ADHD – attention-deficit/hyperactivity disorder

The only eligible MR study found to examine causal relations between diet and incident mental illness was the aforementioned analysis by Choi et al[34], which also examined multiple dietary factors, including salt intake, lamb intake, inconsistent dietary patterns, multivitamin supplement use, tea intake, and cereal intake. There was no firm evidence that any of these factors influenced the risk of developing depression, apart from an unexpected effect of multivitamin supplementation use on increased risk (OR=1.28, 95% CI: 1.11-1.47, p=0.0006), which however was not consistent across sensitivity methods (see Table 6).

No prospective meta-analyses or MR studies examined the relationships between dietary nutrient intake and the risk for mental disorders other than depression.

Sleeping patterns and risk of mental disorders

A meta-analysis pooling all "sleep disturbances" (including insomnia, complaints of sleeping difficulties, and general poor sleep quality) found that they significantly increased the prospective risk for clinical depression or significant depressive symptoms (n=11, N=16,108, RR=1.92, 95% CI: 1.60-2.30, I^2=10.2%), with even greater risk following "persistent" sleep disturbances (n=4, N=3,602, RR=3.90, 95% CI: 2.77-5.48, I^2=27.1%)[70]. There was little heterogeneity between studies.

Beyond generalized sleep disturbances, a large prospective meta-analysis of data from 172,007 individuals in 34 examinations of "insomnia" (primarily identified from night-time symptoms) found that it significantly increased the risk for future depression (RR=2.27, 95% CI: 1.89-2.71, I^2=92.6%)[72]. However, there was high heterogeneity and many studies were of short (<12 months) duration. Nonetheless, a subsequent meta-analysis examining the psychiatric outcomes of insomnia from studies with at least 12 months follow-up similarly found heightened risk in pooled analysis for all psychiatric disorders (n=19, N=133,967, OR=2.60, 95% CI: 1.70-3.97, I^2=96.2%), along with statistically significant relations in all individual conditions examined, including for depression (n=10, OR=2.83, 95% CI: 1.55-5.17, I^2=93.67%), anxiety (n=6, OR=3.23, 95% CI: 1.52-6.85, I^2=96.37%) and psychotic disorders (n=1 only, data not shown)[73].

Concerning sleep duration, individuals with both short (median reference value: ≤6 hours) and long (median reference val-

Table 8 Causal relations of sleep and mental disorders in Mendelian randomization studies

	Outcome	Sample	Exposure	Main results	Summary
Gao et al[76]	ADHD	N=20,183 cases and 35,191 controls from Demontis et al's GWAS[59]	Night-time symptoms of insomnia (15-23 SNPs)	OR=1.08, 95% CI: 0.88-1.34, p=0.46	There was evidence to suggest that having insomnia increases risk for bipolar disorder. The same trend was observed for more pleiotropy robust sensitivity methods, but the evidence was weaker.
	Major depression	N=9,240 cases and 9,519 controls from PGC		OR=0.99, 95% CI: 0.69-1.40, p=0.94	
	Schizophrenia	N=33,426 cases and 32,541 controls from PGC		OR=1.14, 95% CI: 0.93-1.39, p=0.20	
	Bipolar disorder	N=20,129 cases and 21,524 controls from PGC		OR=1.79, 95% CI: 1.40-2.29, p<0.001	
Choi et al[34]	Depression	N=431,394 from Wray et al's GWAS[35]	Daytime napping Hours of sleep	Daytime napping: OR=1.34,95% CI: 1.17-1.53, p=0.00002 Hours of sleep: OR=1.04,95% CI: 0.93-1.15, p=0.49	There was strong evidence for an effect of daytime napping as a risk factor for depression, and this was consistent across sensitivity analyses and survived correction for multiple testing. There was no clear evidence for an effect of hours of sleep on depression risk.
Sun et al[39]	Bipolar disorder	N=20,352 cases and 31,358 controls from Stahl et al's GWAS[40]	Device measured sleep time (14 SNPs)	OR=1.05, 95% CI: 0.77-1.39, p=0.72	There was no clear evidence for an effect of objectively measured sleep on either bipolar disorder or schizophrenia.
	Schizophrenia	N=33,426 cases and 32,541 controls from Ruderfer et al's GWAS[41]		OR=1.13, 95% CI: 0.95-1.75, p=0.10.	

OR – odds ratio, GWAS – genome-wide association study, SNP – single nucleotide polymorphism, PGC – Psychiatric Genomics Consortium, ADHD – attention-deficit/hyperactivity disorder

ue: ≥8 hours) average daily sleep duration were at significantly higher risk of depression over the 7.9 year average follow-up, with no heterogeneity between studies (short sleep: n=7, N=25,271, RR=1.31, 95% CI: 1.04-1.64; long sleep: n=5, N=23,663, RR=1.42, 95% CI: 1.04-1.92)[74]. A separate meta-analysis also indicated that short sleep duration increased the prospective risk of ADHD (n=3, N=2,386, RR=2.61, 95% CI: 1.36-5.00, I^2=83.0%)[75], although the low number of studies and the lack of control for baseline ADHD symptoms decreases confidence in the findings (see Table 7).

Three MR studies assessed the causal role of sleep-related variables on risk for mental illness. Two of these were from the aforementioned two-sample MR studies of physical activity, which also measured sleep time using self-reported[34] and objective[39] measures. There was no evidence for causal associations between hours of sleep with depression, schizophrenia or bipolar disorder. However, it must be noted that MR can only test linear effects, whereas prospective meta-analyses indicate non-linear relations between sleep duration and mental illness[74].

For disordered sleeping, a two-sample MR study found evidence that self-reported difficulties in falling or staying asleep increase the risk for bipolar disorder (OR=1.79, 95% CI: 1.40-2.29, p<0.001), an effect which was consistent across multiple sensitivity methods to test for pleiotropy, whereas no evidence was found for depression, ADHD or schizophrenia[76]. However, the study by Choi et al[34] did find evidence for self-reported inadvertent daytime napping as a risk factor for the onset of depression (OR=1.34, 95% CI: 1.17-1.53, p=0.00002), consistent across pleiotropy robust sensitivity methods (see Table 8).

Lifestyle interventions in the treatment of mental disorders

Efficacy of physical activity interventions for mental disorders

One recent meta-review provided sufficient information on the efficacy of physical activity for the treatment of eligible psychiatric conditions, bringing together the data from 16 meta-analyses of RCTs[77]. The most widely assessed condition was major depression, with four meta-analyses in adult samples finding significant positive effects of exercise interventions in comparison to various control conditions, including waitlist and usual treatment, control interventions of flexibility, stretching/relaxation and meditation, and placebo pills.

The largest and most recent was a meta-analysis showing moderately large benefits of exercise across 35 RCTs in adults with depressive disorders (SMD=–0.66, 95% CI: –0.86 to –0.46, I^2=81%). However, only small, non-significant benefits were observed in four trials deemed of "high quality" and comparing exercise to other active control conditions (SMD=–0.11, 95% CI: –0.41 to 0.18, I^2=62%).

Within the meta-review, two meta-analyses of RCTs examined exercise in youth with depressive disorders, and both found significant effects. The most recent observed a large, positive benefit of exercise compared to both waitlist and attention-matched control conditions (n=4, N=100, SMD=–0.95, 95% CI: –1.37 to –0.53, p<0.001, I^2=0%). Only two trials examined the impact of

exercise in older people with a diagnosis of major depressive disorder, and did not find a significant effect (SMD=–1.883, 95% CI: –4.21 to 0.44, p=0.11, I^2=93%), although exercise did significantly reduce depression in older adults with high levels of depression symptoms (n=8, N=267, SMD=–0.90, 95% CI: –1.51 to –0.29, p=0.004). The cognitive benefits of exercise in major depression were examined in eight trials, showing no overall benefits.

Concerning the treatment of anxiety and stress-related disorders, the most recent meta-analyses found that exercise reduced symptoms significantly more than control conditions in pooled analyses of RCTs in patients with panic disorder, generalized anxiety disorder, post-traumatic stress disorder and social phobia (n=6, N=262, SMD=–0.581, 95% CI: –1.09 to –0.076, I^2=66%) and in people receiving treatment for anxiety in primary care (n=4, SMD=–0.32, 95% CI: –0.62 to –0.01). However, an earlier meta-analysis found inconsistent evidence for significant benefits, with the effects of exercise on anxiety disorders varying with regard to the type of control condition used[77].

In schizophrenia and non-affective psychotic disorders, physical activity interventions across eight RCTs did not significantly reduce total symptoms. However, RCTs of exercise interventions which used at least 90 min of moderate-to-vigorous activity per week did significantly reduce total symptoms (SMD=–0.72, 95% CI: –1.14 to –0.29), positive symptoms (SMD=–0.54, 95% CI: –0.95 to –0.13) and negative symptoms (SMD=–0.44, 95% CI: –0.78 to –0.09) more than control conditions[77]. Exercise was also found to significantly improve global cognition in schizophrenia (n=7, SMD=0.412, 95% CI: 0.19-0.64). Earlier meta-analyses examining the effects of aerobic exercise on comorbid symptoms of depression and anxiety in schizophrenia populations found no significant effects.

The effects of exercise in bipolar disorder were not investigated in any meta-analyses of RCTs. A meta-analysis of RCTs in children with ADHD found moderately large, statistically significant effects of aerobic exercise for various outcomes, including attention, hyperactivity, impulsivity, anxiety and executive functions[77].

Efficacy of smoking cessation interventions for mental disorders

The impact of non-pharmacological smoking interventions on psychiatric symptoms in populations with mental disorders was not found in any eligible meta-analyses of RCTs.

Efficacy of dietary interventions for mental disorders

One eligible meta-review examined dietary interventions in the treatment of a mental disorder, specifically the effects of food exclusion diets in children with ADHD[78]. Four relevant meta-analyses were included, two on "artificial food colouring (AFC) elimination" (i.e., removing all foods from the diet which contain AFCs), and two on "few-foods diets" (i.e., eliminating many potentially symptom-triggering foods, to include only a limited selection of natural foods in the diet).

The results from meta-analyses of placebo-controlled trials indicated a non-significant trend towards improvement in symptoms of ADHD from AFC elimination across parent-rated measures (n=11, SMD=0.21, 95% CI: –0.02 to 0.43, I^2=68%, p=0.07), with no effects for teacher-rated measures (n=6, SMD=0.08, 95% CI: –0.07 to 0.24, I^2=0%) and observed-rated measures (n=4, SMD=0.11, 95% CI: –0.13 to 0.34, I^2=12%)[78].

The few-foods diets were found to have significant positive effects on ADHD symptoms. The recalculated meta-analyses found moderately large effect sizes in RCTs of the few-foods diets for any-rater measures (n=5, SMD=0.75, 95% CI: 0.31-1.19, I^2=58.6%) and parent/ward observation measures (n=5, SMD= 0.78, 95% CI: 0.42-1.14, I^2=48.5%) of ADHD symptoms[78]. The few-food diets were broadly described as "lamb, chicken, potatoes, rice, banana, apple and brassica", although noting that this could be customized to child/parent preference while maintaining the core "few-foods" concept of avoiding artificially sweetened and highly refined foods which could provoke symptomatic response.

No eligible meta-analyses of dietary interventions in the treatment of other mental disorders were identified.

Efficacy of sleep interventions for mental disorders

The efficacy of sleep interventions in the treatment of psychiatric conditions was investigated in two independent meta-analyses. In a pooled analysis of seven RCTs across a mixed psychiatric sample with anxiety, depression or post-traumatic stress disorder, non-pharmacological sleep interventions – predominantly based on cognitive behavior therapy (CBT) – produced a large and significant reduction in depressive symptoms in comparison to control conditions (NIH=6, SMD=0.81, 95% CI: 0.49-1.13, I^2=27%)[79]. While heterogeneity was low, there was some indication of publication bias, with larger effects observed in smaller studies in the meta-analysis[79]. Large, significant reductions in depressive symptoms were also found from continuous positive airway pressure in people with depression and comorbid obstructive sleep apnoea (NIH=6, SMD=2.00, 95% CI: 1.39-2.62, I^2=12%)[80], but included data from only two RCTs in psychiatric samples, and thus no strong conclusions can be drawn.

DISCUSSION

This meta-review provides a systematic and comprehensive appraisal of the current evidence concerning the role of the key modifiable "lifestyle factors" of physical activity, smoking, diet and sleep in the prevention and treatment of mental disorders.

From the literature to date, physical activity emerges as the most widely researched lifestyle factor. There is substantial evidence from multiple meta-analyses of longitudinal data and MR studies that physical activity has a protective role in reducing risk

for certain mental disorders. Furthermore, while further replication in high-quality RCTs is needed, meta-analyses of RCTs have found that exercise interventions may provide effective adjunctive treatment for depression, anxiety and stress-related disorders, psychotic disorders and ADHD.

In public health guidelines, 150 min of moderate activity or 75 min of vigorous activity per week (or some combination of these) are recommended for reducing risk of various health conditions in adults[13,14]. However, it is important to keep in mind that, unlike chronic physical diseases, most mental disorders first arise in young people[6,82]. Simply advising young people to be more active is unlikely to have a substantial impact on behavior change. Instead, realizing the protective role of physical activity will likely require systemic integration of the evidence presented here within environmental modification alongside mental and physical health promotion initiatives for young people[83], which can be feasibly delivered through school settings[84] and as part of cross-sectoral public health strategies. For treatment of diagnosed mental illness, supervised exercise interventions are recommended, incorporating moderate-to-vigorous activity, and delivered by trained exercise professionals either working within mental health services or made available through referral to community-based schemes[9,17].

Current recommendations pertain largely to aerobic activity and cardiorespiratory fitness as the focus of exercise interventions, as the majority of observational and interventional research in this area has focused on overall physical activity levels. While this is well-supported by the literature (with growing evidence of cardiorespiratory fitness itself reducing risk of psychiatric disorders[85-87]), it should also be noted that there is now some evidence that muscular strength and resistance training also are protective against mental illness, even independently of general physical activity[88-90]. Furthermore, strength training interventions can significantly improve mental health[91,92], with effects that may persist over and above those of aerobic exercise alone[93]. Thus, future research and guidelines on physical activity should afford further consideration to the efficacy and feasibility of resistance training interventions, in both the prevention and treatment of mental illness.

There is a significant body of evidence that poor sleep is another key modifiable lifestyle factor, with large-scale meta-analyses showing prospective links with various psychiatric disorders, and supportive findings from MR studies suggesting a causal role in bipolar disorder. Alongside this, sleep disturbances have been found to significantly heighten the risk of suicidal behavior in people living with mental illness[71].

Furthermore, meta-analyses of RCTs also support the efficacy of sleep interventions in reducing symptoms of depression. Of note, whereas many trials have shown the alleviation of subclinical depressive symptoms following sleep interventions, the available evidence suggests that even larger effects of sleep therapies on depression are observed in those with mental illness[79-81,94]. Additionally, a role of poor sleep in severe mental disorders is suggested by a recent RCT showing that CBT for insomnia (CBT-I) significantly reduces the severity of hallucinations and paranoia in youth experiencing symptoms of psychosis[95].

Overall, poor sleep appears to play an important role in the onset and aggravation of mental illness, and CBT-I may provide an attractive non-pharmacological option (which can also be delivered digitally) for improving sleep and other aspects of mental health[94-96]. Establishing the feasibility and effectiveness of CBT-I in people with psychotic disorders is a priority for future research.

The evidence that tobacco use is a significant and modifiable risk factor for a range of psychiatric conditions is becoming increasingly strong. Whereas early MR studies found inconsistent effects, the most recent GWAS studies have improved statistical power to provide strong indications for smoking as a causal factor in the onset of major depression, bipolar disorder and schizophrenia. These findings are in line with multiple meta-analyses showing that smoking is associated with a heightened prospective risk of mental disorders, earlier age of onset, and adverse outcomes in those living with mental illness[53,54].

Collectively, these findings provide additional evidence for public health bodies to justify tobacco control initiatives which can effectively reach vulnerable, deprived or marginalized groups. In fact, people with mental illness have so far not clearly benefitted from the recent reductions in tobacco smoking rates observed in the general population across Western societies[97].

Although we did not identify any meta-analyses of RCTs for smoking cessation reducing symptoms of psychiatric disorders, a consistent body of work shows that stopping smoking does not cause deterioration in mental health among those with mental illness (an assumption which can sometimes be a barrier towards implementation in clinical settings)[98], and in fact appears to improve psychological well-being[99], including in those living with mental illness. Furthermore, the critical need for such interventions in mental health care settings is already acknowledged on the basis of physical health risks – as smoking is a leading cause of the 15 to 30 year premature mortality associated with severe mental illness[100]. Lastly, the role of tobacco use as a cause of psychiatric disorders, and source of health inequalities, warrants further research into the potential benefits of harm reduction strategies such as e-cigarettes.

The causal effects of diet on common and severe mental illnesses are less clear. Several meta-analyses have shown that healthy dietary patterns are associated with a significantly reduced risk of depressive symptoms. However, prospective links with diagnosed depression or other mental disorders were not established. There was also an absence of MR evidence to support causal roles of dietary patterns in the onset of any mental illness.

Furthermore, a recent four-arm RCT examined nutrition-based interventions for the prevention of depressive episodes in 1,025 participants with subclinical depressive symptoms, and found no significant benefits from the behavioral activation intervention promoting healthy eating[101]. However, the null effects may be due to poor intervention adherence, given the very marginal improvements in diet quality reported. Interestingly, the other "active" arm of this RCT provided daily multinutrient sup-

plementation, observing significantly worsened outcomes for depressive symptoms compared to placebo[101]. Although seemingly paradoxical, these counterintuitive findings align with results from the MR study by Choi et al[34], in which the only dietary nutrition factor with evidence for causal relations was multivitamin supplement use relating to increased depression risk.

Clearly, further research is needed to establish how nutrition impacts on mental health. Nonetheless, for those living with current mental illness, a number of existing clinical trials have already suggested that dietary interventions may be used alongside standard care to improve outcomes. Along with the preliminary evidence for specific dietary interventions in ADHD presented above, several recent RCTs (not captured in our meta-review) have reported significant improvements in clinical depression from Mediterranean diet interventions, observing moderately large positive effects[102-104]. While further replication of these findings is still required to determine effects on mental health, the high levels of dietary risk factors and associated cardiometabolic diseases associated with mental illness[6,105] already provides a basis for considering dietary factors within multidisciplinary health care for people with mental illness[106].

Further research is also required to explore the neurobiological pathways through which various lifestyle factors impact mental health, as mechanistic evidence from intervention trials is currently sparse. One potentially shared biological mechanism by which multiple adverse health behaviors could increase risk of mental illness is inflammation, which has been linked with a broad range of psychiatric disorders[112]. As previous research has indicated anti-inflammatory effects from exercise[113], Mediterranean diet[114], improved sleep[115] and smoking cessation[116], this may partially explain the effects of lifestyle interventions on improving mental health.

Further mechanistic insights are available from studies inducing an adverse health behavior in otherwise healthy samples, and then observing the potentially detrimental effects on mental health. For instance, some experimental evidence indicates that administration of "unhealthy" meals (e.g., high in glycaemic index or saturated fats) can increase depressive symptoms and inflammatory markers in healthy human subjects[69,108,109]. Whereas less direct experimental evidence exists for smoking or poor sleep, both of these factors have also been shown to have pro-inflammatory effects in humans[110,111]. However, a recent systematic review found that, although induced exercise cessation in previously active adults did significantly increase depressive symptoms within two weeks, this was not accompanied by increases in inflammatory markers[107], suggesting that other mechanisms must explain these effects.

The role of the gut microbiome in mental health is currently receiving considerable research interest[117]. Since the microbiome appears to be influenced by exercise[118] and diet[119], this could be considered as another potential pathway through which modifiable health behaviors could impact on mental health. However, scientific understanding in this area is still in its infancy, and even the nature of a "healthy microbiome" has yet to be established[120]. Therefore, triangulating the causal relations between lifestyle, mental health and the gut microbiome is currently speculative, although representing an intriguing avenue for future rigorous research.

Besides these possible direct mechanisms, it is also important to consider how the downstream consequences of adverse health behaviors may link lifestyle factors to mental disorders. For instance, insufficient exercise, poor diet, and even sleep disturbances can be contributing factors towards the development of metabolic diseases and obesity, which themselves may adversely impact mental health[121-123], and have been linked to the recent rise of mental illness in young people[7].

The biological, social and psychological pathways through which physical health conditions such as obesity, diabetes and even cardiovascular diseases affect mental health have yet to be fully determined. Nonetheless, the emerging field of "lifestyle psychiatry" must not neglect the body of evidence around previously established health-related and social determinants of psychological well-being, and their interaction with lifestyle factors[6,9], in the development of prevention and treatment initiatives for mental illness.

Additionally, as the field moves forward, further consideration of the role of "newer" lifestyle factors is warranted. Specifically, the widespread use of digital technologies is gaining increasing attention from the public, researchers and clinicians with regards to potential influence on psychological well-being. A growing body of research has identified multiple pathways through which constant Internet usage may be affecting our cognitive and social processes, along with mental health and brain functioning[124]. On the other hand, there is also a rapidly growing body of research examining the potential for using digital technologies in the prevention and treatment of mental illness. Recent meta-analyses of RCTs have shown that psychological interventions for common mental disorders, such as anxiety and depression, can be delivered remotely via smartphone apps[125], with a smaller but emerging evidence base also for psychotic disorders[126].

Despite these recent increases in the amount of empirical research on the interaction between digital technologies and mental health, there is still a need for further large-scale and interventional research to determine what types and quantities of usage impact on mental health, and how this interacts with other lifestyle factors, such as sedentary behavior and diet.

In conclusion, health behaviors may play an important role in prevention and treatment of mental illness. The converging lines of supportive evidence for the roles of exercise, smoking, diet and sleep are summarized in Figure 1 (with further details on quality and consistency of evidence displayed in Tables 1-8). At the public health level, further research is still required to improve evidence-based implementation of health promotion initiatives, and to determine their impact on risk of mental illness. Nonetheless, the positive mental health findings from system-wide approaches to health promotion in children and adolescents[83,84] reinforces the assertion that effectively addressing multiple lifestyle factors in young people presents a promising approach towards tackling the rates of mental illness across the population[6,7,83,84].

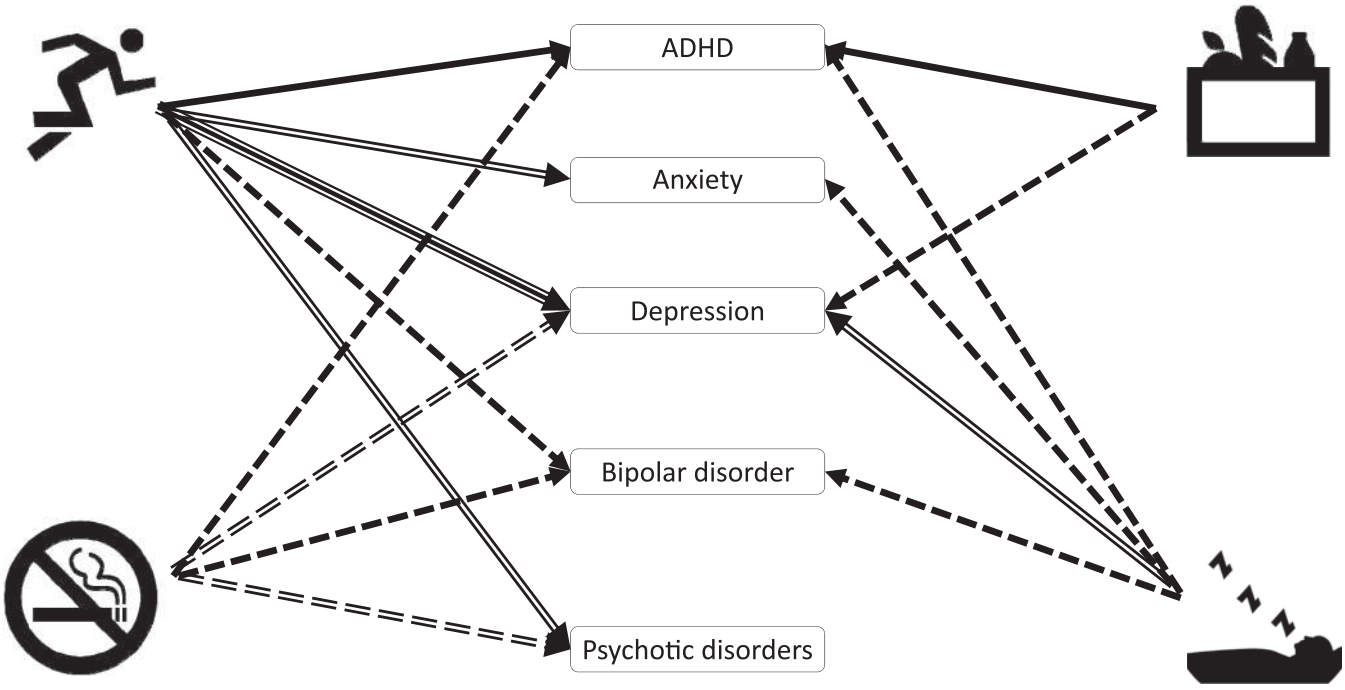

Figure 1 Lifestyle factors in the prevention and treatment of mental illness. The dashed line indicates evidence for protective benefit from either prospective meta-analyses (P-MAs) or Mendelian randomization studies (MRs). The double-dashed line indicates evidence for protective effects from both P-MAs and MRs. The solid line indicates evidence for efficacy in treatment of mental illness from MAs of randomized controlled trials (RCTs). The double solid line indicates convergent evidence from MRs or P-MAs with MAs of RCTs. The treble solid line indicates convergent evidence from all three (P-MAs + MRs + MAs of RCTs). ADHD – attention-deficit/hyperactivity disorder.

For clinical settings, the findings presented above add to the growing rationale for broad-scale provision of lifestyle interventions within primary and secondary care services for people with mental disorders[6,9,17,18]. These should aim to capture all "core principles" of evidence-based lifestyle interventions for mental illness, which briefly can be summarized as: a) using behavior change techniques with specific, measurable behavioral goals and self-monitoring; b) involving dedicated "physical health" staff, such as professionals in specific aspects of health behavior change, delivering supervised sessions for service users; c) training mental health staff in the importance and goals of lifestyle interventions; and d) facilitating peer-support to improve uptake and adherence[9].

Further research is required to address the existing barriers towards implementation and dissemination of lifestyle interventions. For instance, harnessing the reach of digital technologies may present a new option for wide-scale delivery of lifestyle-based prevention and management strategies for mental illness, which may be particularly useful for low- and middle-income settings, where traditional mental health care services are often unavailable. However, further investigation into how certain aspects of digital technologies may pose a new "lifestyle risk factor" for mental health is also required.

Finally, as the field progresses, it must always be considered that the etiology of mental disorders is of course multifactorial, and cases will often occur (and persist) independently of lifestyle factors. Thus, attributing an individual's condition to his/her health behaviors would often be ill-founded, stigmatizing and unhelpful. Instead, the onus to act is on policy makers, public health bodies, and clinical services to properly address adverse health environments and behaviors, in order to reduce risks and improve outcomes of mental disorders.

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The evolution of Kraepelin's nosological principles

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Emil Kraepelin developed a new psychiatric nosology in the eight editions of his textbook. Previous papers have explored his construction of particular diagnoses, including dementia praecox and manic-depressive insanity. Here we are providing a close reading of his introductory textbook chapter, that presents his general principles of nosology. We identify three phases: 1) editions 1-4, in which he describes nosological principles in search of data; 2) editions 5-7, in which he declares the mature version of his nosological principles and develops new disease categories; 3) edition 8, in which he qualifies his nosological claims and allows for greater differentiation of psychiatric disorders. We propose that Kraepelin's nosology is grounded in three principles. First, psychiatry, like other sciences, deals with natural phenomena. Second, mental states cannot be reduced to neural states, but science will progress and will, ultimately, reveal how nature creates abnormal mental states and behavior. Third, there is a hierarchy of validators of psychiatric diagnoses, with the careful study of clinical features (signs, symptoms and course) being more important than neuropathologic and etiological studies. These three principles emerged over the course of the eight editions of Kraepelin's textbook and were informed by his own research and by available scientific methods. His scientific views are still relevant today: they have generated and, at the same time, constrained our current psychiatric nosology.

Key words: Kraepelin, psychiatric nosology, psychiatry textbook, psychoses, clinical pictures, disease forms, scientific naturalism, natural kinds, validators

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Emil Kraepelin (1856-1926) proposed the diagnoses of dementia praecox and manic-depressive insanity in an effort to advance the clinical management and scientific study of the psychoses. Previous papers have explored the history of these diagnostic concepts[1-4]. Here we focus on Kraepelin's general principles of psychiatric nosology, which guided his classification of psychiatric disorders. The primary source texts are the eight editions of his textbook, published between 1883 and 1913[5-16].

Textbooks served an important function when psychiatry emerged as an academic discipline in the second half of the 19th century[17-19]. In those early days of academic psychiatry, it was not clear how best to teach the subject and how to develop research programs[17,20]. On a pragmatic level, textbooks provided a source of income and facilitated the teaching of psychiatry to medical students and assistant physicians. More importantly, textbooks allowed authors to articulate and disseminate their perspective of psychiatry in general, and psychiatric nosology in particular.

TEXTBOOKS BEFORE KRAEPELIN

Kraepelin referenced five textbooks that helped him write his own. Three are less relevant here: the fourth edition of Griesinger's textbook[21], published posthumously in 1876; the textbook by Emminghaus[22], published in 1878 when he was Kraepelin's medical school teacher, and a compendium by Weiss from 1881[23]. The other two are crucial for Kraepelin: the textbooks of Schüle (2nd edition in 1880)[24] and Krafft-Ebing (2nd edition in 1883)[25].

H. Schüle (1840-1916) rose to prominence as asylum director (he turned down several offers to chair psychiatry departments) and as journal editor. He published three editions of his widely-read textbook, known for rich, and sometimes convoluted, language[26].

R.F. von Krafft-Ebing (1840-1902), trained with Schüle, subsequently chaired three psychiatry departments (Straßburg, Graz and Vienna), and was a prolific author of several books, including seven editions of his psychiatry textbook. The last edition was translated into English[27].

Kraepelin acknowledged their influence when he introduced his own nosology of psychiatric disorders: "The sequence and delineation I have chosen … follows in its fundamental conception the systems constructed by Schüle and v. Krafft-Ebing"[7, p.239; 8, p.244].

All three authors – Schüle, Krafft-Ebing and Kraepelin – included a chapter in their textbooks that summarized their general principles of psychiatric nosology.

Schüle proposed a complex and confusing psychiatric nosology[28]. He separated psychiatric disorders into psychic, organic and psychic-organic types. He also distinguished cerebropsychoses (diffuse brain diseases that always affect the motor system) from psychoneuroses (diseases of the mind, not accompanied with brain changes). The resulting nosology was a hybrid of clinical description and etiological speculation, supported by neuropathological findings, if available.

Krafft-Ebing was more practical. He acknowledged three types of nosologies (anatomical, etiological and clinical) and distinguished three major diagnostic groups: illnesses without pathological findings, illnesses with pathological findings, and neurodevelopmental disorders.

In the first three editions of his textbook, Kraepelin's introductory chapter *The Classification of Psychoses* followed the tradition of Schüle and Krafft-Ebing. In the fourth edition, he broadened the title to *The Nosology of Mental Disorders*. We translated the eight editions of this chapter (which we will refer to as the "nosological chapter"), in order to study the evolution of his nosological principles (see Table 1 for details). In our view,

Kraepelin developed his nosology in three phases: editions 1-4, editions 5-7, and edition 8.

PHASE 1: EDITIONS 1-4

First edition

Kraepelin published the first edition of his textbook in 1883, at age 26. He had completed medical school in 1878 and psychiatric training with the anatomist-psychiatrist B. von Gudden (1824-1886) in 1882. In February 1883, he accepted his first psychiatric position, as first assistant to the department chairman P. Flechsig (1847-1929) in Leipzig. After less than four months, Flechsig dismissed Kraepelin[29].

In his *Memoirs*, Kraepelin wrote: "My situation in Leipzig was very uncertain. I tried to help myself out of my difficulties by accepting the offer to write a compendium of psychiatry"[30, p.25].

The first edition of Kraepelin's textbook was indeed a Compendium, a concise compilation, primarily for students. The next three editions were a Short Textbook and the final four editions became the Textbook. Kraepelin dryly stated: "Nothing new is to be expected in a compendium, however, as far as my own experiences sufficed, I have strived for a degree of independence in the presentation"[5, p.VIII].

The nosological chapter of the Compendium was brief. In three pages, Kraepelin reviewed anatomical, etiological and clinical-symptomatic approaches to psychiatric classification. He considered pathological anatomy and etiology to be of limited value, and concluded that clinical presentations had to provide the basis of a preliminary classification. His assessment was in line with Krafft-Ebing's one: "What it offers us are not illnesses, but merely symptom complexes"[5, p.189].

The Compendium included the chapter *The supporting sciences and methods of psychiatric research*, which was not continued in the subsequent editions of the textbook. Here Kraepelin described, in general terms, how neuroanatomy and experimental psychology can support the pathological study and clinical characterization of mental disorders. The influence of his two mentors – the anatomist B. von Gudden and the experimental psychologist W. Wundt (1832-1920) – is unmistakable. Three years later, Kraepelin used much of this chapter for his inaugural lecture as the new psychiatry chair at Dorpat University[30, 31].

Second and third edition

The next two editions of Kraepelin's textbook appeared during his chairmanship in Dorpat (now Tartu), Estonia (1886-1890). He wrote in his *Memoirs*: "I was forced to publish a second edition of my little text-book, which was completed in 1887; a third edition followed in 1889. The unfavorable circumstances of my clinical activity meant that I had to stay on the tracks already taken, without making any particular progress"[30, p.43].

But this is not the full story. In fact, the nosological chapter in the second edition advanced a new vision for psychiatry: "Were we to be in possession of a thorough and exhaustive knowledge of all details in one of the three fields, namely pathological anatomy, etiology or symptomatology of insanity, not only would each of them allow a uniform and thorough division of the psychoses, but *each of these three groups would also – this requirement is the cornerstone of all scientific research – coincide substantially with the other two*"[6, p.211] (italics added).

This single final sentence captured the essence of Kraepelin's philosophy of science and remained largely unchanged in all subsequent editions. In the third edition, he elaborated on the "three fields of knowledge" and added a fourth set: "The cases of illness which occurred due to the same causes would in each case have to display the same phenomena and the same post-mortem findings. It follows from this fundamental view that the clinical classification of mental disturbances has to be based on all three of the classification aids, to which one must add the experience gained from course, outcome and treatment"[7, p.238].

This text in the second and third edition of the textbook anticipated a core concept of current nosology: any classification is preliminary but, in the end, validators will converge and psychiatric disorders will be defined at the level of the brain. It is remarkable that the text appears so early in Kraepelin's career, considering his own assessment of the limited opportunity for clinical research available to him in Dorpat[32]. Only after his move to Heidelberg in 1891 was he able to collect enough clinical material to develop and then support his new nosology.

Despite a lack of available data, Kraepelin made two important claims. First, psychiatric disorders in general, and psychoses in particular, are what philosophers call *natural kinds*: they reflect the structure of the natural world, being discovered rather than invented[33,34]. He asserted that progress in psychiatric research is possible only if validators converge on natural kinds. This is in contrast to the view that psychiatry should be limited to studying the mind[35,36].

Table 1 The nosological chapter in Kraepelin's textbook

Kraepelin's place of work	Leipzig	Dorpat		Heidelberg				Munich
Year of publication	1883	1887	1889	1893	1896	1899	1904	1910
Edition (volume)	**1**	**2**	**3**	**4**	**5**	**6 (2)**	**7 (2)**	**8 (2)**
Die Klassifikation der Psychosen (pages)	187-189	209-212	235-240					
Die Einteilung der Seelenstörungen (pages)				239-245	311-320	1-9	1-12	1-19

Second and third edition used the spelling "Classification" instead of "Klassifikation". Fourth, fifth and sixth edition used the spelling "Eintheilung" instead of "Einteilung".

Second, the various methods of psychiatric research complement each other. Researchers might start from very different vantage points, but their results will converge.

These conjectures became a focus of criticism for a number of his detractors[37]. Kraepelin already anticipated such criticism of his strong naturalism in the third edition of the textbook: "The more the forms which have been gained from the different views correspond, the greater the certainty that the latter really represent particular disorders"[7, p.238].

Kraepelin recognized that psychiatric disorders are not all the same. Some will likely have higher convergent validity than others. This allowed for a hierarchy within psychiatric nosology, with high convergent validity being the closest to the ideal of a natural kind. It also meant that his classification of psychoses may include diagnoses with only modest convergent validity.

Despite his strong philosophical claims, Kraepelin was a pragmatist when designing his classification scheme: "I have not constructed an actual classification and have contented myself with simply placing a number of empirically gained clinical pictures alongside each other"[6, p.211].

There is considerable tension between Kraepelin's bold vision for a new psychiatric nosology and his traditional classification. The first sign that this tension will lead to a rupture is seen in his fourth edition.

Fourth edition

In 1891, Kraepelin left Dorpat to become chair of psychiatry in Heidelberg. The fourth edition of his textbook, published in 1893, represented a transition towards the more mature form of his psychiatric nosology, which he achieved during this chairmanship in Heidelberg (1891-1903).

Much of the nosological chapter in the fourth edition is unchanged from the two previous ones. But Kraepelin added: "There simply exist no pathognomonic symptoms in the field of insanity; instead only the comprehensive picture of a case of illness, in its development from the beginning to the end, justifies inclusion with other similar observations"[8, p.242].

And he advocated for a new method of painstaking, longitudinal studies: "Every psychiatrist knows that we sometimes encounter cases which in every respect, in the manner of emergence, all details of the symptoms, and further course, present a downright baffling similarity to each other. Such observations will form the natural starting point for our classification endeavors"[8, p.243].

Here he anticipated the significant changes of the fifth edition: for the discovery of natural kinds in psychiatry, clinical observation needs to take the lead.

PHASE 2: EDITIONS 5-7

Fifth edition

The *Foreword* of the fifth edition of the textbook, published in 1896, announced a significant change in Kraepelin's nosology: "In the development of this book, the current edition means the last decisive step from a symptomatic to a clinical perspective of insanity. All pure 'clinical pictures' (*Zustandsbilder*) have thus disappeared from the nosology"[9, p.V].

The change to a clinical perspective is a paradigm shift[38] in Kraepelin's nosology: the *symptom complexes* of the Compendium have been replaced by the concept of unitary diseases[39-41].

Kraepelin elaborated on the clinical perspective in the *Introduction*. First, course and outcome have become primary validators: "As soon as we are able to predict, based on the current condition of a patient, the most likely further development of his affliction with a degree of certainty, then the first important step towards a scientific and practical command of the clinical picture has occurred"[9, p.3].

Second, he asserted a causal structure for psychiatric disorders and the special role of clinical observation: "In the course of mental illness, the same causes also have to have the same effects everywhere. If we encounter, as we so often do, seeming deviations from this law, then, without a doubt, either the causes or the effects have not really been the same. Once we have managed to process clinical knowledge to such an extent that we can construct clinical groups with particular causes, symptoms and courses, it will become our task to penetrate the essence of individual pathological processes"[9, pp.4-5].

Finally, a new paragraph in the nosological chapter summarized his mature nosology: "The first task of the doctor at the sickbed is to form a judgment about the further course of the case of illness. The value of each diagnosis for the practical task of the psychiatrist is therefore essentially determined by how far in the future certain forecasts can be made. The same cause of illness will generally also determine the same course of the affliction, and from the clinical symptoms we have to be able to read the further fate of our patients in broad strokes"[9, p.315].

Kraepelin used his new nosological framework to make significant changes to the classification of Schüle and Krafft-Ebing. In fact, with this edition of the textbook and going forward, he no longer referred to them. Kraepelin even added a new subtitle to pages 317 and 319: *Eigene Eintheilung (Own Division)*. He made three major changes.

First, he introduced an etiological dichotomy: acquired mental disorders versus mental disorders due to a pathological predisposition. The former are disorders of a previously normal brain, often with acute onset, and caused by exogenous poisons, brain injury or metabolic disorders; the latter are conditions that arise insidiously in an already abnormal brain.

Second, metabolic disorders are caused by an endogenous poison, a process he called autointoxication, and include endocrine disorders, general paresis and dementing processes. Kraepelin acknowledged that an endogenous poison is only "certain" for the first group, but considered such etiology "most likely" for the other two. The dementing processes are a prequel version of dementia praecox and already include three subtypes: dementia praecox (later termed hebephrenia), catatonia and dementia paranoides.

Third, while dementia paranoides was part of the dementing

processes within the metabolic disorders (i.e., an acquired disorder), paranoia (*Verrücktheit*) was classified as a constitutional mental disturbance (i.e., due to a pathological predisposition).

These were remarkable changes in the classification of psychiatric disorders. Kraepelin made bold claims about distinct disease mechanisms and etiology, especially his speculation about autointoxication and the separation of dementia praecox from paranoia. He now needed to find more evidence from clinical studies to support his new nosologic vision.

Sixth edition

Kraepelin published the sixth edition in 1899, just three years after the previous one. The textbook had grown in size and was now published in two volumes. The nosological chapter was largely unchanged. But Kraepelin revised his classification scheme.

First, he abandoned the etiological dichotomy of acquired and predisposed disorders from the fifth edition. Second, metabolic disorders were split into thyroid conditions and his mature concept of dementia praecox, which now included hebephrenic, catatonic and paranoid subtypes. With this split, he acknowledged more clearly the different forms of autointoxication.

Third, Kraepelin introduced manic-depressive insanity. Together with paranoia (*Verrücktheit*), he defined the new disorder as "an insanity where, in its formation, more and more, a pathological predisposition comes to the fore"[11, p.7].

The sixth edition is of crucial importance for our understanding of the diagnoses of dementia praecox and manic-depressive insanity, but it did not introduce any new general principles to his nosology.

Seventh edition

Kraepelin wrote the *Foreword* to the seventh edition while still in Heidelberg. However, when the two volumes were published, in 1903 and 1904, he was already the new chair of psychiatry in Munich.

The nosological chapter grew from 9 to 12 pages, but did not change substantially. The added new text included an important clarification: "In the course of the same disease process, it was obvious that completely divergent phenomena followed each other, even seeming to indicate the complete opposite. From this arose the clearly recognized necessity, especially by Kahlbaum, to distinguish between temporary clinical pictures and disease forms. A scientific diagnosis can never be content with the determination of a clinical picture, but instead has to shed light on the disease process belonging to a picture"[13, p.4].

Kraepelin inherited the concept of disease form (*Krankheitsform*) from K. Kahlbaum (1828-1899) and E. Hecker (1843-1909), the latter of whom wrote in 1871: "There is an urgent need in psychiatry for a new nomenclature, which allows differentiation between the manifestations and the true clinical disease forms"[42].

What Kraepelin started in the fifth edition had now matured into such a new psychiatric nosology. With his longitudinal observations of large patient samples, he was convinced that he had established true disease forms. The psychiatric researcher could now go beyond a purely descriptive classification and establish a framework for the scientific exploration of psychiatric disorders. Kraepelin built on this in the last edition of his textbook, and used the momentum to build the first research institute devoted to psychiatric disorders.

PHASE 3: EDITION 8

Eighth edition

The eighth and final full edition of the textbook was published in four volumes, between 1909 and 1915. Kraepelin finished writing the last volume in October 1914, three months into World War I[30].

This edition included a wealth of new data (tables, figures, microphotographs of histological specimens) and extensive citations of other researchers. As a result, the nosology was more complex. For example, dementia praecox grew from three to eleven subtypes, as a result of which the dementia praecox chapter grew from 107 to 354 pages. Furthermore, a late-onset subtype was carved out as a novel diagnostic category and given a new name: paraphrenia.

Similarly, the nosological chapter grew from 12 to 19 pages. The ambitious paragraph from the second edition was largely unchanged, but now covered all psychiatric disorders: "If we achieve the goal we have in mind, the recognition of the actual disease processes by means of our clinical descriptions, then the different delineation efforts, whether they occur from a pathological-anatomical, etiological or a purely clinical standpoint, have to finally coincide with each other. I view this requirement as the keystone for the scientific research of mental disturbances"[15, p.14].

It was this unbridled enthusiasm for scientific progress that allowed him to raise considerable funds, in the throes of World War I, for the German Psychiatric Research Institute, which opened in April 1918 and later became the Max Planck Institute of Psychiatry[43-45].

We view the eighth edition as the start of a third, humbler phase of Kraepelin's nosology. As he was approaching retirement in the early 1920s, he published a thoughtful critique of his own classification scheme, questioning the dichotomy of dementia praecox and manic-depressive insanity[46]. But he never changed his mind about the task of psychiatric nosology and the way to make progress in psychiatric research[47].

PRINCIPLES OF KRAEPELIN'S NOSOLOGY

We propose that Kraepelin's nosology evolved over thirty years, from the first (1883) to the eighth (1915) edition of his textbook.

His nosology began with the thesis that psychiatry, like other sciences, deals with natural phenomena. Scientific naturalism is the first principle of his nosology.

At the same time, Kraepelin did not believe that mental states can be reduced to neural states. But he was confident that the proper scientific methods will, in the end, reveal how nature creates abnormal mental states and behaviors. His strong belief in scientific progress is the second principle of his nosology.

Kraepelin was initially undecided about the best approach to make progress in psychiatry. But, after years of longitudinal studies, he concluded that clinical course and outcome were the most important validators in our search for the yet unknown natural disease units. His hierarchy of validators is the third principle of his nosology.

In Table 2 we provide a synopsis of his mature nosology (taken from the eighth edition of his textbook). Table 3 contains a glossary of his main nosological terms. Below we briefly review his three nosological principles.

Scientific naturalism

Psychiatric disorders are natural kinds. They can be validated with the methods of natural science. In the end, all validators will converge on natural disease units. This principle – the first and most important one - attracted many critics[37,48].

A. Hoche (1865-1943), Kraepelin's main academic adversary in the early 20th century, rejected natural disease units and argued that there are only symptom complexes: "We are barking up the wrong tree with this unremitting search for definitive, pure syndromes of a physical kind"[49, p.341].

A. Meyer (1866-1950), who communicated many of Kraepelin's ideas to his American colleagues, remained critical: "Kraepelin bends the facts of psychiatric observation to the concept of disease processes"[50, p.274].

More recently, Weber and Engstrom examined Kraepelin's *Zählkarten* (diagnostic cards) and criticized his "positivist clinical research agenda": "Condensing patient reports was already an interpretative process – a cognitive discrimination and scientific assessment impossible without preconceived categories which Kraepelin had acquired outside, before, or perhaps despite his clinical observations"[51, p.379].

Many contemporary critics of Kraepelin have focused on scientific naturalism as an indefensible philosophical position[35,40,52]. In contrast, the psychiatrist-turned-philosopher K. Jaspers (1883-1969) viewed Kraepelin's principle more favorably[53,54]: "The idea of the disease-entity is in truth an idea in Kant's sense of the word: the concept of an objective which one cannot reach since it is unending; but all the same it indicates the path for fruitful research and supplies a *valid* point of orientation for particular empirical investigations"[54] (italics added).

The view that natural disease units have heuristic value is relevant for Kraepelin's next nosological principle, his unshakeable trust that psychiatry will make progress.

Scientific progress

Kraepelin finished the introduction to the fifth edition of his textbook on an optimistic note: "Psychiatry is a young, still developing science, that must, against sharp opposition, gradually achieve the position it deserves according to its scientific and practical importance. There is no doubt that it will achieve this position – for it has at its disposal the same weapons which have served the other branches of medicine so well: clinical observation, the microscope and experimentation"[9, pp.10-11].

He kept the paragraph in all subsequent editions. Where did Kraepelin see the "sharp opposition" against psychiatry? In his 1918 monograph *One Hundred Years of Psychiatry*[55], he described how empirical research had overcome unscientific views of the human mind.

But Kraepelin was acutely aware that the scientific understanding of psychiatric conditions was uneven. For some clinical presentations there was a clear cause, e.g., an exogenous agent. For many other clinical syndromes, however, disease mechanism and etiology were unknown. Kraepelin viewed advances in scientific methods as the primary drivers of progress. For example, he cited the histological stains by Nissl and Weigert[55, p.86]

Table 2 Synopsis of Kraepelin's nosology (quotes from the 8th edition of his textbook)

"The task of psychiatric nosology is the delineation of individual *disorders* (*Krankheitsformen*) and their grouping according to unified viewpoints. The completion of the first task occurred previously almost exclusively according to the most prominent illness phenomena."[15, p.1]
"Only the purposeful distinction between *clinical pictures* (*Zustandsbilder*) and disorders has made an adequate nosology possible. A diagnosis currently means the recognition of the underlying *disease process (Krankheitsvorgang)* of a particular type in the given clinical picture."[15, p.1]
"We can only view a *disease concept* (*Krankheitsbegriff*) as final and clearly delineated once we are precisely informed about the causes, the phenomena, the course and outcome of the affliction, finally, also about the peculiar anatomical changes."[15, p.2]
"The careful splitting of the forms into their smallest and seemingly insignificant variations… is thus the indispensable precursor for the obtainment of truly uniform *disease pictures which correspond to nature* (*der Natur entsprechende Krankheitsbilder*). Analysis is followed by synthesis… Only observation of the further course will clarify which of the numerous small deviations in the illness phenomena have a close relationship to the nature of the disease process, and based on this permit a recognition of its peculiarity."[15, p.11]
"The method of conducting experiments – in the border region between two illnesses – with diagnostic features, until predictions have achieved the greatest possible degree of reliability, delivers practically useful disease concepts, of which we can assume that they are as close as possible to *natural disease processes* (*natürliche Krankheitsvorgänge*)."[15, p.13]

Table 3 Glossary of Kraepelin's main nosological terms

Nominalist terms
***Disorder (Krankheitsform)*:** The basic unit of psychiatric nosology.
***Clinical picture (Zustandsbild)*:** The cross-sectional description of psychopathology.
***Disease concept (Krankheitsbegriff)*:** Initially a nominalist definition of a psychiatric disorder. When final, it links causes with all clinical phenomena and explains course and outcome.
***Disease process (Krankheitsvorgang)*:** The evolution of clinical pictures over time. Only longitudinal observations can reveal this active process.

Realist terms
***Disease picture which corresponds to nature (der Natur entsprechendes Krankheitsbild)*:** A nosological entity that represents nature.
***Natural disease process (natürlicher Krankheitsvorgang)*:** A process occurring in nature, giving rise to clinical phenomena.

Kraepelin blends nominalist with realist views. The nominalist terms are descriptive and preliminary: they allow us to assign a diagnostic label. The realist terms capture what nature has revealed to us. For Kraepelin, psychiatric nosology progresses, through conjecture and refutation, from constructivism to realism. Kraepelin was not always consistent in the use of his terms[48].

and the serological test by Wasserman[55, p.90] for their impact on revealing new disease mechanisms.

His pragmatic approach to classification included the recognition that mental states cannot be reduced to neural states. In fact, Kraepelin embraced the psychophysical parallelism of his mentor W. Wundt[56] in the Compendium: "Only with the close connection of brain pathology and 'psycho-pathology', it is possible to discern the laws of the interrelationship between physical and mental disturbances and thus advance to a true, deeper understanding of the phenomena of insanity"[5, p.3].

The juxtaposition of scientific naturalism and psychophysical parallelism in Kraepelin's nosology has puzzled many, including W. de Boor in his 1954 review of psychiatric nosologies: "It is astonishing to see how Kraepelin put the need for a dualistic methodology with regard to the somatological and psychopathological side of psychiatry programmatically at the beginning of his work, in order to largely neglect this principle in its nosology"[57, p.20].

As Kraepelin developed his nosology, he recognized that psychiatric disorders are not created equal. As a consequence, he had to determine the method best suited to reveal the etiology and disease mechanism of each psychiatric disorder.

Hierarchy of validators

During Kraepelin's time, some psychiatric disorders had already been validated with biological measures. The neuropsychiatric syndrome in the end stage of syphilis, known as dementia paralytica or general paresis, may serve as the most compelling example[58].

But, for the majority of psychiatric disorders, biological validation was not available to Kraepelin – and is still lacking today[59]. Kraepelin disagreed with T. Meynert (1833-1892), the prominent anatomist and inaugural chair of psychiatry in Vienna, and his student C. Wernicke (1848-1905), that neuroanatomy is the premier method in psychiatry: "The statement by Wernicke that all mental disorders with anatomical findings have approximately the same underlying disease process, can be refuted due to the advances of science"[15, p.3].

Following Kahlbaum[60], Kraepelin established disease course and outcome as the primary validators for psychiatric disorders. But it was not until the fifth edition of his textbook, after he and his assistants had collected longitudinal data in Heidelberg, that Kraepelin declared his hierarchy of validators. Once he had established it, he embraced prediction (of course and outcome) as the most important task of the psychiatrist. This hierarchy of validators might be Kraepelin's most impactful contribution to psychiatric nosology[61,62].

CONCLUSIONS

The principles of Kraepelin's nosology are still relevant today[39]. But we have not been able to hold them together in the way Kraepelin did.

On the one hand, current diagnostic systems (such as the DSM[63] and ICD[64]) have implemented a simpler, nominalist view of mental illness[65]. In such nosologies we diagnose *disorder*, rather than *disease*, which suffices for clinical and forensic practice[66]. *Disorder* avoids premature assumptions about etiology and, by doing so, may reduce stigma and bias[67]. Psychiatric diagnoses also serve many functions in society, only some of which are scientific[68,69].

On the other hand, psychiatric research favors a realist view: causal models of disease allow for stronger hypothesis testing[70]. Accordingly, research communities have established hierarchies of validators that fit their research methods and inference testing[62,71].

The DSM-5 Scientific Review Committee embraced a hierarchy of validators to guide the revision process[72]. But psychiatric clinicians and researchers assess validators differently and often speak a different language[73,74]. As a result, the training of psychiatrists has lost its footing[75]. This is different from the start of the 20th century, when Kraepelin's nosology promised progress in the education of both clinicians and researchers[76,77]. We are still searching for the best avenue to make progress in the nosology of psychiatric disorders[71].

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Rethinking the concept of insight

The psychiatric concept of insight involves recognition that one has a mental illness, that unusual mental events are pathological, and that treatment is needed. This concept has informed both research and clinical practice in several respects[1]. However, recent alternative perspectives on insight are emerging. These perspectives are rooted in the knowledge of people experiencing madness and extreme distress, referred to here as survivors.

Survivors have a long history of formally and informally coming together to share experiential knowledge. This includes through friendships, often formed in shared psychiatric spaces and more recently online social media spaces, inpatient and community-based service user groups, and global consumer movements. The Survivors History Group (studymore.org.uk/MPU.HTM) describes some of these initiatives. At the end of the 20th century, this sharing of experiential knowledge began to be formalized through survivor research.

Survivor research can be understood as the methodical and disciplined exploration of phenomena important to survivors, based on shared experiences and perspectives, leading to new collective and transferable knowledge. Survivor researchers are located inside and outside of academia, including in grassroots organizations, and in countries across the globe.

The overlapping field of Mad Studies has emerged in the last decade. Mad Studies is a fluid discipline that can broadly be understood as psychiatric survivors and their allies, such as critical practitioners, activists and academics, exploring and generating knowledge that is critical of current psychiatric practice and systems[2].

The emergence of survivor research and Mad Studies is creating new opportunities for survivors and others to explore experiential knowledge of madness, distress and extreme and unusual experiences.

Consistent with standpoint epistemology, both survivor research and Mad Studies entail privileging direct personal experience of phenomena, exploring the intersections and departures at broader levels, developing collective empirical and theoretical knowledge and, potentially, generating new understandings of concepts like insight.

In a recent Mad Studies publication, B. Filson described the consequences for personal meaning-making of being deemed to lack insight[3]: "I knew that what I was experiencing made sense, given what had taken place in my life. Even then I understood my reactions as sane responses to an insane world. I was told 'Whatever else might be going on with you is not relevant – it's your mental illness that matters'. This drove me into a frenzy, for now help was just another perpetrator saying 'You liked it, you know you did; that wasn't so bad; it's for your own good'. I was diagnosed and described as 'lacking insight' – ensuring that I would never be able to legitimately represent myself or my own experiences."

As Filson describes, being labelled as lacking insight can prevent credible self-representation and frustrate people's exploration and understanding of their own stories. Whatever a practitioner's motivations, and whatever the external unintelligibility of a person's experiences, claims to epistemic authority silence those who have "stories to tell"[3].

This makes the concept of insight a core site of epistemic struggle. Epistemic injustice – discrimination against and exclusion of particular forms of knowers and knowledge – is widespread in mental health, in part because of the notion that psychiatric illness is defined by lacking insight. However, when experiential knowledge is privileged rather than disqualified, alternative and legitimate ways of conceptualizing insight emerge.

These alternatives begin with people as the owners of their own narratives, with the right to construct personal meaning and explanatory frameworks, alone and collectively. The Hearing Voices Movement, for instance, understands voice hearers as having ownership of their voices and their interpretation, with support given to explore personal meaning-making through spiritual, cultural, trauma or other broad frameworks[4].

From this perspective, insight is not an absence/presence or even a continuum, but an evolving and ongoing process of meaning-making, which may shift over time. This meaning-making process is culturally bound, in the same way that the clinical conceptualization of insight is culturally embedded[5].

When narrative insight – defined as developing a meaningful and useful narrative about one's experiences within cultural contexts[6] – conflicts with the clinical construct of insight, institutional processes relating to the power to define experience become activated. Authoritative claims that others lack insight then become used to justify coercion and compulsion, in contravention of the human right to self-determination and narrative ownership.

One implication of this critique is that clinical practice frameworks are needed that support personal meaning-making: "The behaviours and thoughts that experts in some cultures label psychotic or schizophrenic are usually understandable reactions to our life events and circumstances. So rather than ask 'What is wrong with you?' and 'What shall we call it?', it is more sensible, and useful, to ask 'What happened to you?' and 'What do you need?'"[7].

This indicates the need for trauma-informed approaches to be widely used in mental health systems. These approaches are based on the potential for trauma to be causal in a person's current experiences, and consequently emphasize the need to create safety and to prevent harm and re-traumatization arising from service responses to distress.

One way of achieving this is to respond to people's extreme experiences – which are often terrifying and debilitating – through listening and exploring, rather than denying their basis in reality. Having the support to situate unusual and frightening beliefs and experiences in one's personal narrative is a foundation for post-traumatic growth and recovery[4]. This does not involve abandoning clinical expertise, but rather requires a balanced respect for

practice wisdom[8] and for experiential knowledge.

A second implication is that clinical explanatory frameworks are not universal. Alternative explanatory frameworks exist, and it is simply not possible to know whether it is ultimately more beneficial to a person to frame his/her experience as, for example, a spiritual crisis, a trauma-related response, or an illness relapse. This is challenging, since some people experiencing mental health-related crisis actively want "psychiatric rescue", i.e. an authoritative institutionalized response which temporarily takes decisions on behalf of the person in order to restore stability.

However, the phenomenon of revolving door and the challenges of improving long-term outcomes in psychosis indicate the limits of any single explanatory framework. Therefore, any clinical explanation for experiences should be offered with tentativeness rather than authority, and clinicians might usefully sign-post service users towards alternative perspectives, such as Alternatives To Suicide, Hearing Voices Network, Mad Pride, positive psychotherapy for psychosis, post-traumatic growth, spiritual emergence, and trauma-informed approaches.

More challengingly, a focus on the experience of social exclusion may generate momentum away from individual-level explanations of experience and towards activities to generate collective action to improve mental health and social care system compliance with human rights legislation[9]. Modesty in clinical knowledge claims is empirically justified.

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An update on Individual Placement and Support

Disability experts and public officials in countries around the world now acknowledge that people with chronic health conditions and disabilities, including serious mental illnesses, have a right to participate fully in community life, including regular employment. Employment is not only a determinant of health and well-being, including mental health[1], but also an antidote to social exclusion[2].

Individual Placement and Support (IPS) has become the standard of supported employment for people with serious mental illness, such as schizophrenia and bipolar disorder. It incorporates eight core principles that have been well researched with a validated fidelity scale used worldwide for quality improvement purposes[3].

These principles are: a) focus on the goal of competitive employment (agencies providing IPS are committed to regular jobs in the community as an attainable goal for clients seeking employment); b) zero exclusion (every client who wants to work is eligible for services regardless of "readiness", work experience, symptoms, or any other issue); c) attention to clients' preferences (services align with clients' choices, rather than practitioners' expertise or judgments; IPS specialists help clients find jobs that fit their preferences and skills); d) rapid job search (IPS programs help a client look for jobs soon after he/she expresses interest in working, rather than providing lengthy pre-employment assessment, training and counseling); e) targeted job development (based on clients' interests, IPS specialists build relationships with employers through repeated contact, learning about the business needs of employers, and introducing employers to qualified job seekers); f) integration of employment services with mental health treatment (IPS programs closely integrate with mental health treatment teams); g) personalized benefits counseling (IPS specialists help clients obtain personalized, understandable and accurate information about how working may impact their disability insurance and other government entitlements); h) individualized long-term support (follow-along supports, tailored for the individual, continue for as long as the client wants and needs them to keep a job or advance career opportunities).

Evidence for the effectiveness of IPS continues to grow, starting with early studies in the US in the 1990s and 2000s and extending to replication studies throughout Europe, Canada, Australia, Hong Kong and Japan. IPS is the most extensively and rigorously researched of all employment models and the only evidence-based employment model for people with serious mental illness.

In 28 randomized controlled trials assessing the effectiveness of IPS for people with serious mental illness, all but one in mainland China found competitive employment outcomes significantly favoring IPS. Across the 28 studies (N=6,468), 55% of IPS participants achieved competitive employment, compared to 25% of control participants receiving other vocational services (https://ipsworks.org/index.php/evidence-for-ips/).

Over the last decade, a number of systematic reviews and meta-analyses have confirmed this basic finding[4,5]. One meta-analysis reported moderate to large effects favoring IPS for a range of other employment outcomes[5]. Another meta-analysis found that, compared to control participants, IPS participants gained employment faster, maintained employment four times longer during follow-up, earned three times the amount from employment, and were three times as likely to work 20 hours or more per week (https://ipsworks.org/index.php/evidence-for-ips/).

Long-term studies show that half of all clients enrolled in IPS become steady workers, maintaining employment for 10 years or

longer. A recent follow-up study of a large, multisite trial found that significantly higher earnings for IPS clients compared to controls persisted over a five-year period after the two-year intervention[6]. Cost-effectiveness analyses of randomized controlled trials of IPS have generally found the aggregated costs of vocational and mental health services to be no higher, and sometimes significantly lower, for IPS than for standard services[2].

IPS has expanded steadily, spreading to new clinical populations and more mental health settings in the US and worldwide. Recent randomized controlled trials of IPS include six trials for people with common mental disorders, two for people with substance use disorders, and one for veterans with spinal cord injuries. Eight of these nine studies showed employment outcomes significantly favoring IPS[7].

Several large-scale IPS trials in other populations are in progress, including three for people with substance use disorders: Project BEES in the US, the IPS-AD study in the UK, and a similar study in Norway. Several small randomized controlled trials of IPS for people with criminal justice involvement have been completed, with a large-scale US trial, the Next Gen study, to start soon. Following pilot work, large IPS trials are planned or underway for people with autism spectrum disorder, borderline personality disorder, and chronic pain.

IPS also helps young adults negotiate the pathway to meaningful adult roles in employment and education, e.g., as a standard component of early intervention programs for clients with a first episode of psychosis. Other subgroups of the young adult population also appear to benefit from IPS (https://ipsworks.org/index.php/evidence-for-ips/).

The effectiveness of IPS has been well established since at least the turn of the century. The key question for IPS, as for other evidence-based psychosocial practices, is how to close the gap between the known population of those who want and need these evidence-based services and those who have access. In the US, approximately 60% of people with serious mental illness want to work, but less than 2% have access to IPS. The primary barriers have been inadequate funding and the lack of methodology for large-scale expansion[2].

While adequate financing remains elusive worldwide, some governments have made national commitments to fund IPS access[8]. The second ingredient is a mechanism to facilitate adoption, high-fidelity implementation, growth and sustainment of IPS. Since 2002, our group has led an international learning community that coordinates education, training, technical assistance, fidelity and outcome monitoring, and regular communications through newsletters, bimonthly calls, and an annual meeting[9].

The learning community has continuously reported employment rates for participating IPS programs in the US every three months for 18 years. During this time, the overall quarterly employment rate has not dipped below 40%, even during the Great Recession. The learning community helps programs sustain IPS services over time: in one prospective study, 96% of 129 IPS programs were sustained over two years. Participation has expanded steadily, with a mean annual growth rate of 26% in the number of IPS programs in the US. The learning community helps to maintain over 450 IPS programs, including 366 in the US and 100 outside the US, most at high fidelity with good employment outcomes.

Rapid expansion of IPS across the world[8] includes at least 19 high-income countries outside the US over the past 20 years (Australia, Belgium, Canada, China, Czech Republic, Denmark, France, Germany, Iceland, Ireland, Italy, Japan, New Zealand, the Netherlands, Norway, Spain, Sweden, Switzerland, and the UK). The flexibility and adaptability of the IPS model facilitate successful adoption with high fidelity and good employment outcomes in countries with diverse sociocultural conditions, labor laws, welfare systems, and economic conditions[4].

The steady growth of programs, sustainment of services, and expansion to new populations makes IPS a unique evidence-based practice. We attribute success to client interest, continuous research-based improvements, and a vibrant learning community.

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Delivering on the public health promise of the psychosis risk paradigm

The clinical high-risk (CHR) paradigm was developed in the 1990s as a framework for early detection and prevention of psychotic disorders[1]. Now, after about 25 years of experience, it seems opportune to reconsider the goals of the paradigm in relation to its aspired impacts on public health. In particular, it is reasonable to question whether the focus on conversion to a fully psychotic form of illness as the singular endpoint of interest is well-placed.

Although many *research* goals have been advanced using this endpoint, including the development and validation of individualized risk calculators[2] and the identification of neural mechanisms associated with the onset of psychosis[3], the *clinical* impacts of these advances are at present limited.

The difficulty translating findings on predictors and mechanisms of onset of psychosis into practice is due in part to the intrinsic uncertainties of attempting to prevent a future diagnostic outcome. Such uncertainties include whether widespread application of CHR criteria could ascertain all or most first-episode cases prior to onset, and ambiguity concerning the length of follow-up required to demonstrate prevention.

At the same time, it has become increasingly apparent that the CHR syndrome is itself associated with significant burdens in terms of symptom severity and functional impairments, independently of its role as a predictor of risk for onset of psychosis. Therefore, our public health interests may be better served by developing and testing interventions targeting remission of the CHR syndrome as a primary endpoint.

Doing so first requires recognition of CHR status as a psychiatric condition in its own right and making its diagnosis a routine matter in community mental health settings. In the nosological tradition of our field, diagnostic constructs are based on constellations of co-occurring symptoms that are distressing and interfere with social and occupational functioning. The individuals meeting CHR criteria who have been recruited into observational research studies and clinical trials are distressed and seeking treatment[4]. Although by definition their positive symptoms (i.e., delusions, hallucinations, thought disorder) are of sub-psychotic intensity, these symptoms are nevertheless disruptive and rate-limiting for social and role functioning[5], on average at about the level associated with major depressive disorder with comorbid alcohol abuse[6].

Criteria are in fact available in the Section III of the DSM-5 to diagnose a condition – attenuated psychosis syndrome (APS) – that is based on the CHR syndrome defined in the Structured Interview for Prodromal Risk Syndromes (SIPS)[7] and the Comprehensive Assessment of At-Risk Mental States (CAARMS)[8].

These two interviews have been extensively used in research settings, where they can be implemented with high reliability among trained diagnosticians. However, the training programs needed to become proficient in their use are somewhat demanding (typically requiring 2+ days of in-person training), and the instruments themselves take quite a bit of time (typically, 1.5 to 3 hours) to administer, primarily because they include ratings for many symptoms that are not actually used in the clinical diagnosis of APS. These features create too large a burden for the SIPS or CAARMS to serve as "front-line" vehicles for the clinical diagnosis of APS in the community. Thus, there is an urgent need to develop a significantly streamlined interview and training module for APS diagnosis that could be feasibly and reliably implemented in community mental health sites around the world.

Assuming we can reach agreement on APS as a diagnostic construct and make its reliable diagnosis a matter of routine, developing and testing interventions that can bring about its remission is the next major challenge. Currently available treatments may be helpful in this regard for part of the APS population. In about 30% of such individuals enrolled in observational studies and receiving usual and customary treatment, positive symptoms decline to below-prodromal intensity during the 12 to 24-month follow-up intervals typical of these studies[9]. While this percentage no doubt includes some who remit spontaneously (some of whom may have been "false positives" from a psychosis risk perspective), the fact that "usual and customary" treatments tend to be crisis-oriented and non-specific suggests that there may be room for improvement with more intensive therapeutic approaches that include a focus on the development of thinking and social skills.

It would be useful for data from randomized clinical trials involving APS cases to be re-analyzed using remission (on symptomatic and/or functional grounds) as the endpoint of interest. Any indication that targeted interventions increase remission rates over and above those achieved during a waiting period or with usual and customary treatment would be a useful initial signal that could be pursued in future treatment trials.

That only about 30% of APS cases remit with usual and customary treatment also means that 70% of these individuals have outcomes that imply a continuity or worsening of symptoms, distress, and functional impairment (such as maintenance of APS or conversion to a psychotic disorder). Together, these features seem consonant with the requirements of a diagnostic construct and imply the need for more intensive and targeted treatment.

Paradoxically, a corollary benefit of re-focusing on remission of APS as a primary endpoint may in fact be a reduction in psychosis risk in the population. Given that the APS criteria are a potent predictor of psychosis, risk is much lower among the population that does not meet these criteria. Though it is not known precisely what the risk is among those cases who previously met the criteria and then remitted – this issue needs to be systematically evaluated – the risk is much lower than among those who currently meet APS criteria. It follows that treatments that cause remission of APS would also likely result in a delay or reduction in risk for progression to full psychosis.

The CHR paradigm continues to be a useful approach for studying mechanisms associated with psychosis onset. As such, observational studies will no doubt continue to focus on conversion to a fully psychotic form of mental illness as a key outcome. Nevertheless, recognizing APS as a diagnostic construct in its own right, and focusing on its remission as a primary endpoint in intervention studies, would more readily facilitate translation of findings emanating from this approach into clinical practice, and thereby help address the unmet health needs of a vulnerable population.

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Alcohol and the developing adolescent brain

Despite cannabis, vaping and opioid use garnering significant media attention recently, alcohol is still, by far, the most commonly used substance worldwide[1]. Alcohol use is related to significant health, economic and social burden, and accounts for 5.3% of all deaths in the world every year. It contributes to over 200 medical conditions and is responsible for 5.1% of the global burden of disease and injury[1]. Excessive alcohol use is a pervasive international public health problem that deserves greater attention.

Historically, alcohol use research focused almost solely on adults. A large portion of research in the US was funded in Veterans hospitals, and therefore findings were predominately applicable to older white males. However, over the past two decades, there has been a greater appreciation that alcohol use disorders affect all people, regardless of age, sex, race or ethnicity.

Alcohol use is typically initiated during adolescence, with worldwide estimates indicating that 27% of youth aged 15 to 19 years drank alcohol in the past month[1]. Earlier use of alcohol can have significant implications for problematic use in the future. For example, youth who began drinking before age 15 are four times more likely to develop an alcohol use disorder than youth who do not start drinking until age 21. The odds of subsequently developing problems with alcohol are reduced by 14% with each increasing year of age at first use[2]. These findings are important for prevention programming and encouraging youth to delay their age of first use, a more realistic goal than abstinence-only approaches that have been consistently ineffective[3].

The manner and pattern in which youth use alcohol can differ greatly from adults. Youth tend to drink less frequently than adults, but when they do drink, they tend to drink in much higher quantities, typically in what is referred to as binge drinking episodes (i.e., having 4+ drinks on an occasion for females, and 5+ for males)[4].

The high rates of teen drinking, and binge drinking in particular, are concerning because adolescence is a period of significant neural, social, emotional and cognitive development. While teens may physically look like adults, their brains do not typically reach adult-level maturation until around age 25[5]. Therefore, any disturbances to brain development during this critical growth period could have long-lasting effects.

In the early 2000s, several studies suggested that there was a relationship between alcohol use and brain development. However, due to the cross-sectional nature of these studies, the direction of the relationship was not clear. In the past decade, prospective longitudinal studies have tried to answer the "chicken or egg" question: were the neural abnormalities seen in adolescent heavy drinkers a pre-existing risk factor for initiation of alcohol use, a consequence of heavy drinking, or both?

As it would be highly unethical to randomize youth into "drinking" and "non-drinking" groups, the original studies examining this question were observational[6]. At baseline, only non-drinking youth were enrolled, allowing for assessment of pre-alcohol use cognitive and neural functioning. Naturally, over time, some youth initiated alcohol use, while others remained non-users through adolescence and into young adulthood.

Findings from these studies suggest that it is both the chicken *and* the egg: there are neural and cognitive features that predict who initiates heavy alcohol use during adolescence, and subsequently heavy alcohol use interferes with normal neural developmental trajectories[7].

Specifically, poorer performance on inhibition and working memory tests, smaller gray and white matter brain volume, and altered brain activation during tasks of inhibition, working memory, and reward processing have been related to greater initiation of alcohol use during adolescence.

Once heavy alcohol use is initiated, there are ensuing aberrations in normal development, including poorer inhibition and decision making, atypical maturation of both gray and white matter, and greater brain activation during cognitive tasks, despite equal performance (suggesting that the brains of youth who are drinking have to "work harder" to keep up)[7].

Of course, alcohol is not the only substance that youth typically initiate during adolescence, or the only issue that arises during this developmental period. Larger, multisite studies are currently underway and will help disentangle the complicated picture of concurrent substance use, and the interactive nature of psychopathology, demographics, health habits, and genetic vulnerabilities. These projects include the US Adolescent Brain Cognitive Development (ABCD) and the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA), as well as the European IMAGEN Consortium. Findings from these investigations will help identify a clearer picture of how alcohol affects neural development.

While these studies will help us learn more about the way alcohol and other substance use affects the developing brain, it is critical that we, as clinicians, utilize this information to inform prevention and treatment of adolescent substance use disorders. Knowing the risk factors for future problematic use can shape educational prevention efforts, while understanding the mechanisms of substance use will improve youth treatment.

This is important, as more effective treatments are desperately needed. Only 6% of adolescents and 8% of young adults who meet criteria for a substance use disorder receive treatment[4]. The current gold standard for adolescent substance use treatment is psychosocial intervention or "talk therapy" (e.g., cognitive behavioral therapy, motivational interviewing, and family therapy)[8]. However, these treatments are only modestly effective, with one-third to one-half of youth returning to substance use within 12 months following treatment.

Utilizing the past two decades of data from the neuroscience field about the effect of substance use on brain development could allow for focused creation of alternative and more efficacious approaches. Neuroscience-informed medications and cognitive interventions that can counter the effects that alco-

hol has had on the brain may enhance the effectiveness of our current treatment options. New techniques to prevent and treat adolescent substance use disorder are necessary to alleviate the extensive public health burden related to this problem at the international level.

In sum, it is clear that alcohol use interferes with cognitive and neural development during adolescence. Early intervention has the potential to prevent substance use escalation and reduce the chronic psychological and physical health problems associated with substance use disorders in adulthood. Our technology has improved significantly over the past two decades and has allowed us to better understand the impact of alcohol use on the developing brain. Translating this information into better prevention and treatment techniques is key in moving the field forward.

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Dr. Strangelove, or how we learned to stop worrying and love uncertainty

"We demand rigidly defined areas of doubt and uncertainty!"[1]

If the 1980s and 1990s are commemorated, in the short history of psychiatry, for the revolution in the taxonomy of mental illness, the last decade will be remembered for the struggles with the by-product we have created over this reform: diagnostic silos as the organizing principle for mental health care[2].

After years of dominance of the psychoanalytical formulation, psychiatry embraced the medical model in the DSM-III. This was a necessary paradigm shift that achieved some of its goals to a large degree (e.g., increasing reliability, improving communication among clinicians and researchers, establishing the ground for empirical research), while failing to deliver some of its promises (e.g., validity and the discovery of the [biological] origins of mental illness).

Recent years have seen growing dissatisfaction with the DSM. Researchers have criticized its atheoretical and agnostic essence, with no reference to "brain-based" concepts or "psychological" constructs. Clinicians have complained about the lack of meaningful clinical utility for case management and treatment selection, with many observed clinical cases either falling under several diagnostic categories or not easily fitting into any. Patients and their families have objected to the "mechanic" operationalized reductionist procedure that ignores the individual. What once was a celebrated revolution has become the scapegoat – the culprit for all our failures, almost.

Do we have a real exit strategy from this Greek tragedy? The paradox is that we fail to generate new knowledge in a system that is irreplaceable without new knowledge. Given that research and clinical practice have different needs and priorities, several alternative frameworks have recently been proposed: the research-oriented, Research Domain Criteria (RDoC); the model-driven, network approach towards psychopathology; the all-purpose, Hierarchical Taxonomy of Psychopathology (HiTOP); and the utilitarian, transdiagnostic clinical staging. In this brief piece, we will follow a pragmatic approach and attempt to discuss how we can at least mitigate the issue of diagnostic silos in clinical practice by applying a few adjustments until we establish a better diagnostic system, ideally a pathoetiology-based taxonomy.

One shall tolerate uncertainty to embrace pluripotency. In contrast to the culture of science, where absolute confidence is considered a cardinal sin, the culture of medicine often fails to acknowledge uncertainty: (scientific) hypotheses vs. (practical) diagnoses[3]. Notwithstanding the deep-rooted uncertainty, psychiatry makes no exception. Early psychopathology consists of a pluripotent mixed bag of phenotypic expressions that follow diverse trajectories defying traditional diagnoses. However, psychiatry has constructed balkanized frameworks modeled after traditional diagnostic silos, such as the clinical high-risk concept[4,5]. More recently, the transdiagnostic clinical staging model has been introduced to capture heterogeneity in clinical and functional outcomes, in order to improve prediction and prevention of illness progression[6].

In comparison to the RDoC and the HiTOP, the transdiagnostic clinical staging model appears to be motivated by a pragmatic clinically-oriented mindset, and can therefore be easily and readily integrated to the current clinical practice and further applied in quality enhancement projects to iteratively test and improve practice at youth mental health services. However, there are important caveats to this model that require some further thinking.

First, it represents yet another categorization (in the temporal domain), the boundaries of which remain to be determined, with implicit referencing to etiological distinctiveness and clinical relevance, for which no more proof exists – or *a priori* should exist – than for traditional categorization. Second, importantly, the structure and the semantics instantly remind us of cancer. The staging system should allow for a bidirectional (up and down) shift between stages as opposed to the currently proposed progression (unidirectional) model. In this regard, the current staging model implies that mental suffering is devoid of plasticity. This is a strong assumption that is difficult to support by current scientific evidence. In addition, the transdiagnostic progression model would not be practical, given the fact that one-fourth of the population would ultimately end up reaching at least transdiagnostic stage 2, even though the use of the clinical staging system is being limited to the age group 12-25 years[7]. Also, many would agree that we should avoid associating mental disorders with cancer, which would add further negative connotations – imagine using the staging terminology to communicate with young patients and their families. Nevertheless, the staging system may at least help to a degree with overcoming diagnostic silos in practice.

One shall decrease quantity to increase utility. No current classification system has the claim for diagnostic categories as representatives of true distinct entities, yet diagnoses have been reified over time. Furthermore, the number of mental disorder categories has increased with each new edition of the DSM – so-called diagnostic inflation – even though accumulating evidence shows that mental disorders lack clear boundaries, with large phenotypic and pathoetiological overlap. It is questionable how often many of these categories are used in routine clinical practice. Broad umbrella spectrum disorder diagnoses, such as psychosis spectrum disorder, enriched with a transdiagnostic dimensional assessment of symptoms and functioning, may suffice[8].

One shall characterize to personalize. Psychiatry should embrace its limitations and uniqueness in medicine and return to the roots by putting the "person" at the center. The advent of the DSM has devalued clinical characterization and inadvertently reduced the case formulation into a standard operating procedure, easy yet insufficient. As discussed in a recent review[9], we should "pay more than lip service" to better clinical characterization,

that should go beyond a mere symptom checklist. Psychiatry, like other branches of medicine, is an art form that applies science in practice. The classical art of psychiatry has not been "cool" for a long time; the focus of the "clinical" psychiatry training curriculum should, nevertheless, be on psychiatric interview skills and clinical reasoning based on the characterization, until research delivers algorithms that can support or automate parts of the clinical reasoning.

One shall collaborate to alternate. Academic psychiatry should invite a wide range of stakeholders (e.g., patients, their families, carers, mental health practitioners, and policy makers) to actively take part in this process from the beginning, by identifying key issues and proposing solutions to meet the needs of our society.

Until convincing evidence is provided, the current classification system is unlikely to be superseded by the proposed alternatives for use in clinical practice. In the meantime, the above adjustments may help to overcome the issues arising from diagnostic silos in psychiatry.

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Managing dual disorders: a statement by the Informal Scientific Network, UN Commission on Narcotic Drugs

Since 2015, the United Nations Office on Drugs and Crime (UNODC) – World Health Organization (WHO) Informal Scientific Network has strived to bring the voice of science as it pertains to drug use disorder treatment and care, to inform critical discussions at the Commission on Narcotic Drugs, the policy-making body of the United Nations (UN) with prime responsibility for drug control matters. In recent years, the public health dimensions of the world drug problem, including prevention and treatment of drug use disorders, have become prominent in policy debates within the UN system[1].

Drug use disorders can have devastating consequences for affected individuals, their families and communities. They are associated with lost productivity, security challenges, crime, and myriad negative health and social consequences. Caring for and treating individuals with drug use disorders exacts a heavy toll on the public health networks of UN Member States. Availability of effective treatments for these disorders is very limited, and far from achieving the universal health coverage target set in the Sustainable Development Goals 2030.

This situation is further exacerbated by the frequent co-occurrence of drug use disorders with other mental health conditions (dual disorders)[2], a phenomenon associated with increases in emergency department admissions[3] and psychiatric hospitalizations[4], higher risk of relapse to drug use[5], and increased likelihood of premature deaths[6], including those resulting from suicide[7]. The individual, social and public health impact of dual disorders is very high, and a multidisciplinary and comprehensive response to the needs of persons with these disorders is required. Unfortunately, there are many gaps in the global system, which is ill prepared to meet this challenge.

Lack of attention is driven in part by lack of training of clinicians on how to diagnose and treat dual disorders, as well as by the structural differentiation and lack of coordination, in many countries, between programs to treat drug use disorders and those to treat mental illnesses. Other contributing factors include "diagnostic overshadowing"[8], whereby individuals suffering from a drug use disorder and a comorbid mental illness have their morbidity frequently attributed to the former, potentially neglecting the contribution from mental health (and somatic) conditions. Such neglect is partly due to the implicit bias and discrimination towards drug use disorders and the lack of familiarity of the provider with the condition that receives the attribution.

Another contributing factor is the "wrong door syndrome"[9], which connotes the difficulty not only for treating but also for diagnosing drug use disorders among mental and medical treatment services and vice versa. Furthermore, people with dual disorders are often excluded from studies on effectiveness of treatment interventions, which hampers the development of evidence-based recommendations for treatment of these patients.

The examples highlighted above are just some of the many systemic challenges that the Informal Scientific Network considered during its recent discussions to craft evidence-based guidance for national health systems interested in developing coordinated, multiple system-level interventions to address the unmet needs of people affected by dual disorders.

The following recommendations reflect the unanimous consensus reached by the Network membership during those discussions:

- Dual disorders must be addressed as an integral part of universal health coverage.
- Policy-makers should devise strategies to address the com-

mon biopsychosocial factors that are associated with the development of dual disorders.
- The high prevalence and related disability of dual disorders require active intervention from policy-makers at a systems level and active advocacy from health professionals.
- Service providers should be trained in the management of dual disorders and sufficient financial support should be granted for this purpose.
- Systematic screening for other mental disorders through validated instruments by trained health service providers is an essential component of adequate care for people with drug use disorders.
- Availability of and accessibility to adequate treatment should be provided, regardless of the entry point to care systems, in line with the principle of "no wrong door".
- Sex- and gender-based knowledge and a stigma-free approach are required in the effective management of dual disorders.
- Age-specific interventions are required across the lifespan, especially for minors and the elderly.
- Science-informed prevention interventions that address common risk factors, such as early life adversity, should be available to children living with parents and/or caregivers with dual disorders.
- Attention should also be given to other at-risk and vulnerable populations, in accordance with local needs.
- Access to services for dual disorders in the criminal justice system, particularly in prison settings, youth detention or correctional centres, should be secured.
- Collection and analysis of data to monitor the magnitude of the problem, the quality of care and the outcomes of policies and interventions should be encouraged.
- Implementation and scale up of effective and efficient interventions, with consideration of cultural and country specificities, is a priority.
- Finally, the Informal Scientific Network urges UN Member States to further support scientific research on new and enhanced interventions to effectively prevent and treat psychiatric comorbidities in people with drug use disorders.

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A 16-year follow-up of patients with serious mental illness and co-occurring substance use disorder

Individuals with serious mental illnesses, such as schizophrenia and bipolar disorder, experience high rates of co-occurring substance use disorders (approximately 41% across many studies)[1]. Patients with these co-occurring disorders are prone to a range of short-term adverse outcomes: relapses, hospitalizations, violence, homelessness, incarceration, family problems, suicide, and serious medical illnesses such as HIV and hepatitis C[2]. Despite these negative prognostic indicators, few studies have addressed the long-term course of patients with co-occurring disorders.

We previously reported on a cohort of such patients in New Hampshire who were followed prospectively for 10 years[3,4]. Our follow-up study showed that those who avoided early mortality tended to improve steadily over time, not only in terms of psychiatric symptoms and substance abuse, but also in functional areas such as independent living and employment. The present report extends the follow-up of the New Hampshire cohort to 16 years.

A grant from the Robert Wood Johnson Foundation facilitated implementation of integrated treatment services for patients with co-occurring disorders in New Hampshire in 1988. The integrated services included residential dual-diagnosis treatment, assertive community treatment teams, dual-diagnosis groups, illness management training, family psychoeducation, supported employment, and other evidence-based practices. A subsequent grant from the National Institute of Mental Health extended the follow-up of these patients prospectively for 16 years.

At baseline and yearly thereafter, our interviewers assessed 223 adults with co-occurring serious mental illness (schizophrenia spectrum or bipolar disorder) and substance use disorder (predominantly alcohol and cannabis) in New Hampshire, which is a rural Northeast state in the US. We used standardized measures, described elsewhere in detail[3], to assess diagnoses, psychiatric symptoms, substance abuse, independent living, competitive employment, social supports, and quality of life.

We defined dichotomous recovery outcomes as follows: a) psychiatric symptoms: no subscale of the Brief Psychiatric Rating Scale with an average score higher than 3; b) substance abuse: no use in the past month and pursuing long-term abstinence; c) independent living: residing independently and responsible for paying rent and making housing decisions; d) competitive employment: working in a regular job in an integrated setting and earning at least minimum wage, with a contract to the individual rather than to a social service agency; e) social support: regular contacts with friends who were not abusing substances; f) quality of life: expressing general satisfaction with one's life (>5 on the 7-point Quality of Life Inventory global satisfaction rating).

At baseline, the 223 patients were predominantly young (average age 34.4 years), male (74%), white (96%), and never married (61%). Diagnostically, 74% had schizophrenia spectrum disorders and 26% had bipolar disorder. The most common substances of abuse were alcohol, cannabis and cocaine. By the 16-year follow-up, 42 patients (19%) in the study group had died, 60 (27%) had been lost or dropped out, and 121 (54%) remained in the study. Thus, the 16-year follow-up on 121 patients included 54% of the original study group and 81% of the surviving patients. The attrition analysis showed that only older age predicted early mortality.

The proportion of patients in recovery on each of our six measures increased steadily and significantly over 16 years, including the interval between 10 and 16 years. For each outcome, the results (improvement reflected by time trend) from linear mixed-effects models were significant at $p<0.001$ (estimate = 0.014 for psychiatric symptoms; 0.037 for substance abuse; 0.018 for independent living; 0.009 for competitive employment; 0.017 for social support; and 0.012 for quality of life). The proportion of participants living independently increased from less than 40% in the first three years to more than 65% in the last three years, and the proportion in substance abuse recovery increased from less than 30% in the first three years to more than 65% in the last three years.

Thus, these patients with co-occurring serious mental illness and substance use disorders, despite having poor adjustment and numerous risk factors at baseline, tended to improve steadily and achieve multi-dimensional recovery outcomes over many years, as long as they did not succumb to early mortality. Recovery encompassed not just clinical domains, such as psychiatric symptoms and substance abuse, but also functional domains, such as independent living, social support, and employment. Quality of life also improved.

The most parsimonious interpretation of these findings is that the course of patients with co-occurring disorders who receive evidence-based treatments involves gradual but substantial improvements over many years. These patients often appear to be extremely impaired early in the course of co-occurring disorders, perhaps because the disorders exacerbate each other. For example, patients who are using street drugs often stop using antipsychotic medications, and psychosis often interferes with participation in substance abuse treatments. Both of these interactions increase the risks of negative outcomes. Nevertheless, these patients tend to recover over many years.

This interpretation accords with long-term studies of individuals with serious mental disorders, as documented by E. Bleuler[5] over 100 years ago and more recently by others[6]. Long-term studies of individuals with substance use disorders have also documented a trend toward recovery[7].

Several caveats deserve mention. Our New Hampshire cohort could have responded to unusually strong dual-disorder treatment services, which were widespread in the state due to a series of federal research projects and policy supports from local leaders. Beginning in the 1980s, effective treatments for patients with co-occurring disorders developed steadily[8]. The most effective interventions, such as residential treatment, peer groups, and assertive community treatment, were available in New Hampshire during this period. All these elements could limit the generalizability of the findings reported here.

Patients could also have benefitted from the relatively rural and benign environment of New Hampshire, although we found similar positive outcomes over several years in an urban dual-diagnosis study[9]. Differential attrition could have influenced the results, because more severely ill patients may have dropped out or died early, although this interpretation was not supported by our attrition analysis. In addition, specific drugs of abuse change over time: the current increased prevalence of methamphetamine and opioid abuse in the US may be producing greater rates of negative outcomes.

In summary, patients with serious mental illnesses (schizophrenia spectrum and bipolar disorders) and co-occurring substance use disorders (primarily alcohol and cannabis) are poorly adjusted and at high risk of negative outcomes in the short term. However, they tend to improve steadily over many years if they avoid early mortality. Participation in evidence-based integrated treatments for dual disorders is likely to contribute to recovery outcomes. These positive long-term outcomes should be a hopeful message for patients, families and clinicians, and an incentive to develop and implement integrated treatments for patients with co-occurring serious mental illness and substance use disorders.

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Hikikomori: a hidden mental health need following the COVID-19 pandemic

As lockdown measures ease in several countries, returning to a life with dramatically altered economic and social circumstances will pose significant mental health challenges[1]. Early population prevalence data from China suggest that the COVID-19 pandemic may induce a fivefold increase in problems such as anxiety and depression[2]. However, these estimates will miss people who remain socially withdrawn but undetected by services because a defining feature of their condition is the desire to become invisible from society. We already know something of the phenomenology and social costs of this problem through studies of the syndrome known as hikikomori[3,4].

Hikikomori is a Japanese term, comprised of the verb *hiki*, "to withdraw", and *komori*, which means "to be inside". It was first introduced in the 1990s to describe young people who displayed extreme and long-term social withdrawal and an eschewing of social conventions around obtaining an education and pursuing a career[3]. It is currently viewed as a sociocultural mental health phenomenon, rather than a typical mental illness, but population prevalence data indicate that it is a significant public health issue.

The Japanese Cabinet Office estimates the presence of more than 1.1 million people with hikikomori in Japan, and there is now increasing recognition of the hikikomori phenotype in a variety of other countries and cultures[4,5]. With this increased international recognition, there has been debate about the relationship of hikikomori to autism spectrum disorders, mood disorders, social anxiety and agoraphobia[4]. The core diagnostic feature, however, is that the affected person has physically isolated himself/herself at home for at least 6 months, cut off from meaningful social relationships, with significant functional impairment and distress[4].

While many people will gladly emerge from enforced lockdown, those at risk of hikikomori will choose not to re-engage with their pre-COVID-19 life. Data from across cultures show that the typical onset of hikikomori is in late adolescence and early adulthood, often following an experience of shame or socio-culturally relevant defeat events (e.g., failing key academic examinations, not achieving a cherished job role). Hikikomori people avoid re-traumatization by choosing to opt out of the normative pathway set out for them by society[3-5].

In the wake of the COVID-19 pandemic, many young people will confront dramatically altered goals and aspirations, and they will be highly vulnerable to impacts arising from precarious employment and economic vulnerability. Many Japanese Hikikomori cases are seen as a product of the economic downturns of the 1990s, that severely restricted employment opportunities. The widespread economic and social consequences of COVID-19 are likely to far exceed any shock to the prospects of young people seen for generations.

As we write, the UK has been in the state of lockdown for over three months. In non-pandemic circumstances, social withdrawal for three months would equate to the pre-hikikomori stage, halfway to the minimum of six months of extreme social isolation proposed for a full diagnosis. This phase is sometimes recalled by those that go on to develop hikikomori as a period of solace, in which they were no longer exposed to the trauma that triggered the social withdrawal.

Not responding to the needs of this group will be hugely costly. Transnational studies of hikikomori show that without intervention the withdrawal period may last for years and in some cases the entire adult life. Japan now has had three decades of tracking the epidemiological trajectory of hikikomori, with many of those affected starting to outlive their parents. As lockdown measures are gradually lifted, we enter a critical period for identifying and preventing those who are vulnerable to following the classical hikikomori trajectory.

Because people with milder forms of hikikomori may leave home for non-social reasons two or three times a week[4], the COVID-19 social distancing rules may allow them to "hide in plain sight". This complicates the disentangling of behavioural adaptation to lockdown from attempts to become invisible from society as a way of minimizing further mental trauma. Aspiring to social death and avoiding physical death is a core feature of people with hikikomori – they want society to forget them, but they cannot forget society[5]. Many of them will continue to passively observe the world via online gaming and social media and, as long as parents act to ensure that their child's basic living needs are met, there will be few natural triggers for help-seeking. External therapeutic attention typically takes years, and is most commonly triggered by a parent following a crisis. Addressing this type of largely invisible problem will require adapted help-seeking pathways.

This is now a global problem. Hikikomori has been described across diverse cultures and levels of per capita income[3,4,6]. As with so many problems of adaptive functioning, people at elevated risk will include those with pre-existing mental health problems, people affected by adverse childhood experiences[7], plus those whose life-path has been severely derailed by the pandemic. There is a clear and time-sensitive need for a proactive and multidisciplinary effort to respond to the mental health consequences of the COVID-19 pandemic[8]. But, because of the invisible nature of hikikomori, standard pathways to care will be unlikely to operate. Instead, coordinated multi-agency collaboration will be needed to identify those at risk of continuing to "shelter in place" instead of re-engaging with pre-pandemic roles.

Vigilance for school non-attendance or a failure to re-join work or training may signal a need for outreach to check if there is problematic social withdrawal. The increased use of digital options for accessing health and social care services should be leveraged to provide new ways of finding and supporting new hikikomori people before they become too entrenched. Experience in Japan suggests that the creation of digital peer

networking may significantly improve engagement with sources of help and recovery.

Virtual reality and digitally-delivered psychological treatments may also be particularly suitable for this group, whose preferred medium for accessing the world is the Internet. Finally, public mental health campaigns via digital means may prove particularly effective for reaching out to potential hikikomori people and their families to capitalize on the known interest in online activities of this group. Investing in the detection and support of new people with hikikomori should be added to the growing list of mental health research and treatment priorities in the post-COVID-19 era.

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The network structure of ICD-11 complex post-traumatic stress disorder across different traumatic life events

The ICD-11 describes complex post-traumatic stress disorder (CPTSD) as consisting of six symptom clusters: re-experiencing of the trauma in the present, avoidance of traumatic reminders, sense of current threat, affective dysregulation, negative self-concept, and disturbed relationships[1].

The network approach estimates and quantifies symptom-specific associations, and symptoms that have many and/or strong associations are deemed highly central to a network. In theory, the most central symptoms should reflect the most significant aspects of a disorder and, potentially, the most important treatment targets. Considering that exposure to a traumatic life event is a defining feature of CPTSD, it is important to explore if CPTSD symptom expression varies depending upon the type of trauma.

We used network analysis to: a) examine the structural validity of CPTSD across six different index trauma experiences (unexpected death of a loved one, physical or sexual assault, life-threatening accident, life-threatening illness, natural disaster, childhood poly-traumatization), and b) explore differences in the overall importance (i.e., centrality) of specific symptom clusters across the six index trauma events.

Data were drawn from general population surveys in the US (N=1,839), the UK (N=1,051), Israel (N=1,003) and the Republic of Ireland (N=1,020). In every case, participants were recruited from existing online research panels that are representative of the general population of each country. In total, 4,913 adults participated across the four samples. Their mean age was 44.9± 15.0 years (range 18-90 years), and 60.5% were female. Clinical data were also pooled from three cohorts of clients (N=588, mean age 39.6±12.2 years, 54% female) recruited from a national health service trauma centre in Scotland.

Traumatic exposure was measured using the Life Events Checklist for DSM-5[2] or the International Trauma Exposure Measure[3]. The Childhood Trauma Questionnaire[4] was also used in the clinical samples to measure childhood trauma exposure. CPTSD symptoms were assessed using the International Trauma Questionnaire[5].

Participants from the community samples were classified into six groups based on their index trauma: unexpected death of a loved one (28.4%, N=1,393), physical/sexual assault (19.3%, N=949), life-threatening accident (15.2%, N=745), life-threatening illness (8.3%, N=409), and natural disaster (6.2%, N=307). All participants from the clinical sample reported multiple traumatic life events in childhood and were thus classified in the group of childhood poly-traumatization.

Symptom networks were estimated separately in each trauma sub-sample with the R-package Isingfit, using the default hyperparameter value of 0.25. The resultant networks were visualized using the R package qgraph[6]. This package visualizes networks as nodes (points in space reflecting symptoms) and edges (lines connecting the nodes, indicating the presence, direction and strength of associations). The overall importance/influence of each symptom node was determined using the expected influence (EI) measure of centrality. EI is calculated by summing the edge weights of a given node, and thus provides an indication of a node's direct influence over all other nodes in the given network[7]. We tested for significant differences in EI across the trauma groups using non-parametric permutation tests[8].

Networks, EI values and results from the permutation tests are available at https://www.traumameasuresglobal.com/na2020. The EI values were highly inconsistent across the different groups, suggesting that specific symptom clusters had a different relevance depending on the type of index trauma. This was supported by the permutation tests, with 31% of EI values differing significantly across the trauma groups (α=0.05).

For those who had experienced accidents or assaults, avoidance was a particularly influential symptom cluster. Sense of current threat and disturbances in relationships were influential nodes for those in the illness group. Avoidance and disturbances in relationships were high in EI for those who had experienced the unexpected death of a loved one. For those who had experienced a natural disaster, avoidance and negative self-concept

were high in EI. Finally, negative self-concept was particularly central for the poly-traumatized sample.

The prominence of sense of threat in the illness group might be suggestive of fear of recurrence. The centrality of avoidance in accidents and assaults might suggest that people are less likely to put themselves in positions where these events can re-occur. Poly-traumatization, especially when occurring in childhood, can lead to a failure to develop age-appropriate competencies, which in turn can lead to a sense of self as defective, helpless, deficient and unlovable.

These results have important implications for the treatment of CPTSD using person-centred approaches. We previously argued[9] that symptoms of CPTSD can be targeted and prioritized in therapy according to the severity or prominence of a given cluster, alongside the patient's readiness to tackle these symptoms. We now provide evidence that the expression and structure of CPTSD symptoms is associated with the index trauma event. It may be, therefore, beneficial to prioritize different symptom clusters, when planning treatment, depending on the index trauma.

Further research on exploring the salience of different symptoms clusters in CPTSD is important and may contribute to effective and efficient treatment planning.

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Effectiveness of cognitive remediation in the ultra-high risk state for psychosis

Individuals at ultra-high risk (UHR) for psychosis suffer significant cognitive deficits that can hamper functional recovery[1]. The beneficial effect of cognitive remediation on cognition and functioning is documented in individuals with established psychosis[2,3], but little is known about the effect of this intervention in those at UHR for psychosis.

Cognitive remediation may potentially be more beneficial in the psychosis UHR state than in more advanced illness stages, owing to the potential of greater brain plasticity[4,5]. For the same reason, reduced doses may be sufficient to produce change.

The randomized, assessor-blinded, parallel-group, superiority clinical trial called FOCUS is the hitherto largest trial to report on the feasibility and efficacy of intensive neurocognitive and social cognitive remediation in the UHR state.

Participants aged 18-40 years who fulfilled the Comprehensive Assessment of At Risk Mental States (CAARMS) UHR criteria were recruited to the FOCUS trial from the psychiatric in- and outpatient facilities in the greater catchment area of Copenhagen, Denmark from April 2014 to December 2017[6].

On completion of baseline assessments, participants were randomly assigned to either 20 weeks of cognitive remediation as an add-on to treatment as usual (TAU+CR) or to treatment as usual alone (TAU). Randomization was stratified by current use of antipsychotic medication (yes/no) and IQ score (≤100/>100).

The CR intervention comprised two hours of group training (one hour of neurocognitive training, with subsequent 15 min of bridging session, and one hour of social cognitive training) once a week for a total of 20 weeks. For this group training, we used the Neuropsychological Educational Approach to Cognitive Remediation (NEAR)[7] and the Social Cognition and Interaction Training (SCIT)[8] manuals. Additionally, the participants received 12 individual sessions with a cognitive-behavioral format designed to maximize the transfer of the effect of the CR to their daily lives.

The TAU consisted of a regular contact with health professionals in the in- and outpatient facilities, involving monitoring of medication and supportive counselling but not cognitive remediation.

A total of 146 UHR individuals were assigned to either TAU or TAU+CR. Socio-demographic variables were well balanced between the groups. The TAU+CR group attended an average of 10.9±7.6 cognitive remediation sessions and had an average of 11.9±16.4 hours of total neurocognitive training.

The comparisons between the two groups on continuous outcomes at cessation of treatment and at 12-month follow-up were conducted using a generalized linear model adjusted for stratification variables and baseline imbalances, with missing data handled by multiple (m=100) imputations.

At cessation of treatment, we found no between-group difference on the primary outcome, i.e. global neurocognition as indexed by the Brief Assessment of Cognition in Schizophrenia (BACS) composite score (b=–0.125, 95% CI: –0.423 to 0.172, p=0.41). We also did not find a treatment effect on secondary outcomes, i.e. scores on Personal and Social Performance Scale

(PSP), Brief Psychiatric Rating Scale (BPRS-E), Scale for the Assessment of Negative Symptoms (SANS), and Montgomery-Åsberg Depression Rating Scale (MADRS).

Concerning explorative outcomes, we found a treatment effect on the Emotion Recognition Test (ERT) latency total score and ERT latency happiness, sadness, and fear (b from –152.0 to –226.8; p from 0.01 to 0.002), with the TAU+CR group demonstrating faster emotion recognition processing speed.

At the 12-month follow-up, we found a significant between-group difference on the Cambridge Neuropsychological Test Automated Battery (CANTAB) executive functioning Stockings of Cambridge measure and the Paired Associate Learning visual memory measure (b=0.759, p=0.03 and b=–1.98, p=0.02, respectively), with the TAU+CR group performing better than the TAU group.

So, the CR intervention did not result in improvements in global measures of cognition, functioning and symptoms in this sample of UHR subjects. The CR may, though, have been underdosed to drive meaningful global improvements, as the TAU+CR group attended an average of 10.9 sessions and had an average of 11.9 hours of neurocognitive training, which is about half the usual dose for people with first-episode schizophrenia.

While the integrative CR format was designed to achieve synergistic benefits of targeting both neurocognition and social cognition, our findings indicate that this may not be a viable approach to the UHR population, that is known to be difficult to engage in treatment[9].

Our exploratory findings indicate improvements in some areas of social cognition and neurocognition after even a few CR sessions, which points to a potential for cognitive plasticity if UHR individuals can be engaged sufficiently to practice the skills.

In secondary regression analyses, the social cognitive improvements (emotion recognition latency total and domain scores) were consistently predicted by better baseline social and role functioning. This finding indicates that UHR individuals with better functioning at ascertainment may be more able to benefit from a CR intervention. On the other hand, greater improvements in executive function and visual memory at 12 months were predicted by worse baseline performance on these neurocognitive measures. If confirmed, these findings support taking baseline patient characteristics into account when implementing CR in the UHR population.

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The WPA celebrates its 70th birthday

The success of the World Congress of Neurology in Montreal in 1948 made the psychiatrists who were present (at that time psychiatry and neurology were not yet separated) decide to create an Association for the Organization of the World Congress of Psychiatry. J. Delay, a Professor of Psychiatry from France, took the presidency of the Association and H. Ey, also a French psychiatrist and philosopher, became the secretary of the new Association. One of the reasons for getting actively engaged in this endeavour was the wish of the French psychiatrists to celebrate the 50th anniversary of the first World Congress of Psychiatry held in Paris in 1900.

After World War II, many people sought to establish links and recreate partnerships. The United Nations were created in 1945, the United Nations International Children's Emergency Fund (UNICEF) and the United Nations Organization for Education, Science and Culture (UNESCO) in 1946, the World Health Organization (WHO) in 1948, and the World Federation for Mental Health in 1948. The WHO even had a Mental Health Unit, because its first Director General, B. Chisholm, a psychiatrist and colonel from Canada, felt that there is no health without mental health.

At that time psychiatrists had few, mainly personal, contacts with their colleagues in other countries. In Europe, links were mainly within zones defined by the four languages of communication – German in Germany, Austria and the countries along the Danube; French in Belgium, France, Italy, Romania and Serbia; Russian in the Soviet Union and its satellites; and English in the UK, Ireland and to an extent in the Netherlands and Scandinavia. UK psychiatrists were in contact with anglophone societies in the US, Canada, Australia and New Zealand, and with some of the Asian societies using English; the French and Spanish societies with colleagues in countries using their language. There were very few psychiatrists who had contacts with colleagues from a different language zone.

J. Delay and H. Ey began organizing the congress upon their return to France. Since neither of them spoke any language but French, they invited a young psychiatrist who was fluent in several languages, P. Pichot, then in J. Delay's department in Paris (and later a WPA President), to help. Pichot wrote the invitations on his typewriter or by hand and undertook to send them to leading psychiatrists in many countries, including Germany.

The French government supported the notion of having the World Congress in France and so the first World Congress of Psychiatry of the new era took place in Paris in 1950. Many mythical psychiatric figures – M. Klein, A. Freud, A. Lewis, E. Stromgren and M. Bleuler among others – came to meet in the Great Amphitheatre of the Sorbonne University. The President of France received the participants. The Congress addressed important topics: the limits of psychiatry, the creation of a common language for the discipline, an international classification of mental disorders, and the standardization of psychological tests for use in psychiatry. It was a great success.

The Association for the Organization of International Congresses, now composed of up to fifty members from each of the participating countries, started to prepare the next congress. In 1954, a committee selected Zurich as the congress venue. As its date approached, the liquidation of the Hungarian uprising in 1956 made Bleuler and Ey hesitate about the invitation to psychiatrists from the Soviet block countries, but otherwise everyone was to be invited and welcomed.

The second World Congress of Psychiatry took place in Zurich in 1957 and its main topic was schizophrenia. Russian psychiatrists were not invited, and some of the psychiatrists in Eastern European countries could not get a visa from their government to attend. Those who did get a visa were not allowed by their government to bring their spouses along.

The vast majority of the world's leaders in psychiatry were among the 3,000 psychiatrists who attended the congress. The participants could speak English, German, French, Italian or Spanish, using a brand-new apparatus for simultaneous translation. All aspects of schizophrenia were given attention, but there were also a few presentations dealing with other matters. One of them was the talk given by R. Kuhn, who presented a new way of treating depression – by imipramine. There were only 17 persons in the audience at that session, one of them being the speaker's spouse.

The Association for the Organization of International Congresses mutated into the World Psychiatric Association (WPA) in 1961. It was registered in Switzerland, and its members were societies of psychiatrists, although individual psychiatrists could also be members. World Congresses of Psychiatry followed with 5 to 6-year intervals among them – in Montreal (where it was agreed to create scientific sections in order to give sustained attention to selected topics), Madrid, Mexico City, Honolulu, Vienna, Athens and Rio de Janeiro. The abuse of psychiatry for political reasons emerged as an issue during the congress in Madrid (1966), dominated the public discussions during the Mexico City congress, led to the Hawaii Declaration in 1977, and to the withdrawal of the Russian as well as of the Bulgarian, Czech and Cuban Psychiatric Associations from the WPA in 1983. During the congress in Athens six years later, the Russian Psychiatric Association invited a WPA commission to visit Russia to explore the conditions in psychiatric practice there, and re-joined the WPA.

In 1996 the congress, for a second time in Madrid, attracted nearly 10,000 psychiatrists. The Association's General Assembly significantly redrafted the WPA Statutes and Bylaws. The Madrid Declaration on Ethical Standards for Psychiatric Practice was approved[1]. The WPA initiated several educational programs for psychiatrists and other mental health workers[2]. New WPA scientific sections came into existence, bringing their total number to 60. The WPA produced a guidance document about the teaching of psychiatry followed in a number of countries[3], and started a large international collaborative program against stigma ("Open the Doors") involving more than 20 countries[4]. Another major interna-

tional program dealt with mental health in children and adolescents[5].

In the next three years, WPA meetings attracted more than 40,000 psychiatrists, and the Association started producing a series of *Evidence and Experience in Psychiatry* publications (nine volumes)[e.g.,6], which were followed by other books, such as three volumes on mental disorders and physical illness[e.g.,7]. All these books were translated in several languages.

The WPA official journal, *World Psychiatry*, started its life in 2002 and is now published in ten languages, with an impact factor higher than any other of the 3,000 journals in the social sciences area. The journal reaches an estimated 60,000 psychiatrists worldwide and can be obtained free of charge.

The WPA also made a special effort to facilitate becoming acquainted with the most important works of psychiatry blocked from general distribution by language: over the years, seven anthologies of key papers produced in languages other than English were published[e.g.,8].

The WPA organized, sponsored or cosponsored numerous regional, international and thematic scientific meetings in various parts of the world. Some of the material presented during these meetings was published locally, and in addition the Association published many presentations given during world congresses – the most comprehensively published was the congress in Paris, whose proceedings appeared in six volumes, and the congresses in Yokohama and Madrid, whose proceedings consisted of three volumes[e.g.,9].

The next World Congress of Psychiatry, held in Hamburg in 1999, was the first major psychiatric meeting after the World War II in Germany. It was followed by the first World Congress of Psychiatry held in Asia (Yokohama, 2002) and by the first World Congress on the African continent (Cairo, 2005). That year the WPA also started the institutional program on psychiatry for the person, resulting in a textbook and other publications[10]. The congresses in Prague (2008), Buenos Aires (2011), Madrid (2014) and Berlin (2017) followed. Subsequently, the WPA switched to having an annual World Congress of Psychiatry. Those in Mexico City (2018) and Lisbon (2019) were the first congresses of what is to become a practice of having a congress every year, rotating across Europe, Africa and the Middle East, the Americas and Asia.

The WPA now has national psychiatric societies in 120 countries as its members, and assembles more than 250,000 psychiatrists worldwide. It is not only the largest international organization in the field, but also the most ecumenical, covering the many fields of action in psychiatry by its scientific sections, publications and meetings. It is managed by an Executive Committee, has a Board of Zonal Representatives, and a Council bringing together its Past Presidents. Its Secretariat is in Geneva.

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Report on the WPA Action Plan at the end of the triennium 2017-2020

One of the tests of an organization is its response in a crisis. As we review the current triennium, the world is experiencing turmoil and change with the impact of the COVID-19 pandemic. As governments struggle to support and stabilize the health systems and economies in countries, psychiatrists and their colleagues in the health professions face extraordinary challenges.

WPA's work over the last three years has been guided by a strategy for expanding the contribution of psychiatry to improve mental health for people across the globe[1]. We have emphasized working with women and men living in adversity, and those with long-standing mental illnesses and psychosocial disabilities and their caregivers; and the role of psychiatry as a discipline central to medicine and health care and vital to sustainable development in each country[2,3]. The emergency we now face draws on these perspectives, the work we have done, and the new face of the WPA over the past three years.

Mobilizing for the emergency response began in March 2020. We founded the Advisory Committee for Response to Emergencies (ACRE) to facilitate practical and concrete aid to Member Societies in need, as well as foster education, information collection and the development of local, national and international strategies to cope with the mental health consequences of emergencies. We established an emergency assistance fund in April 2020 and in May provided funding to colleagues in Nepal for outreach services to support child and adolescent mental health. We have since, for example, provided aid in cash and in-kind for personal protective equipment in Ukraine and other parts of the world.

Our online library of COVID-19 mental

health resources (www.wpanet.org/covid-19-resources) has developed rapidly, with the support of WPA Member Societies and Sections. It provides access to the resources curated by them and other trusted partners, with materials in several languages. Accelerated development of the WPA education portal and learning management system has promoted the launch of new education and training modules to support the emergency response. The first of these modules supports psychiatrists in using e-mental health tools. The portal also gives ready access to WPA's existing training materials, including the International Competency-Based Curriculum for Mental Health Providers on Intimate Partner Violence and Sexual Violence against Women, available in several languages[4].

During the triennium, the WPA has worked closely with people with lived experience and their families, has built gender and geographic diversity in its leadership and scientific face, and engaged with international organizations and policy-makers. The Action Plan has provided a clear strategic intent that is framed by and builds on three characteristics.

The first characteristic is WPA's contribution to the representation, reputation, development and knowledge of the profession. This has been achieved through several initiatives:

- The Service User and Family Carer Advisory Group coordinated by M. Amering has contributed to WPA's response to the emergency, to its congresses, and to other challenging and important projects during the triennium[3,5].
- We have moved successfully – in scientific, social and financial terms – to the annual convening of the World Congress of Psychiatry, supported by our professional congress organiser Kenes International. The congresses have featured diversity by gender and regions, and partnership with a range of organizations including the World Medical Association, the International Association of Women's Mental Health, the International Federation for Psychotherapy and a dozen more. WPA regional and thematic congresses in Australia, Ethiopia and North Macedonia have also been appreciated.
- Our revamped website and program of regular communications have kept Member Societies, WPA leadership and all those interested in WPA connected and informed.
- The new Standing Committee on Science, Education and Publications chaired by N. Sartorius has made a major contribution to the integration of WPA's scientific work and its presentation at WPA Congresses.
- The Standing Committee on Ethics and Review chaired by S. Tyano revised the proposed WPA Code of Ethics. A Task Force convened by P. Appelbaum reviewed the WPA recommendations for relationships of psychiatrists and others with the pharmaceutical industry[6].
- The WPA has continued its collaboration with the World Health Organization (WHO) Department of Mental Health and Substance Use, including consultation on the work of the WHO Commission on Non-Communicable Diseases, the WHO/United Nations International Children's Emergency Fund (UNICEF) initiative on Helping Adolescents Thrive, and the EQUIP workforce development in psychological interventions.
- The WPA has partnered with the US Carter Center and the International Center for Journalists to promote mutual understanding between psychiatrists and journalists.

The second characteristic of the Action Plan framework is the development of operational, project-based work that focuses on selected and critical mental health topics at a global level:

- A discussion paper and position statement on "Implementing alternatives to coercion in mental health care" has been developed by a Task Force chaired by S. Galderisi and J. Allan, in consultation with Member Societies and the Service User and Family Carer Advisory Group[2]. This work and three case studies linked to it – in Colombia, India and Australia-New Zealand – are supported by the Royal Australian and New Zealand College of Psychiatrists. The position paper with recommendations for action and an optional protocol are designed to support Member Societies to engage with this work in ways that suit their local circumstances[3].
- A report has been published on collaborative work with the World Organization of Family Doctors (WONCA) on competencies in mental health for family doctors[7].
- A survey of the demography and training of psychiatrists in WPA Member Societies, led by R. Ng and set to be published in 2020, will give us a first glimpse of the age and gender patterns and the training experiences of our profession worldwide.

The third characteristic of the Action Plan is the attraction of new investment to WPA to support its work, especially through relationships with organizations that share our objectives. We have succeeded in attracting new resources from philanthropy and other sectors, as well as more traditional sources, to support programs:

- An important external investment in our work has come from citiesRISE[8], which is in turn supported by Pivotal Ventures (a Melinda Gates company), Co-Impact and other philanthropic and development funders. We have worked in Nairobi, Chennai and Bogota with our Member Societies and their branches[9,10]. This work locally and across cities has contributed in several ways to promoting the mental health of disadvantaged young people: by promoting mental health in schools; revising training and in-service curricula for psychiatrists and other mental health workers; and preparing the ground for implementing programs of perinatal care in scarce resource countries.
- Support for the Lancet-WPA Commission on Depression[11] has come from several external sources, including the University of Melbourne, the American Foundation for Suicide Prevention, the Wellcome Trust, and UNICEF. The latter two organizations have supported young people with lived experience of depression in consulting on the recommendations and their dissemination. Past WPA President and Editor of *World*

Psychiatry M. Maj has had a prominent role in preparing the report, which is due for publication in early 2021. The WPA will be invited to have a continuing role in the life of the Commission.

- As president of WPA, I co-chair the World Economic Forum Global Future Council 2019-2020 on Technology for Mental Health, that aims to promote the ethical adoption of technologies[12] and has acted to facilitate positive working relationships in the field.

WPA's ability to promote sustainable change in our field of work – in the midst of an emergency or at any time – depends on two main factors. The first is the capacity to collaborate successfully with other organizations. The second is its potential to engage psychiatrists in new challenges. The WPA has engaged in both these endeavours and has been fortunate in the support received from its Member Societies and all other components, its Secretariat and consultants, and from the new sources of philanthropic and development support we set out to attract. Just as fortunate is the message of continuity, as the preparation for the new triennium encourages the extension of current initiatives, including the emergency responses.

Helen Herrman
WPA President

Throughout the triennium, the WPA has enjoyed a productive partnership with Community Works, whose team has supported the implementation of the Action Plan. Consultants V. Cameron and A. Pound have provided invaluable help in enabling the Action Plan.

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COVID-19 and psychiatrists' responsibilities: a WPA position paper

The SARS-CoV-2 virus has changed our world, endangering health, lives, social connections and economies[1], with the likelihood and consequences of future waves of infection still unknown. In this context, the WPA Standing Committee on Ethics and Review has produced a position paper to provide ethical guidance to the profession on the issues raised by the pandemic[2]. This essay summarizes and builds on this position paper, adding more recent information.

During the COVID-19 pandemic, psychiatrists must continue to care for their patients by all possible means, including telepsychiatry and other forms of virtual care[3,4]. Their role, however, goes well beyond primary duties to prevent, diagnose, treat and keep safe individuals with mental disorders[1,3-5].

To be effective, psychiatrists must have accurate information about COVID-19 and act accordingly. This includes appropriate knowledge of and adherence to physical distancing, frequent hand washing with soap and water or disinfectant, and proper protocols for masking, face shields and other protective equipment, which may vary over time and jurisdiction. Psychiatrists should also be prepared to debunk myths about the origin of the virus, unproven treatments, potential harms of vaccines, and protective measures. Of course, psychiatrists should safeguard their own health with proper nutrition, sleep, rest and exercise, and promptly seek professional help if they become physically or mentally unwell[5].

Some health care professionals, working long hours in life-threatening conditions, often without appropriate protective equipment, may develop anxiety, depression, post-traumatic stress disorder (PTSD), insomnia, and excessive irritability and anger[3,4,6]. Psychiatrists should assist in developing self-help, group or individual supports or treatments for distressed colleagues and their families. However, they should also support the resilience and pride in their roles experienced by many health care workers during the pandemic.

As psychiatrists are physicians, they may volunteer or be redeployed to assume other duties in their institutions or communities, such as working in emergency departments, primary care, internal medicine, critical care or long-term care homes. They may also be called on to support medically ill patients or their families during illness or following bereavement[3]. This is especially critical as isolation often prevents the usual social supports.

As leaders in their hospitals, health care agencies and communities, psychiatrists may also participate in COVID-19 decision-making committees (including triage), where they should safeguard the rights of persons with mental disorders. They may participate in educational and media activities for patients, health care workers, the public or policy makers about the mental health distress caused by physical distancing, home quarantine, shelter-in-place, isolation, and loss of social support, work and income[3,7]. Psychiatrists should also advocate for interventions by governments and others to reduce distress and suicide in the general population.

Social disadvantage and inability to follow public health advice places individuals with mental disorders at higher risk for COVID-19. In addition to older people, it is now clear that ethnic minorities, malnourished individuals and long-term care home residents, recent migrants and indigenous peoples also face higher risks of COVID-19 and adverse outcomes[1].

Mortality/morbidity data are missing for people with mental illness, who may not only share the above risk factors, but also be unable or unwilling to protect themselves against COVID-19 due to apathy,

depression, paranoia or other psychiatric symptoms. They may also lose their ongoing social and psychiatric supports, including experiencing early discharge from care.

Psychiatric inpatients should be screened for COVID-19 symptoms before admission and carefully monitored thereafter[3]. Protective public health measures such as physical distancing, hand washing and masking should be enforced, and patients who are unable or unwilling to comply should be isolated to protect themselves, staff and other patients. When rates of infection in the community are high, inpatient units should prohibit visitors, but virtual visiting should be encouraged.

Symptomatic patients should immediately be retested for COVID-19 and, if positive, promptly isolated either in an infection-controlled area of the unit or special unit for infected psychiatric patients or in an intensive care unit[4]. However, the need for isolation should never imply neglect of human rights, misuse of coercive measures, or disregard of treatment needs. Psychiatric patients should receive appropriate COVID-19 treatments and vaccines without discrimination now and in the future.

Outpatients who require assessment or treatment for mental disorders should be seen virtually where possible but, if they must be seen in person, all public health protocols – including screening prior to visits – should be strictly followed as asymptomatic individuals may also be infected with the virus.

It is becoming clearer, as with previous epidemics, that many individuals may experience anxiety, depression, PTSD and other neuropsychiatric disorders during and following COVID-19, whether or not they were infected. Stay-at-home quarantine has been shown to increase child abuse, intimate partner violence, excessive alcohol and drug use, and suicidality[1]. Psychiatrists should alert policy makers and other authorities of the long-term consequences and likely increase in mental health service demand.

Triaging of resources has now become necessary in several jurisdictions, as health care capacity is outstripped by demand. Triage may occur in emergency departments or any clinical unit (including intensive care units) or treatment allocation. The aim of triage is to use scarce resources for individuals most likely to survive, but mental disorders must never be used to exclude patients from medical resources or treatments. Comprehensive triage protocols should be established beforehand by a multidisciplinary expert committee that ranks medical comorbidities without reference to social position, disability, age, and cultural or religious affiliations. All individuals being triaged should be reviewed by this committee to ensure adherence to the protocols and avoidance of improper influence.

The WPA position paper concludes: "While variations across countries will exist in responding to the COVID-19 pandemic, the human rights of individuals with mental disorders must be protected, and appropriate and safe services provided for their treatment. Moreover, the negative impact of the pandemic on government budgets should not be used as an excuse to reduce essential services for people with mental illness during or after the pandemic. Psychiatrists can play important roles in advocating for these measures and in supporting their patients, colleagues and the healthcare system's response to the pandemic"[2].

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Strengthening the functioning of WPA through its Secretariat

The WPA Secretariat has been most active in the current triennium (2017-2020). The main focus has been to strengthen the functioning of the WPA to achieve its main objective to promote the advancement of psychiatry and mental health for all citizens of the world.

The WPA occupies a unique position and is regarded as the global parent organization in psychiatry. It has a formal relationship with the World Health Organization (WHO). The WPA Action Plan 2017-2020[1-3] aimed to improve mental health for people across the globe through consultation, mental health promotion, and equitable access and quality of mental health care.

All these are facilitated and monitored through the WPA Secretariat[4-6]. This is located at the Geneva University Psychiatric Hospital, with which we have an "accord of collaboration" for 20 years, valid until 2024, subject to renewal thereafter. Here we focus on some of the main activities of the Secretariat during the triennium.

Member Societies constitute the backbone of the WPA. Our emphasis has been to partner and support these Societies in achieving our common goals through constant communication and fruitful interactions. Concerns of Societies have been brought to the attention of the President and the Executive Committee; they have been addressed properly and solutions found whenever possible.

The expansion of the WPA to hitherto unreached areas has been another priority. Four new Member Societies have been admitted on an *ad-hoc* basis, pending their final approval by the next WPA General Assembly. These are the Zimbabwe College of Psychiatrists and the Zambia Psychiatric Association (both in WPA Zone 14 - Eastern and Southern Africa); the Association of Specialists Working in

the Field of Mental Health - Kazakhstan (in WPA Zone 10 - Eastern Europe); and the Society of Psychiatrists, Narcologists, Psychotherapists and Clinical Psychologists of the Republic of Moldova (in WPA Zone 9 - Central Europe). We have now a total of 144 Member Societies (including four *ad-hoc*), which is at the top among all medical associations worldwide.

We have been supporting the work of the WPA Board, consisting of 18 Zonal Representatives from all regions of the world. The WPA Secretary General and the Secretariat maintain close liaison with this Board. The Zonal Representatives have the advantage of first-hand knowledge of the happenings related to mental health in the countries under their jurisdiction. They in turn relate these concerns to the President and the Executive Committee through the Secretary General and the Secretariat, leading to timely action.

We have been facilitating the activities of the 70 WPA Scientific Sections, which since their inception have been WPA's scientific backbone, affording depth and continuity to our global Association[7]. These Sections cover practically every aspect of psychiatry, bringing together psychiatrists from across the world and their expertise in relevant disciplines. Their work is coordinated by the WPA Secretary for Sections, and the Secretariat provides all necessary logistical support.

The re-designed WPA website (www.wpanet.org) is now more dynamic and interactive than ever[6]. It has gone live since May 2019 and has now a number of features that make it a tool which is useful and user friendly. The largest number of visitors to our site are seeking information on meetings and publications, especially *World Psychiatry*. The website provides the most up-to-date information on our finger tips. With the help of the WPA Secretary for Education, we are trying to ensure that all our educational resources are accessible via one central point[8].

In the wake of the recent pandemic, we have created a section on COVID-19 Mental Health Resources on our website. This provides resources from trusted partners, reputed journals, collaborative initiatives (webinars), and from WPA Sections and working groups.

We have been contributing to the refinement of WPA normative instruments in an orderly manner, for their review and approval by the proper WPA bodies. The new and revised Manual of Procedures, approved by the Executive Committee, has been made available.

Governance responsibility is entrusted with the Secretary General, who ensures that the Secretariat properly supports the work of the WPA and its Executive Committee. The Secretary General acts as the liaison between the WPA Board and Committees, and ensures that Member Societies are kept informed of any discussions and decisions. The Secretary General also seeks the advice of the WPA Council when appropriate.

Concerning administration, a new filing system has been put in place at the Secretariat, with two entries for WPA documents: one to be accessed by WPA components with appropriate password, and the other to be accessed by Secretariat staff. Other innovations have been the preparation and documentation of various policies approved by the Executive Committee, the creation of a WPA privacy policy, a new WPA logo, procedures for regional and thematic meetings, procedures for applying to WPA co-sponsorships and continuing education credits, administrative support for the various Task Forces and Standing Committees, and maintenance of service during COVID-19 lockdown.

F. Sotgiu was appointed as the Chief Executive Officer in December 2017. Leading the work of the Secretariat, she liaises closely with the Executive Committee, in particular the Secretary General and the President, whilst also managing two administrative staff. She is responsible for all day-to-day activities of the Secretariat, including management of the Association's finances, legal and human resource requirements. Let me appreciate her excellent work for the WPA.

Thus, the WPA Secretariat has been performing its primary objective of strengthening the WPA, although working within administrative and financial constraints. This mission could not have been accomplished without the dynamic leadership of WPA President H. Herrman. We are also obliged to the WPA President-Elect A. Javed, and the members the Executive Committee, Council and Board for their guidance. Above all, we thank the WPA Member Societies for their constant support and cooperation. Together, and finding strength in our unity, the WPA will march ahead!

Roy Abraham Kallivayalil
WPA Secretary General

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WPA Scientific Sections: a strengthened backbone for the 2020-2023 triennium

At the beginning of his six-year term, the WPA Secretary for Scientific Sections laid out a work plan[1] comprised of the following main goals: a) improve and streamline communication between the Sections and facilitate research and publication projects; b) continue and expand the WPA's intersectional activities; c) leverage the Sections' experiences and resources to further WPA's activities for early career psychiatrists; d) promote gender equity at all levels of Sections and their activities; e) establish cross-country peer networks of researchers to facilitate and share access to knowledge, resources and

strategies to publish successfully; and f) establish truly authentic and compassionate relationships with organizations representing patients and caregivers.

The implementation of these goals is meant to strengthen the Sections as the backbone of the Association and thus to enable the WPA to forcefully fulfill its triennial Action Plans, to swiftly react to challenges to global psychiatry, and to communicate its mission not only to the psychiatric community but to society at large.

Since a powerful information technology infrastructure is a prerequisite for an umbrella association of 140 national psychiatric societies to meet the demands of today's world, the Secretary for Sections has established a flexible online meeting platform in order to communicate with the Sections, and for the Sections to communicate with each other. For the past two years now, the Secretary has held online videoconferences with the leaderships of the various Sections about every three months. Participation ranges from 10 to 30 Sections. The time slots are rotated so as to accommodate for different time zones, regional and religious holidays.

While being a simple tool, the introduction of this platform has tremendously propelled cross-talk between Sections. It has been instrumental in increasing the number of intersectional activities at WPA congresses and meetings, such as symposia, workshops, and panel discussions. It has furthermore contributed to a more prominent role of the Sections in the program committees of the WPA's signature World Congress of Psychiatry, with Section members now making up more than a third of program committee members, being balanced for geographic diversity.

This heightened visibility and level of engagement of the Sections has greatly contributed to the shaping of a novel signature initiative of the WPA: the Education, Science, Publication, and Research Initiative (ESPRI)[2]. ESPRI is dedicated to jump-starting innovative and promising programs in low- and middle-income countries (LMIC). The WPA will award $15,000 USD to three projects ($5,000 USD per project) per year. These funds should be matched with funds that the applicants have been able to secure through other national and/or international organizations, including academia, governments, non-governmental organizations (NGOs) and/or industry.

The first project to be awarded seed funding through the ESPRI mechanism, which was jointly developed with the Secretaries for Education and Publications, focuses on training mental health professionals in diagnosis and reporting of trauma related to torture and persecution in people from Syria and other countries of the Middle East and North Africa region. This project is being spearheaded by the Section on Psychological Consequences of Torture and Persecution.

This Section, in close collaboration with that on Psychotherapy, was furthermore instrumental in bringing a strong WPA component and thinking to a conference on psychotraumatology at the University of Duhok, Kurdistan (June 23-24, 2019), which in turn inspired a publication collaboration between the WPA and the *British Journal of Psychiatry*, resulting in a special issue on "Bringing the toll of disasters and trauma on mental health to the forefront of psychiatric discussion"[3].

The beginning of the next WPA triennium (2020-2023) will be marked by a thematic congress on "Psychological trauma: global burden on mental and physical health", taking place in Athens on December 11-13, 2020, conceptualized as an entirely intersectional meeting (www.wpathematic.org).

The interaction between the Secretary and the Early Career Psychiatrists (ECP) Section has proven to be very fruitful, and has helped shape a signature ECP project, the ECP Exchange Programme, which will allow early career psychiatrists to acquire intercultural competencies, and gain awareness of different expressions of illnesses and available treatments across the world[4]. The Secretary is now working together with ECP members to actively contribute to and shape WPA's social media presence. The Section on History of Psychiatry has recently seen a major influx of early career psychiatrists and has become a very active and diverse Section under a new leadership, demonstrating that the history of our field is a dynamic process.

In addition to the ones discussed above, the Secretary would like to briefly point the reader to the recent activities (e.g., large-scale book projects, development of guidelines, congresses, active involvement with various NGOs) of the Sections on Disaster Psychiatry; Evidence-based Psychiatry; Exercise and Sports Psychiatry; Family Research and Intervention; Immunology and Psychiatry; Interdisciplinary Collaboration; Medicine, Psychiatry and Primary Care; Neuroimaging in Psychiatry; Old Age Psychiatry; Pharmacopsychiatry; Philosophy and Humanities; Positive Psychiatry; Preventive Psychiatry; Stigma and Mental Illness; Urban Mental Health; and Women's Mental Health.

The COVID-19 pandemic has proven to be a major challenge to psychiatrists and psychiatric services around the globe, underscoring WPA's role for guidance in these trying times[5]. The WPA has risen to the occasion and launched a web resource providing important information to mental health specialists worldwide, which is continuously updated and offers latest state-of-the art educational material in various languages (www.wpanet.org/covid-19-resources). Sections have been crucial in gathering, collating, reviewing and adapting the various pieces of information.

The ongoing implementation of new, powerful information technology infrastructure, with a newly designed web presence, will greatly benefit the Sections' active participation in WPA's educational and research activities over the next triennium. Sections are encouraged to share their work with the mental health community on WPA's news section on its website (www.wpanet.org/news).

The Secretary's focus over the next three years will lie in making sure that Sections are at the forefront of bringing diversity to the everyday work of WPA. Furthermore, helping members from Sections, in particular from LMIC, to be actively involved in research projects and grant applications will be another major objective of the Secretary's agenda. Finally, the Sections will be encouraged to dedicate a major part of their work to the integration of service users and carers[6].

In summary, over the past three years, the WPA Scientific Sections have shown that they are essential to implementing

WPA's Action Plan[7]; that they are the glue between clinicians, researchers and policy makers; and that they continuously strengthen the bond that connects psychiatrists from every corner of the world to each other and to our common goal, that is promoting mental health and well-being as a human right[8,9].

Thomas G. Schulze
WPA Secretary for Scientific Sections

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WPA activities in the field of publications during the 2017-2020 triennium

During the triennium which is coming to an end, as in the previous ones, the WPA publications were largely dominated by the importance of *World Psychiatry*, its official journal. The influence of this journal has grown enormously since its launch by Mario Maj at the beginning of his term as WPA Secretary for Scientific Publications, in 2002.

Supporting him in his task as Editor of the WPA publications' flagship and in his efforts to lead this journal towards scientific excellence has, since that date, been one of the first priorities of the WPA Action Plans[1] and of its Secretaries for Scientific Publications[2]. To this end, this last triennium focused on an area which we think to be useful: the promotion of *World Psychiatry*'s global dissemination by supporting (or reactivating), as much as possible, its translations in various languages (Arabic, Chinese, French, Portuguese, Russian, Spanish).

This does not mean, of course, that the WPA calls into question the role of English as the current dominant language of science (among other fields), but that it considers one of its duties to reduce, as much as possible, the obstacle that this linguistic dominance generates to many of our colleagues in the world who do not feel comfortable enough with English. Some of the translations of the journal are being produced regularly (in particular, the Spanish and Russian ones). For others, based essentially on the voluntary commitment of actors from Member Societies, the WPA is looking for a way to increase their sustainability.

Considering that, for an organization as international as ours, linguistic diversity is indeed a concern, translation issues have to be considered as well in other types of publications, including books and Internet resources. This question remains to be addressed properly by our organization, but we see some promise in the fact that, based once again on the voluntary efforts of actors from its Member Societies, the WPA has fostered the translation in Russian of various books of its successful Anthology Series: those focusing on German psychiatry, French psychiatry and Russian psychiatry.

Concerning the Internet, we recently took advantage of the renewal of the WPA website[3] to include documents in languages other than English in the resources it offers. A first step was taken recently with the integration of documents in French among those included in the COVID-19 section of the website. The idea of using more systematically in our website the linguistic flexibility of new technology is still to be discussed more thoroughly by our governance. However, we know already that it would certainly boost the use of our website, helping it to become, more and more, a first line channel to provide reliable global resources to the psychiatric community and its partners. The COVID-19 crisis is showing us that this would be particularly helpful for hot or controversial topics, in an era in which they can so easily be contaminated by rumors and fake news.

Another important pending issue of WPA publications is the complexity of their objectives. Beside disseminating, as widely as possible, the scientific advances and recognized good practices in psychiatry, a task so successfully ensured by *World Psychiatry*, the Secretary for Scientific Publications' Action Plan[2] proposed to implement initiatives to address the global inequalities in research visibility and dissemination. Indeed, we believe that it is a duty for the WPA to provide psychiatrists who are less favored by their context with greater opportunities to have their work published and acknowledged. We have to be aware that this problem affects not only researchers from low- and middle-income countries, but also promising colleagues who, even if they work in well-resourced countries, do not do so in contexts that favor regular publications.

In that sense, WPA is a scientific association different from any other. We think that its aim should not be limited to the promotion of scientific excellence, but include as well the support to research and publications in least favored contexts, whatever the reasons of this disadvantage, either "external" (economic, linguistic, cultural or political) or "internal" (related to the topics addressed, which, in spite of their relevance for psychiatric practice, may sometimes be less likely to be published in high impact journals)[2].

In line with this concern, another objective in this triennium has been the diversification of the WPA publications offer. Given that papers in indexed journals whose language is English are currently the best and most agile way for disseminating the results of scientifically valuable research, of various levels, the WPA launched a project of regular co-sponsored thematic issues in global or regional psychiatric jour-

nals[4]. After a very successful experience with the *British Journal of Psychiatry* (a thematic issue on psycho trauma initiated by T. Schulze, our Secretary for Scientific Sections[5]), similar projects are currently in progress in two respected regional journals published in English: the *Brazilian Journal of Psychiatry* (with a thematic issue on cannabis legalization) and the *Asian Pacific Journal of Psychiatry* (with a thematic issue on transcultural psychotherapy). Papers for these issues will soon be collected through international calls for papers. Additionally, our plan is to commission, in each of these issues, a review of the state of the art in mental health and psychiatric research and publications in that specific region.

In the same spirit, the WPA continues to promote the production of books related to its objectives and resources. In this perspective, a new tradition has been established in each of the World Congresses of this triennium: the organization of a session specifically dedicated to the presentation of new books of the year by one of their authors or editors. The project includes loading these books and their presentation, subsequently, in the publication section of the WPA website (www.wpanet.org).

Michel Botbol
WPA Secretary for Scientific Publications

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WPA Action Plan 2020-2023: a way forward

Psychiatry is currently facing several challenges, but there are also many opportunities that can help us consolidate our profession as an inspiring branch of medicine. The WPA is the umbrella organization for psychiatrists worldwide and thus has a major responsibility for leading the profession. The WPA prepares Action Plans for each triennium[1], that provide directions about emerging needs and priorities for the Association's future work from a worldwide perspective.

The proposed Action Plan 2020-2023 specifically looks at areas that need attention and input from various WPA components[2-5]. There is an outstanding need to provide access to high quality mental health care in all countries and to support psychiatrists in their important roles as policy makers, direct service providers, trainers and supporters of health care workers in primary and community health care systems. The recommended plan will work within an international perspective focusing specifically on promotion, interventions, and teaching and training of mental health professionals. It will also build on the previous Action Plan to ensure continuity in the WPA's work[6].

The key features of the next triennium plan include promotion of psychiatry as a medical specialty in clinical, academic and research areas; promoting public mental health as a guiding principle; highlighting the specific role of psychiatrists in working with other professionals in health, legal and social aspects of care; and ensuring the Association's positive engagement with Member Societies and its other components.

Public health is assuming a central role in the delivery of health care, including mental health care[7]. The Action Plan includes raising awareness, acceptance, and prioritization of public mental health in mental health intervention strategies, and ensuring the availability of public mental health training programmes in the general health care systems.

Mental disorders are the single most common cause of disability in young people. First onset of mental disorders usually occurs in childhood or adolescence, although treatment typically starts several years later. The failure to address child and adolescent mental health problems, including developmental and intellectual disorders, especially in low-resource settings, adds significantly to major public health issues and inflicts far-reaching consequences[8].

There are significant gaps in what we know about how best to treat mental illness in children and youth. There is inadequate support for research into developmental neurobiology, the causes of mental illnesses, and the most effective, safest and best-tolerated treatments. Child and adolescent mental health will be a priority, and plans will include supporting epidemiological work exploring the prevalence of mental health problems, promoting early detection for psychosis, and developing crisis intervention centres for adolescents. Parenting interventions for preventing persistent conduct disorders in children, screening for early detection of mental health problems among the young workers, and promoting well-being in the workplace will also be guiding principles of the proposed plan.

Comorbidity is another important issue facing health systems in today's world, including mental health systems. Single disease approaches cannot address this problem appropriately. Comorbidity can be due to increased life expectancy and/or more intense exposure to risk factors, particularly smoking, alcohol abuse, physical inactivity and obesity. Patients with comorbidity face complex physical, social and emotional problems. It is important to address issues of comorbidity as a priority. The Action Plan 2020-2023 will support epidemiological work exploring the prevalence of physical comorbidities in people with mental health problems, and development of guidelines for joint work with non-psychiatrist professionals, early detection of physical comorbid conditions in mentally ill patients, and early recognition of mental health problems in the context of chronic medical illnesses. Strategies for teaching and training psychiatrists and non-psychiatrist colleagues about joint work will be taken as a priority for future work.

The optimal approach to building capacity in mental health care around the world requires partnerships between professional resources and promising health-related institutions. These partnerships need to be

sustainable, develop quality in clinical care and research, and build a productive environment for professionals to advance their knowledge and skills. There are mutual benefits to all stakeholders working jointly if patients are the prime beneficiaries of such efforts. The WPA will, therefore, explore opportunities for partnerships with medical professionals such as general physicians, neurologists, paediatricians, geriatricians, cardiologists, diabetologists and other specialists in medicine, non-governmental organizations, and non-medical mental health organizations.

The World Health Organization declared COVID-19 a public health emergency this year[9]. Since then, it has spread rapidly all over the world. It has created problems for psychiatric patients, particularly those in long-term care facilities. The WPA will work with Member Societies and other organizations to reduce suffering and promote best practice to deal with psychological sufferings in this and similar pandemics[10].

Fostering the continuous improvement of psychiatric education and training among medical students is an equally essential step in this process, and a premier objective of the WPA. Similarly, previous WPA Action Plans, particularly the Action Plan 2017-2020, set out strategies for expanding the contribution of psychiatry to improved mental health across the globe. The unfinished plans formulated in 2017-2020 will be continued through current partnerships and new partners[11].

All areas covered in the proposed Action Plan are of high priority. However, due to time limitations and scarcity of resources, only specific areas may be addressed. During the current triennium, expert working groups are focusing on different areas of the Action Plan[12-15]. Once the findings of these pilot projects are available, we will seek funding to implement these ideas in different settings and countries.

It is hoped that the WPA Action Plan 2020-2023 will generate interest among all WPA components to develop guidelines and directions for future work. The WPA is optimistic that it will receive support, active input, and advice from its membership in setting these priorities and making a real difference in mental health.

Afzal Javed
WPA President-Elect and Chair of WPA Planning Committee 2017-2020

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