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World Psychiatry

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

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Primary psychosis: more to know, much more to do

In this issue of the journal, Maj et al[1] make clear the implications for a field that has turned slowly from concepts of various psychotic disorders as disease entities to recognition of the heterogeneity within each diagnostic group and the shared psychopathology across traditional diagnostic groups.

The concept of "primary psychosis" brings clinical attention to a range of disorders where disorganization of thought and behavior and/or delusional thinking and/or hallucinatory phenomena are prominent, and cases are not easily distinguished by specific causation or mechanism of pathophysiology. With a focus on clinical intervention, the authors make clear the numerous therapeutic targets potentially present and the necessary evaluation of each case with the goal of comprehensive and personalized treatment.

Eighteen leaders of psychosis research, in their words, describe "systematically the salient domains that should be considered in the characterization of the individual patient with primary psychosis aimed at personalization of management". They succeed beautifully, with much to offer everyone. It is a comprehensive guide. I will here provide a view on why this is a remarkable contribution by stating what can be done with the content. Please find yourself below:

- As an experienced and well informed clinician, you will be surprised at a few areas not quite on your radar screen. A gift for you is the information on assessment interviews that you may wish to use, or better understand their value in research, or enable a team member to utilize in order to acquire information otherwise neglected. You will assume integrated care as a mandate.
- As a person in training for a career in mental illness services, you will find in one place a clear and succinct description of what you need to evaluate with each patient and a guide to where you may wish to develop special expertise. The assessment approaches, carefully developed for research, will help clarify each concept and provide a method you may wish to use when evaluating patients.
- As a person responsible for a clinical care program, you will find a clear view of the range of management and treatment expertise that you will need to provide. This will support clinical care staff in understanding potential patient needs and clarify where and what expertise is needed in each case.

The above comments assume available staff, expertise and time. Not likely in most settings. But the material presented can support the effort to develop resources for comprehensive care. Examples are:

- What it would cost to provide the expertise, time and knowledge to support clinical care based on this information. I hope economists will develop models based on this material informing on finance of the necessary services.
- A new view on essential staffing for clinical care will emerge. Training programs will have guidance on essential knowledge and skills to be acquired by trainees.
- Services experts may develop a view as to how to institute personalized care in low and middle income countries.
- In locations already supporting integrative care for the mentally ill, a broader mission may evolve from a heightened awareness of the range of issues in the context of primary psychosis.
- For wealthy countries failing to support accessible and informed clinical care, the content of this report, backed with organizational and financial information, may enable advocates to lobby for full implementation of required structure for comprehensive and personalized clinical care. This is critically important in a country such as the US where clinical care is not accepted as a moral obligation and most persons with psychotic disorders do not have access to care that approaches expectations of this model. The neglect of fundamental clinical care results in large numbers of homeless or imprisoned persons struggling with psychosis. This presentation from experts provides a critical understanding of what is required for personalized medicine related to primary psychosis. This is a powerful information document in the effort to influence leaders responsible for developing and funding clinical care for persons with psychotic illness.
- Services investigators can address comparative clinical and functional outcomes with comprehensive integrative personalized care contrasted with treatment as usual in various settings. Here costs related to housing, employment, hospitalization, prison as well as clinical, functional and quality of life assessments are essential.
- Those involved in the creative acquisition of knowledge aimed at identifying prevention and therapeutic targets on which to base novel treatment advances will find many areas of current scientific neglect. The roadmap for personalized treatment of primary psychosis makes clear that diagnostic categories are not an adequate basis for comprehensive treatment. Antipsychotic drugs, for example, are approved for schizophrenia but have efficacy for only one aspect of the multiple psychopathologies that may be present. But the same drug will be efficacious for that same psychopathology associated with some or many other diagnostic categories. Many of the issues detailed as essential to personalized care in Maj et al's paper may help identify targets for development of novel therapeutics.

There is anticipated "payoff" in science as new concepts guide the effort to understand mechanisms for discreet aspects of psychopathology. The needs addressed by the authors provide many targets. I believe regulatory bodies concerned with drugs and devices are early in a shift from DSM/ICD diagnoses as guiding entities. This shift requires recognition of clinical syndromes with movement to more precise elements of psychopathology as a target for medication or device approval. Syndrome status

was made explicit in the DSM-5 for schizophrenia spectrum disorders. The influence on clinical trials methodology will be profound. Many therapeutic and management approaches must be developed without commercial finance and it will be challenging for funders of public science to adequately address the need for knowledge acquisition in the range of psychopathology essential for broadly integrative care.

This report would be valid if addressing schizophrenia rather than primary psychosis. The authors have given emphasis to transdiagnostic conceptualization of psychopathology related to psychosis. This advance has been unnecessarily slow. A personal milestone is our 1974 paper[2] summarizing data that made clear, to us, that schizophrenia was a clinical syndrome rather than a disease entity. Six aspects of psychopathology were viewed as separate targets for discovery not unique to schizophrenia. However, in 1983, the DSM-III viewed schizophrenia as a disease based on the belief that heterogeneity would be addressed when clinicians used specified symptoms for the diagnosis and gave prominence to Schneiderian first-rank symptoms. It was three decades later that the DSM-5 made explicit the syndrome status and identified dimensions of psychopathology relevant for psychotic illnesses.

A turn to transdiagnostic psychiatry is being supported by the US National Institute of Mental Health's Research Domain Criteria[3]. Very controversial at the outset, the view that dimensions of psychopathology can be investigated across diagnostic boundaries has taken hold. The comparison of schizophrenia patients versus non-ill controls is gradually giving ground to paradigms involving specific aspects of psychopathology with potential relevance across diagnostic boundaries. A nosology with specific diagnoses is necessary for many reasons, and schizophrenia is not an exception. The key is understanding the implications of the diagnosis and the need for a further clinical characterization in order to personalize management.

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From exception to the norm: how mental health interventions have become part and parcel of the humanitarian response

Humanitarian psychiatry is the provision of services for mental health and psychosocial support in a humanitarian context – that is, to populations exposed to collective violence, forced displacement or natural disasters. Unfortunately, humanitarian needs have grown: nearly 80 million are forcibly displaced in the world today, that is one in a hundred people, with diminishing numbers returning home. These figures do not include those with humanitarian needs who are not displaced, but who are also in danger, as for example in Yemen at this time.

When the first author of this paper began her career in humanitarian psychiatry 30 years ago, during the Balkan wars, psychiatry in humanitarian settings focused largely on one diagnosis (post-traumatic stress disorder, PTSD) and individualized medical interventions to prevent and/or address it. She encountered the same approaches in Iraq in 2003, and after the 2004 South-East Asian tsunami[1].

The publication in 2007 of the Inter-Agency Standing Committee (IASC) Guidelines on Mental Health and Psychosocial Support in Emergency Settings heralded a new understanding and a new approach. Namely, that tightly defined psychiatric problems are only part of a spectrum of mental health and psychosocial needs. These may be prevented or mitigated if people's basic needs for food, shelter and security, and their social needs for connection and justice, are addressed in a dignified and equitable manner that respects human rights (see Silove[2] in this issue of the journal).

This requires multi-sectoral action, with different levels of intensity and specialization. Clinical services constitute a modest part of the pyramid of multi-layered mental health and psychosocial services and supports, the others being: a) focused non-specialized psychosocial support, b) strengthening the capacity of individuals, families and communities to support themselves, and c) embedding social and psychological considerations into the way basic needs and security are delivered.

That is not to say that clinical needs are insignificant. The latest World Health Organization (WHO) figures show that more than one in five people in post-conflict settings have depression, anxiety disorder, PTSD, bipolar disorder or schizophrenia[3]. Fortunately, certain barriers to addressing psychiatric disorders in emergency settings have been removed. Prior to 2009, mental health problems were not included in the health information system of the United Nations High Commissioner for Refugees (UNHCR), which meant they were invisible. Since then, the inclusion of seven, and currently nine, mental and neurological categories has highlighted the significance of these conditions[4]. Another problem was that only three psychiatric medications were included in WHO essential drug kits for emergencies. The increase to five in 2011, continued in 2017, has meant that pharmacological treatments are now available in emergencies[5].

The first most significant development of the last decade is the recognition that the provision of essential mental health services is not the exclusive realm of mental health specialists. It can be done by non-specialized health workers, particularly in primary care, if they are well trained and supervised. The development

and rollout, by the WHO and UNHCR, of the Mental Health Gap Action Programme Humanitarian Intervention Guide (mhGAP-HIG) for clinical management of mental, neurological and substance use conditions in humanitarian emergencies has played a pivotal role in making non-specialized, community-based delivery possible[6].

The other main development has been the emergence of a range of brief psychological interventions that can be easily taught to non-specialized staff and community volunteers. These have the potential to be rapidly brought to scale in a relatively cost-effective manner[7]. Many of these interventions have been purposely developed for, and tested in, humanitarian contexts rather than simply being superficial adaptations of existing tools from high-income settings[8].

In addition, other actors and sectors now recognize that addressing mental health is a major component of humanitarian response. In the last decade, mental health has become increasingly engrained within policy documents and guidelines. For example, the Sexual and Gender-Based Violence Clinical Guide now includes a chapter on mental health needs; the UN Children's Fund (UNICEF) emphasizes the need for infant stimulation in food emergencies, and the Child Protection Minimum Standards include mental health and psychosocial support.

The Sphere Handbook, the most authoritative guide for emergency responses, has mental health and psychosocial support integrated throughout. Moreover, the IASC Principals, the highest decision makers for emergencies, in their meeting of December 5, 2019, agreed to "treat mental health and psychosocial support as a cross-cutting issue that has relevance within health, protection, nutrition, education and Camp Coordination and Camp Management sectors/clusters, in all emergencies". The recent UN Global Humanitarian Response Plan for the COVID-19 pandemic contains multiple references to mental health and psychosocial support throughout the document[9]. Three UN agencies (WHO, UNICEF and UNHCR) are developing a Minimum Service Package for mental health and psychosocial support which will include interventions in health and protection for children and adults.

But there are continuing challenges**.** Those with severe pre-existing disorders and learning disabilities are still among the most neglected and underserved groups in emergencies, often languishing in horrifying conditions within asylums or still chained at home or in camps. Humanitarian interventions are still on many occasions only short term and fail to build back better.

Meanwhile, the recent climate related fires and floods and the global COVID-19 pandemic have allowed many people in high-income countries to learn first-hand what it feels like to live in continual stress and have lives turned upside down. This has perhaps created greater understanding of how emergencies affect mental health. Paradoxically, lockdown in the global North has also helped us realize the strengths and abilities of local actors, a point emphasized by a growing international Black Lives Matter movement, that is calling for the decolonizing of humanitarian aid.

Where do we go from here? Our immediate priorities are to improve the care for people with severe mental disorders and learning disabilities through a combination of recovery-oriented community interventions and decent medical treatment; to address the neglected domains of alcohol/substance use and prevention/response to suicidal behaviour; and to foster community-based psychosocial methods that focus on social connectedness and interpersonal "healing". Underpinning all of this is continued support and empowerment of local actors on the ground, including affected persons themselves, and a commitment to listen and learn from them.

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The clinical characterization of the patient with primary psychosis aimed at personalization of management

Mario Maj[1], Jim van Os[2-4], Marc De Hert[5,6], Wolfgang Gaebel[7], Silvana Galderisi[1], Michael F. Green[8,9], Sinan Guloksuz[3,10], Philip D. Harvey[11], Peter B. Jones[12], Dolores Malaspina[13], Patrick McGorry[14,15], Jouko Miettunen[16,17], Robin M. Murray[4], Keith H. Nuechterlein[18], Victor Peralta[19], Graham Thornicroft[20], Ruud van Winkel[3,6,21], Joseph Ventura[8]

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The current management of patients with primary psychosis worldwide is often remarkably stereotyped. In almost all cases an antipsychotic medication is prescribed, with second-generation antipsychotics usually preferred to first-generation ones. Cognitive behavioral therapy is rarely used in the vast majority of countries, although there is evidence to support its efficacy. Psychosocial interventions are often provided, especially in chronic cases, but those applied are frequently not validated by research. Evidence-based family interventions and supported employment programs are seldom implemented in ordinary practice. Although the notion that patients with primary psychosis are at increased risk for cardiovascular diseases and diabetes mellitus is widely shared, it is not frequent that appropriate measures be implemented to address this problem. The view that the management of the patient with primary psychosis should be personalized is endorsed by the vast majority of clinicians, but this personalization is lacking or inadequate in most clinical contexts. Although many mental health services would declare themselves "recovery-oriented", it is not common that a focus on empowerment, identity, meaning and resilience is ensured in ordinary practice. The present paper aims to address this situation. It describes systematically the salient domains that should be considered in the characterization of the individual patient with primary psychosis aimed at personalization of management. These include positive and negative symptom dimensions, other psychopathological components, onset and course, neurocognition and social cognition, neurodevelopmental indicators; social functioning, quality of life and unmet needs; clinical staging, antecedent and concomitant psychiatric conditions, physical comorbidities, family history, history of obstetric complications, early and recent environmental exposures, protective factors and resilience, and internalized stigma. For each domain, simple assessment instruments are identified that could be considered for use in clinical practice and included in standardized decision tools. A management of primary psychosis is encouraged which takes into account all the available treatment modalities whose efficacy is supported by research evidence, selects and modulates them in the individual patient on the basis of the clinical characterization, addresses the patient's needs in terms of employment, housing, self-care, social relationships and education, and offers a focus on identity, meaning and resilience.

Key words: Primary psychosis, schizophrenia, personalization of treatment, psychosocial interventions, recovery, positive dimension, negative dimension, neurocognition, social cognition, social functioning, psychiatric antecedents, psychiatric comorbidities, physical comorbidities, family history, obstetric complications, environmental exposures, protective factors, resilience, practical needs, internalized stigma

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Primary psychoses represent a heterogeneous group of mental disorders that: a) are characterized by delusions and/or hallucinations, along with other clinical manifestations such as disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms (i.e., affective blunting, alogia, asociality, anhedonia or avolition); b) are not due to the effects of a substance or a medication on the central nervous system, and are not secondary to another medical condition (e.g., a brain tumor or an autoimmune disease) or a mood disorder (depression or mania).

Our current diagnostic systems, the DSM-5[1] and the ICD-11[2], include several categories that fulfill the above definition, but neither the list of these categories nor their definition is consistent between the two systems.

In the DSM-5, primary psychoses include schizophrenia, schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, delusional disorder, "other specified schizophrenia spectrum and other psychotic disorder", and "unspecified schizophrenia spectrum and other psychotic disorder". In the ICD-11, primary psychoses (the expression "primary psychotic disorders" is explicitly used in this system) include schizophrenia, acute and transient psychotic disorder, schizoaffective disorder, delusional disorder, and "other primary psychotic disorder".

In the DSM-5, the definition of schizophrenia requires that "continuous signs of the disturbance persist for at least six months", whereas this requirement is absent in the ICD-11 (it is only stated that "symptoms must be present most of the time for a period of one month or more"). As a consequence of this,

the DSM-5 category of schizophreniform disorder (marked by a duration of the disorder of at least one month but less than six months) does not appear in the ICD-11. People with a diagnosis of schizophreniform disorder according to the DSM-5 will be diagnosed as having schizophrenia according to the ICD-11.

Furthermore, social dysfunction is an integral part of the diagnostic criteria for schizophrenia in the DSM-5 ("for a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset")[1], whereas this element is absent in the ICD-11 definition. In the "additional features" subsection of the section on schizophrenia of the ICD-11 diagnostic guidelines, it is indeed specified that "distress and psychosocial impairment are not requirements for a diagnosis of schizophrenia"[2].

The symptomatological criterion for the diagnosis of schizophrenia lists, in both the DSM-5 and ICD-11, delusions, hallucinations, negative symptoms, disorganized thinking, and grossly disorganized behavior. However, the ICD-11 also includes "experiences of influence, passivity or control" (subsumed under the heading of delusions in the DSM-5), and "psychomotor disturbances" (which are part of the item "grossly disorganized or catatonic behavior" in the DSM-5).

Schizoaffective disorder is defined quite differently in the two diagnostic systems. In fact, the longitudinal criterion ("delusions or hallucinations for two or more weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness") is absent in the ICD-11, in which the disorder is just defined by the concurrent fulfillment of the definitional requirements for schizophrenia and a mood episode for at least one month. So, a number of patients will receive a diagnosis of schizoaffective disorder according to the ICD-11 but not the DSM-5.

There are also significant differences in the DSM-5 definition of brief psychotic disorder vs. the ICD-11 characterization of acute and transient psychotic disorder. In particular, the presence of negative symptoms is excluded in the definition of the latter but not the former disorder, and the duration of symptoms is required to be "less than one month" in the DSM-5, while it "does not exceed three months" in the ICD-11. Furthermore, the requirement that "symptoms change rapidly, both in nature and intensity, from day to day or even within a single day" is present in the ICD-11 definition but not in the DSM-5 criteria.

Also due to the above discrepancies, that were already present in the previous editions of the two diagnostic systems, there is no clarity about the prevalence of the individual primary psychotic disorders either in the general population or in clinical settings. What can certainly be argued is that there is a predominant focus on schizophrenia both in research and in clinical practice. For instance, research on neurocognitive impairment has been conducted almost exclusively in patients with a post-DSM-III diagnosis of schizophrenia[3], and its results may not be generalizable to all patients with an ICD-11 diagnosis of schizophrenia or to patients with ICD-11 "other primary psychotic disorder".

On the other hand, the awareness that the term schizophrenia has been traditionally associated with the notion of a poor outcome, and has acquired in ordinary language a derogatory connotation[4], is leading many clinicians and researchers to use the generic term "psychosis" as a synonym for schizophrenia or as equivalent to the expression "primary psychosis". This is generating confusion in the field – e.g., obscuring the need for the differentiation between primary psychosis and substance induced psychosis.

Of note, one of the few comprehensive population-based epidemiological studies available in this area (which used DSM-IV criteria, that are very close to DSM-5 ones)[5] found the lifetime prevalence of all primary psychotic disorders to be 1.94%, while that of schizophrenia was 0.87% (so, according to this study, schizophrenia accounts for just 43.8% of cases of primary psychotic disorder). The lifetime prevalence was 0.32% for schizoaffective disorder, 0.07% for schizophreniform disorder, 0.18% for delusional disorder, 0.05% for brief psychotic disorder, and 0.45% for psychotic disorder not otherwise specified. The lifetime prevalence of affective psychoses was 0.59%, that of substance induced psychotic disorder was 0.42%, and that of psychotic disorder due to a general medical condition was 0.21% (so that schizophrenia accounted for only 26.9% of all cases of psychotic disorder)[5].

The current approach to schizophrenia (or to "psychosis") in routine clinical practice worldwide is often remarkably stereotyped. In almost all cases an antipsychotic medication is prescribed, with second-generation antipsychotics usually preferred to first-generation ones[6]. Cognitive behavioral therapy (CBT) is rarely used in the vast majority of countries, even though there is evidence to support its efficacy[7]. Psychosocial interventions are often provided, especially in patients with chronic illness, but those applied are frequently not validated by research[8]. Evidence-based family interventions[9] and supported employment programmes[10] are seldom implemented in ordinary practice. The notion that patients with schizophrenia (or "psychosis") are at increased risk for several physical diseases and that their life expectancy is dramatically reduced is now widely shared, but it is not frequent that appropriate measures be implemented to address this problem as part of the management plan[11].

The view that the management of a patient with schizophrenia (or "psychosis") should be personalized is endorsed by the vast majority of clinicians, but the awareness that this would require a comprehensive assessment of the patient, beyond the mere diagnosis, is not equally shared, and personalization of management is actually lacking or inadequate in most clinical contexts worldwide[12].

Finally, although many mental health services would declare themselves "recovery-oriented", in practice a resilience-promoting environment is rarely provided, and a focus on the skills that people with primary psychosis need to learn in order to live a fulfilling life despite persistent disabilities is not common[13].

The present paper, which has been produced in parallel with a similar one focusing on depression[14], aims to address the situation we have just described. Its main objectives are: a) to reinforce the emerging awareness of the need to personalize the management of patients with primary psychosis, taking into account all the available treatment modalities whose efficacy is supported by research evidence; b) to help in the identification

of the salient domains to be considered in the characterization of the individual patient with primary psychosis aimed at personalization of management (see Table 1); c) to help in the selection of simple assessment instruments that can already be considered for use in clinical practice today, and can be included in comprehensive batteries of measures to be tested in large observational studies in order to guide the development of standardized decision tools[15]; and d) to encourage a clinical practice that is recovery-oriented as well as evidence-based.

On the basis of the above discussion, we will preferentially use the expression "primary psychosis" throughout the paper, except in those cases in which the available research evidence specifically refers to patients with a post-DSM-III diagnosis of schizophrenia.

We are fully aware that a significant effort is ongoing to identify biological measures or markers that may help in the personalization of the management plan in patients with primary psychosis. However, since none of these measures or markers is currently ready for use in clinical practice, we do not consider them in this paper. On the other hand, we do believe that biological research can benefit from a systematic characterization of patients with primary psychosis, since this is likely to facilitate the identification of more homogeneous subtypes within this group of disorders.

POSITIVE DIMENSION

The conceptualization of the positive dimension as the core of primary psychosis has continuously evolved over the last four decades. There is common agreement that this dimension includes delusions (persistent false beliefs based on an incorrect inference about reality, that are firmly maintained despite obvious contrary evidence, and are not shared by others with a similar cultural background) and hallucinations (perception-like experiences with the clarity and impact of a true perception but without the external stimulation of the relevant sensory organ). Other symptoms – i.e., disorganized thinking (covered in another section of this paper) and self-disturbances – are sometimes regarded as part of this dimension.

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

1. Positive dimension
2. Negative dimension
3. Other psychopathological components
4. Onset and course
5. Neurocognition
6. Social cognition
7. Neurodevelopmental indicators
8. Social functioning, quality of life and unmet needs
9. Clinical staging
10. Antecedent and concomitant psychiatric conditions
11. Physical comorbidities
12. Family history
13. Obstetric complications
14. Early environmental exposures
15. Recent environmental exposures
16. Protective factors / Resilience
17. Internalized stigma

Self-disturbances are alterations in the sense of self as the subject of one's experience and agent of one's actions[16]. They have been hypothesized by some authors to represent the "core Gestalt" of schizophrenia[17]. Empirically, there is evidence for the validity and relevance of self-disturbances from studies using the Examination of Anomalous Self-Experience (EASE)[18]: EASE scores are increased in people with a diagnosis of schizophrenia compared to those with other mental disorders[19]. Anomalous self-experiences have been reported to be among the most common symptoms in the prodromal phase of primary psychosis, and scores on the Inventory of Psychotic-Like Anomalous Self-Experiences (IPASE)[20,21], a self-report measure of minimal self-disturbances, have been found to correlate with those for subclinical positive symptoms as assessed by the Comprehensive Assessment of At Risk Mental States (CAARMS)[22] and the Community Assessment of Psychic Experiences (CAPE)[23].

In the ICD-11[2] (but not in the DSM-5[1]), "experiences of influence, passivity or control" are regarded as a separate symptom from delusions. If these experiences are explained in a delusional manner, then the presence of both these experiences and delusions should be recorded.

The ICD-11 and DSM-5 provide a dimensional assessment of positive symptoms beyond the categorical classification. The ICD-11 enables clinicians to indicate the severity of positive symptoms in patients with primary psychosis using a symptom qualifier, with scores ranging from "0 - not present" to "3 - present and severe", based on patient report or observer rating during the last week. This qualifier combines hallucinations, delusions, disorganized thinking and behavior, and experiences of influence, passivity and control to an overall score indicating the severity of the positive dimension. The ICD-11 also specifies degrees of severity for each of those four symptoms. The DSM-5 contains dimensions of psychosis symptom severity covering hallucinations, delusions and disorganized speech (each rated on a 5-point scale). These measures help to improve clinical decision-making beyond the diagnostic categories and allow the monitoring of course and outcome.

The positive scale of the Positive and Negative Syndrome Scale (PANSS)[24] is the most widely used instrument for the assessment of positive symptoms. The PANSS allows clinicians to rate the severity of seven positive symptoms (delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspiciousness/persecution, and hostility), each on a 7-point scale ranging from "1 -symptom not at all present" to "7 - symptom extremely severe". For these ratings, information from a clinical interview and, if available, other sources (e.g., family members) is used. There is a large body of evidence indicating good reliabil-

ity, validity and sensitivity of the PANSS[25], which is available in several languages. However, the scale contains items that are not clearly part of the positive dimension of primary psychosis (e.g., hostility and excitement).

The PANSS-6[26], an abbreviated version of the PANSS that could be more suitable for use in routine clinical practice, contains a subscale including three items that refer to the positive dimension of primary psychosis: delusions, hallucinations and conceptual disorganization.

Across different instruments and classification systems, clinicians should resort to different sources of information to assess positive symptoms in primary psychosis (i.e., self-report, clinical observations, information provided by care staff or family members). Integrating these sources is particularly necessary when information about longer time periods is required (e.g., to assess whether a person meets the time criterion of six months for schizophrenia according to the DSM-5).

Depending on the illness stage, people with primary psychosis are usually able to reliably report positive symptoms[27]. The assessment of these symptoms may be more problematic in patients lacking insight, where it can be facilitated by the technique of "Socratic questioning"[28], a form of cooperative argumentative dialogue based on asking and answering questions to stimulate critical thinking and to draw out ideas and underlying presuppositions.

The presence of positive symptoms has immediate consequences for an integrated management plan. On the pharmacological side, antipsychotic drug treatment is strongly recommended for people with acute positive symptoms. Although there may be differences among the various antipsychotic drugs regarding their efficacy on positive symptoms[29], these are not sufficiently clear to guide the clinician's choice in the individual case, which is usually based essentially on issues concerning possible side effects. The assessment of the severity of positive symptoms over time, using one of the above-mentioned tools, is crucial to monitor their evolution and to lead, if treatment resistance emerges[30], to the prescription of clozapine.

In patients with a diagnosis of schizophrenia, antipsychotic maintenance treatment (i.e., continuous treatment with the lowest effective dose of oral or long-acting antipsychotic medication) is recommended to prevent relapse[31], although there is not a consensus about how long this treatment should be continued[32,33], due to the lack of randomized controlled trials beyond the second year following the first psychotic episode.

Particularly in acute stages with limited judgement, delusional loss of reality control, and lack of coping with everyday life, positive symptoms may require inpatient care. Close monitoring of positive symptoms and a corresponding adjustment of medication or inpatient admission is always required, in the framework of a person-oriented, individualized and human-rights respecting approach of evidence-based treatment and care.

CBT, in addition to antipsychotic medication, can produce further improvement in positive symptomatology for people with primary psychosis[7]. Considering the type and severity of positive symptoms is crucial to tailor the psychotherapeutic approach accordingly, for example in the presence of disorganized thinking[34]. There are also effective psychotherapeutic interventions for specific positive symptoms (e.g., cognitive therapy for command hallucinations)[35]. Family interventions, including illness education and crisis intervention, can lower the levels of distress and burden associated with positive symptoms in primary psychosis[9].

Positive symptoms have been reported to be associated with cognitive biases, which can be addressed in psychoeducation and may be targeted in CBT. The Cognitive Biases Questionnaire for psychosis (CBQp)[36] measures five specific cognitive biases: jumping-to-conclusions (making firm decisions based on little evidence), intentionalizing (interpreting events or behaviors as deliberate), catastrophizing (worst-case-scenario thinking), emotional reasoning, and dichotomous (i.e., "black or white") thinking.

NEGATIVE DIMENSION

Negative symptoms have long been conceptualized as a core aspect of primary psychosis, especially schizophrenia[37,38], and their treatment is increasingly recognized as an important unmet need. They play a key role in the functional outcome of the disorder[39,40], and largely contribute to the burden that the disorder poses on affected people, their relatives and the society[41]. Unfortunately, so far, most available treatments have shown a limited impact on these symptoms, especially when they are primary and persistent.

According to recent studies and expert opinions[41-44], negative symptoms include five domains, also known as the 5 As: affective blunting, alogia, asociality, anhedonia and avolition.

Affective blunting, more often referred to as blunted affect, is a reduction in the expression of emotion and reactivity to events. It is assessed during the clinical interview by inspecting spontaneous or elicited changes in facial and vocal expressions, as well as the amount of expressive gestures. In the assessment of blunted affect, clinicians should avoid a quite common mistake, i.e. the tendency to include the subjective experience of decreased emotional range or a general decrease in spontaneous movements, as these aspects are non-specific and more relevant to depression.

Alogia refers to a reduction in the quantity of spoken words and the amount of information spontaneously given when answering a question. The person with alogia provides very short answers, with few words strictly needed to answer the question. The poverty of content of speech in the presence of a normal quantity of spoken words is not included in the alogia construct, but is part of the disorganization dimension.

Asociality is a reduction in social interactions and initiative due to indifference or lack of desire for them. The clinician should investigate both the behavioral aspect (e.g., the reduction of interpersonal relationships) and the decreased interest in social bonds.

Anhedonia should be further characterized as consumma-

tory or anticipatory. The former is a reduction in the experience of pleasure during pleasurable activities. The latter involves a reduction in the anticipation of pleasure for future pleasurable activities.

Avolition, also referred to as amotivation or apathy, refers to a poor engagement in any activity due to a lack of interest and motivation. It is important that the examiner evaluates both subject's behavior and internal experience. The clinician can be confident about the presence of avolition when behavior shows poor engagement in activities and the subject does not miss or feel the need to participate in those activities.

From a clinical standpoint, it is important to distinguish primary from secondary negative symptoms. Currently, this distinction remains a major challenge. Suggestions provided hereafter are meant to support clinicians in this effort.

Primary negative symptoms are supposed to stem from the pathophysiological process underlying psychosis. They are often persistent across the different stages of the disorder[45], and do not show a substantial improvement with most treatments available so far. The only head-to-head study supporting the superiority of an antipsychotic drug to treat primary negative symptoms compared cariprazine with risperidone and found the former to be more effective[46]. However, the study was sponsored by the manufacturer and no independent replication is available so far. Results provided by trials exploring the efficacy of drugs with mechanisms different from D2 antagonism or D2/D3 partial agonism (e.g., glutamatergic or dopamine agonists) remain inconclusive[41].

When signs and symptoms resembling negative symptoms are due to other illness dimensions, in particular positive symptoms, depression, extrapyramidal symptoms, sedation, environmental deprivation, or substance use, they are referred to as secondary negative symptoms. In this case, they can improve when the underlying factors are correctly identified and adequately treated.

In case of negative symptoms secondary to positive symptoms, patients may be reluctant to talk and interact with the examiner. They (or others) may report an asocial behavior due to persecutory delusions and/or difficulties in initiating and persisting in goal-directed activities due to engagement in delusional thinking or abnormal perceptions. If this is the case, clinicians should treat positive symptoms aiming at their remission, by using adequate doses of antipsychotics, improving adherence to treatment, and prescribing clozapine in case of failure with at least two other antipsychotics. When treatment leads to an improvement of psychotic symptoms, negative symptoms often improve as well.

Depression may also underlie secondary negative symptoms, such as a reduced range of emotional expression, diminished amount of speech, social withdrawal, anhedonia and lack of motivation. The co-occurrence of sadness, feelings of guilt, and suicidal ideation or attempts strongly suggests that these features are due to depression. In this case, treatment with second-generation antipsychotics should be preferred to first-generation medications, which could worsen depression, and add-on treatment with antidepressants should be considered.

Side effects of antipsychotic drugs, in particular high doses of first-generation antipsychotics, may also produce secondary negative symptoms: akinesia or bradykinesia, for instance, can result in reduced expression and amotivation, due to reduced dopaminergic transmission. The presence of other extrapyramidal side effects (tremor or rigidity, gate instability) can confirm this interpretation and indicate the need to reduce the doses or change the class of antipsychotics (e.g., switching from first- to second-generation drugs or to a D2/D3 partial agonist).

Among non-pharmacological interventions for negative symptoms, preliminary evidence of beneficial effects of social skills training, CBT and cognitive training is available. In particular, there is evidence of superior efficacy of social skills training vs. treatment as usual and active comparators[47,48]. The evidence for CBT is weaker, and trials in large samples of patients with severe negative symptoms, based on CBT approaches specific for those symptoms, are needed[47,49]. Cognitive training, although primarily aimed to treat cognitive dysfunctions, seems to have small to moderate beneficial effects on negative symptoms too[50]. However, a certain degree of overlap between cognitive dysfunctions and negative symptoms does remain, and makes it difficult to draw clear conclusions on the efficacy of this intervention for negative symptoms.

Available evidence also suggests that repetitive transcranial magnetic stimulation (rTMS) of the left prefrontal region may possibly be an effective treatment for patients with negative symptoms that do not improve with other interventions[51].

The relevance of the above non-pharmacological treatments to primary and persistent negative symptoms remains to be tested in controlled trials.

The most widely used instruments for the assessment of negative symptoms are the PANSS[24] and the Scale for the Assessment of Negative Symptoms (SANS)[52]. However, the use of these tools is problematic, due to the inappropriate inclusion of symptoms that are not relevant to the negative dimension (e.g., difficulty in abstract thinking and stereotyped thinking in the PANSS).

Two state-of-the-art instruments, the Brief Negative Symptom Scale (BNSS)[53] and the Comprehensive Assessment of Negative Symptoms (CAINS)[54], are increasingly used in research settings, but unfortunately their dissemination to clinical practice is still limited. Neither scale contains irrelevant items; both focus on inner experience in addition to behavioral aspects, and allow the assessment of anticipatory and consummatory anhedonia. For both instruments, training is advisable and can be conducted online.

The BNSS consists of 13 items covering the five domains of blunted affect, alogia, asociality, anhedonia and avolition. The scale has been found to have an excellent inter-rater and test-retest reliability and a strong internal consistency[53]. The CAINS also has 13 items, loading on two modestly correlated subscales: expression and motivation/pleasure. The former has been found to be related to independent living and family functioning, while the latter has been related to all aspects of functioning. The inter-rater and test-retest reliability of the tool has been documented[54].

Clinicians often express the desire for an instrument specifically designed for clinical assessment, and taking less time than either BNSS (about 20 min) or CAINS (about 35 min). Unfortunately, for the time being, no tool is available that provides an accurate and at the same time shorter assessment of negative symptoms.

OTHER PSYCHOPATHOLOGICAL COMPONENTS

Psychopathological components of primary psychosis other than positive and negative symptoms include disorganization, motor disturbances, mood states, and lack of insight.

The disorganization component of primary psychosis comprises positive formal thought disorders (thought disorganization), bizarre behavior, and inappropriate affect. From a network perspective, disorganization has been reported to be the most central and interconnected domain of psychotic disorders[55]. It is strongly related to neurocognition and represents an integral link in cognitive pathways[56], although this association may be due to some conceptual overlap with neuropsychological constructs such as abstraction and attention. Formal thought disorders appear to be the psychotic symptoms whose contribution to everyday functioning is most significant[57].

There is a lack of specific instruments for assessing the various subcomponents of disorganization, yet they can be reliably derived from wide-ranging scales such as the Comprehensive Assessment of Symptoms and History (CASH)[58] and the Manual for Assessment and Documentation of Psychopathology (AMDP)[59]. Formal thought disorders, the core manifestations of disorganization, are reliably evaluated by the positive formal thought disorder subscale from the CASH and, more comprehensively, by the Thought, Language and Communication (TLC) rating scale[60].

Disorganization symptoms tend to co-vary with positive symptoms during acute psychotic episodes, and with negative symptoms in chronic schizophrenia. There is no specific pharmacological treatment for these symptoms, although they respond well to antipsychotic medication during the acute phases of primary psychosis. In chronic stages, disorganization symptoms appear to be better addressed by psychosocial rehabilitation programs, although controlled trials thereof are lacking.

Motor abnormalities comprise a broad array of manifestations that are usually subdivided into two overlapping subdomains: catatonia and extrapyramidal signs (EPS). EPS are usually linked with side effects of antipsychotics; however, they may also be an indigenous feature of primary psychosis, the so-called spontaneous EPS, which are tied to the underlying pathophysiology of the illness. Spontaneous EPS are observed in 15-25% of drug-naïve subjects with schizophrenia spectrum disorders; hence, it would be useful to assess motor abnormalities before and after starting antipsychotic medication, to disentangle their primary or secondary origin. Such a differentiation, however, may be challenging even for experienced clinicians. Currently, a balanced view of motor signs in subjects on antipsychotics is that they result from an interaction between medication and illness-related factors[61].

Motor signs are poorly represented in the assessment instruments for psychosis; thus, it is necessary to make use of specific tools. For catatonia, the Bush-Francis Catatonia Rating Scale[62] is preferred for routine use, because of its validity, reliability and ease of administration. For dyskinesia and parkinsonism, the most commonly used instruments are the Abnormal Involuntary Movement Scale[63] and the Simpson-Angus Scale[64], respectively. The St. Hans Rating Scale for Extrapyramidal Syndromes[65] rates comprehensively all EPS, including dyskinesia, parkinsonism, akathisia and dystonia.

Acute and severe catatonia is best managed using electroconvulsive therapy, although less severe catatonia symptoms may respond to benzodiazepines or second-generation antipsychotics. Established drug-induced EPS should be managed by reducing or changing antipsychotic medication, particularly in subjects treated with first-generation antipsychotics. In this regard, clozapine and quetiapine are among the second-generation antipsychotics with the lowest risk of producing neurological side effects[66].

Major mood symptoms are found in about 30% of cases of primary psychosis during an index episode, and their prevalence rate reaches 70% when lifetime mood ratings are considered[67].

A frequent diagnostic problem during an acute episode is the differentiation between mood disorders with psychotic features and primary psychosis[68]. In this regard, examining the temporal pattern of the association between psychotic and mood syndromes, and using specific mood rating scales that do not include psychotic symptoms, are highly desirable. The Calgary Depression Scale for Schizophrenia[69] is the best option for assessing depression in the context of psychotic symptoms. Unfortunately, a similar instrument does not exist for mania, since all available mania rating scales also include psychotic symptoms to some degree. The mania subscale from the CASH[58] may be reliably used. The relevance of mood symptoms for the management plan in primary psychosis is discussed elsewhere in this paper.

Lack of insight is a hallmark feature of primary psychosis, entailing three relatively overlapping subcomponents: awareness of symptoms, awareness of illness, and collaboration with treatment. Poor insight is strongly related to reality distortion and disorganization symptoms; in contrast, higher cognitive ability and depressive symptoms are associated with better insight. Poor insight has important clinical and management implications, since it is associated with a number of interrelated factors, including longer duration of untreated psychosis, poor collaboration with treatment, and aggressiveness, all of which result in poor outcomes[70].

The standard instrument for assessing clinical insight is the Scale to Assess Unawareness of Mental Disorder[71]. This scale, however, may be too time-consuming for use in routine clinical practice. An alternative option is to use the three AMDP[59] items covering the insight domains referred to above.

Recently, a distinction has been made between clinical insight and cognitive insight, the latter describing the subject's flexibility towards his/her beliefs, judgments and experiences. The self-report Beck Cognitive Insight Scale[72] examines two subcom-

ponents of cognitive insight: self-certainty (i.e., overconfidence in the validity of one's beliefs) and self-reflectiveness (i.e., capacity and willingness to observe one's mental productions and to consider alternative explanations). These two distinct but related aspects of cognitive insight in psychosis appear to be differentially associated with clinical insight, symptoms and functioning.

During an acute episode, improvement of insight co-varies with improvement of psychotic symptoms. However, in a substantial proportion of subjects with chronic schizophrenia, lack of insight may represent a major therapeutic challenge. Insight-focused CBT is often recommended, although research findings are conflicting about its efficacy. Metacognitive reflection and insight therapy (MERIT), an individual psychotherapy seeking to enhance the reflective capacity necessary for people who have experienced severe mental illness to form a complex and integrated sense of self and others, has been proposed as an alternative[70].

Depressive symptoms and the presence of insight are associated with a higher risk for suicide in patients with primary psychosis. Being young, male and with a high level of education, prior suicide attempts, active hallucinations and delusions, a family history of suicide, and comorbid substance abuse are also positively associated with later suicide, while the only consistent protective factor is delivery of and adherence to effective treatment[73]. The Columbia-Suicide Severity Rating Scale[74] is a validated tool for the assessment of suicide risk, whose administration requires a specific training that is available online.

Sleep disturbances, in particular insomnia, are common in persons with primary psychosis[75], and can have a significant impact on their quality of life[76]. Their presence should be explored in the clinical characterization of the individual patient, because they can be targeted in CBT and considered in the choice of the antipsychotic medication. Furthermore, obstructive sleep apnea has been reported to be more frequent in these patients than in the general population, and can be related to the dosage of the antipsychotic medication[77].

ONSET AND COURSE

The onset of primary psychosis usually occurs in adolescence or early adulthood[78]. On average, men are diagnosed in their late teens to early twenties, whilst women tend to get diagnosed in their late twenties to early thirties.

Onset of primary psychosis should be distinguished from the expression of premorbid developmental alterations in the domains of cognition, motor function and social adjustment. Follow-back studies indicate that the first changes often involve affective and negative symptoms, appearing years before diagnosis. Positive symptoms emerge later and typically trigger contact with mental health services. Indicators of social disability appear 2-4 years before onset. Cannabis use is associated with an earlier onset of psychosis.

Onset can be considered as a three-stage process, consisting of: a) a prodrome, in which a period of non-specific "unease" precedes "non-diagnostic" symptoms in the form of disturbances of perceptions, beliefs, cognition, affect and behavior; b) first expression of psychotic symptoms; and c) increase in characteristic symptoms resulting in a definite diagnosis. The prodrome can be absent or not identifiable in several patients.

The Nottingham Onset Schedule (NOS) is a short guided interview and rating schedule to assess onset in psychosis, defined as the time between the first changes in mental state and behavior to the appearance of psychotic symptoms[79]. Other instruments providing comparable onset assessment are the CASH[58] and the Symptom Onset in Schizophrenia (SOS) inventory[80].

The International Pilot Study of Schizophrenia[81] categorized mode of onset into three groups: a) acute (psychotic symptoms appear within hours, one week or one month since first noticeable behavioral change); b) gradual (psychotic symptoms appear within one to six months since first noticeable behavioral change); and c) insidious (psychotic symptoms appear incrementally over a period of six months or greater since first noticeable behavioral change). There is some evidence that the insidious mode of onset is associated with poorer and the acute onset with better outcome.

The course of primary psychosis after onset is highly variable both within and between patients. There is a broad range of possible course patterns, ranging from complete recovery to continuous unremitting psychopathology, cognitive alterations and social disability. Between such extremes, a substantial number of patients present with multiple episodes of psychosis interspersed with partial remission[82]. On average, within the primary psychosis syndrome, patients with a diagnosis of schizophrenia have the poorest outcome, with schizoaffective patients occupying an intermediate position between schizophrenia and affective psychosis[83]. Patients diagnosed using a broad definition of schizophrenia generally have better outcomes than those diagnosed with narrowly defined (post-DSM-III) schizophrenia.

The Life Chart Schedule[84] was designed to assess the course of psychotic disorder in four key domains (symptoms, treatment, residence and work) over several time periods. Course type can be rated as episodic (no episode longer than six months), continuous (no remission longer than six months), neither episodic nor continuous, and not psychotic in this period. Type of remission can be coded as "mainly complete", "mainly incomplete" and "mixed". A "usual severity of symptoms" rating is made to indicate the symptomatic level of the patient during most of the period under observation. Ratings are "severe", "moderate", "mild" and "recovered". The amount of time spent in a psychotic state is also rated, as are parasuicidal acts and instances of assault. A rating is also given as to whether there was clear evidence of negative symptoms over the period under observation. In addition, the life chart rates the proportion of the period spent unemployed (time in institutions not counted; full-time students and housewives rated as employed), living independently, in hospital, in prison, or without accommodation. In addition, treatment variables over time (hospitalization, use of antipsychotic medication, other interventions) are recorded.

In a given patient with a given length of illness, the assessment of preceding course is essential, because it allows for the forma-

tion of hypotheses about the effectiveness of treatment across different outcome domains to date. The first five years of the illness are considered "critical", referring to the hypothesis that early energetic treatment may causally impact on the later course of the syndrome. After the first episode, around 90% of patients will experience a remission of symptoms. After five years, however, 80% will have experienced one or more relapses. With each episode, a small proportion of patients will develop a continuous illness course, displaying a mix of persistent positive and negative symptoms, cognitive difficulties and catatonia. Over the course of five years, around 40% of patients with primary psychosis can be expected to show "good" outcome (with 15% showing complete recovery), 20% "poor" outcome, and 40% "intermediate" outcome[85]. Thus, assessment of course to date is necessary to place the patient at the right position on dimensions of illness episodicity and inter-episode recoverability, thus informing continued clinical management.

After the first ten years after onset, the illness course tends to plateau. Cross-sectional outcome measures of psychopathology do not differ substantially according to study duration, suggesting that there is no clear pattern of deterioration or "progression", although this may occur in a subgroup of patients. Careful assessment of course over time in a patient with long duration of illness can reveal signs of progression and possible reasons thereof.

Course and outcome cannot be defined unidimensionally. For patients, the most important outcome, apart from societal participation (education, work, housing, relationships), is restoration of perspective, in the sense of feeling that life is meaningful and worth living (existential recovery)[86]. The Recovery Assessment Scale can be used to evaluate the course of existential recovery over the period preceding the assessment[87]. This evaluation is essential, as it provides information on the causes of variation and the possible role of the health system herein, including unintended iatrogenic hopelessness, antipsychotic polypharmacy, and post-traumatic stress after admission. These may be counteracted by facilitating peer-supported interventions focusing on hope, connectedness, identity, meaning and empowerment.

Over time, patients (and their environment) learn about their mental vulnerability, the relativity of formal diagnosis, the limitations of treatment, the gaps in knowledge, and the weak spots in local service provision. As a result, they become more involved in and opinionated about treatment and services[88], so that the process of shared decision-making becomes even more essential. It is therefore important to assess, before planning the clinical management, the preceding course of decision-making about diagnosis and treatment, and the experience to date in being able to experiment with dosing and even discontinuation of antipsychotic treatment, to engage in alternative therapies and in general to take risks in pursuit of life goals.

In order to be able to deal with an intense mental vulnerability, characterized by an often unpredictable waxing and waning expression over time, a long-term therapeutic relationship of trust and mutual commitment is essential. Assessment of course, therefore, should include the quality and level of therapeutic continuity over time, and its impact on outcome to date.

NEUROCOGNITION

Neurocognitive alterations have been identified as a key component of schizophrenia since the clinical observations of Bleuler and Kraepelin, but they have gained much more clinical and research attention in recent years[3,89]. These alterations are present in many cases years before the first psychotic episode[90], persist into clinical remission[91], and may be present in a milder form in first-degree relatives of patients[92].

As the role of neurocognitive alterations in predicting and influencing everyday functioning in people with schizophrenia became more widely recognized[93], the US National Institute of Mental Health promoted the development of a consensus on the major dimensions of this neurocognitive impairment, their measurement in clinical trials, and the design of trials to evaluate potential treatments[94]. This initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), led to the identification of seven major dimensions: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and verbal comprehension[95].

Speed of processing refers to the speed with which simple perceptual and motor tasks can be performed, which is believed to reflect the pace of cognitive processing. Attention/vigilance refers to sustaining a focus on relevant information over a prolonged period of time. Working memory involves temporary maintenance and manipulation of information in consciousness, usually over a few seconds. Verbal learning and memory refers to the initial encoding and later recognition and recall of words and other information involving language. Visual learning and memory involves similar encoding, recognition and recall processes for visuospatial information such as shape, color, spatial orientation, and movement.

Reasoning and problem solving refers to processes of strategic and logical thinking, planning, formation and maintenance of goals, and coordinating these processes flexibly over time. Reasoning and problem-solving abilities are sometimes also called executive processes. Finally, verbal comprehension refers to verbal information that is accumulated over many years and stored in a widely distributed neural network, such as vocabulary and common shared information in a culture.

While all of these dimensions are impaired in schizophrenia, the MATRICS Neurocognition Committee concluded that verbal comprehension is not likely to be impacted to a notable degree by pharmacological or psychosocial interventions and is therefore less relevant as a focus for clinical trial or clinical practice assessment.

The typical person with a post-DSM-III diagnosis of schizophrenia scores between 0.75 and 2.00 standard deviations below community samples of similar age and gender on each of these neurocognitive domains[96], which corresponds to a percentile

between 2% and 24%. Thus, the cognitive alterations, on average, are large and generalized across cognitive domains, with perhaps larger alterations in speed of processing than in other domains[97]. While the overall picture is one of a generalized impairment across neurocognitive domains, there is also notable heterogeneity in the profile of alterations from one patient to the next, which may to some extent also be due to a different impact of interfering factors such as disturbances in motivation and emotion[3,98]. The variability in neurocognitive performance is likely to be even higher in patients fulfilling the broader ICD-10/ICD-11 definition of schizophrenia and in those with ICD-10/ICD-11 "other primary psychotic disorder", although no research evidence is available in this respect. The clinical importance of these domains of neurocognitive impairment is very clear, as each one is significantly related to the level of work/school and social recovery that a patient is able to achieve[99,100].

In clinical practice, the options for assessing neurocognitive alterations fall into three categories: comprehensive cognitive performance assessment, brief cognitive performance assessment, and interview-based measures of cognition.

Comprehensive cognitive performance assessment batteries allow the clinician to identify the individual profile across the six neurocognitive domains, and to plan tailored interventions and clinical management accordingly. The MATRICS Consensus Cognitive Battery (MCCB) was developed through a systematic expert consensus process, and measures each of the domains with tests that are reliable, repeatable and sensitive to change[101]. It requires about 65 min to administer and yields standardized scores for each cognitive domain and for a neurocognitive composite across domains[102]. Other well-developed comprehensive batteries include the Cambridge Neuropsychological Test Automated Battery (CANTAB)[103] and the CogState[104], both of which consist of reliable, repeatable measures of most or all MATRICS neurocognitive domains.

The disadvantages of these comprehensive batteries for clinical practice are that they are relatively lengthy and require adequate professional training for administration and interpretation. An alternative would be to complete one of these batteries at initial assessment and then choose one to three of their tests for tracking change based on the initial profile of neurocognitive alterations.

Brief cognitive performance assessments have the advantage of being less time-consuming, while still allowing changes in at least overall cognitive performance to be evaluated over time. The Brief Assessment of Cognition in Schizophrenia (BACS)[105] involves six tests and 35 min for administration, while the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[106] covers five cognitive domains in about 30 min. Both yield reliable and valid measures of global cognitive functioning that correlate well with overall scores from comprehensive batteries, as well as some information about the pattern of alterations.

Even shorter cognitive screening measures include the 15-min Brief Cognitive Assessment[107] and the 10-min Brief Cognitive Assessment Tool for Schizophrenia (B-CATS)[108]. Both of these brief tools yield a global cognitive score that correlates well with comprehensive battery composite scores, but they do not allow any pattern of alterations to be evaluated. All of these measures still require professional training, but less than the comprehensive batteries.

Finally, interview-based measures of cognition are intuitively attractive for ordinary practice, as clinicians are accustomed to interview formats and can more easily adapt to their administration. The Cognitive Assessment Interview (CAI)[109] requires 15 min to administer, and has high test-retest reliability and moderate relationships to performance-based cognitive measures and everyday functioning. The Schizophrenia Cognition Rating Scale (SCoRS)[110] also takes about 15 min per interview, has good test-retest reliability, and moderate relationships with cognitive performance measures and everyday functioning. The SCoRS yields stronger relationships when an informant is used rather than solely a patient interview.

Both these interview-based measures of cognition require some training. While both yield an overall cognitive score, the relationship of these scores to cognitive performance measures is weaker than the interrelationship of cognitive performance measures to each other. They also do not provide a reliable pattern of alterations across cognitive domains.

Given the clear influence of neurocognitive alterations on everyday functioning in primary psychosis, the importance of treatment plans that address these alterations is increasingly recognized. Although attempts to develop cognition-enhancing adjunctive medications have promise for the future, so far cognitive remediation[111], aerobic exercise[112], and perhaps their combination[113] are most relevant for clinical practice.

Aerobic exercise has thus far been shown to improve overall neurocognition and specifically attention/vigilance and working memory[112]. Cognitive remediation produces moderate gains in overall cognition and several cognitive domains, with larger neurocognitive and everyday functioning improvements being achieved when it is implemented in the context of active rehabilitation programs[111]. Emerging evidence indicates that forms of cognitive remediation that emphasize perceptual processes vs. higher-level executive processes impact on different neurophysiological mechanisms[114]. Furthermore, perceptual training may be beneficial only for patients with initial perceptual processing impairments[115].

Thus, beyond assessment of the level of overall cognitive impairment, identifying neurocognitive domains with particularly severe alterations is becoming of increasing importance in the clinical characterization of the patient with primary psychosis.

SOCIAL COGNITION

Social cognition refers to mental operations needed to perceive, interpret and process information for adaptive social interactions. The term encompasses a very broad range of domains. In the context of primary psychosis, most of the attention has focused on four aspects of social cognition: emotion identification, mentalizing, social perception, and attributional bias[3,116].

Emotion identification includes one's ability to perceive emotion in faces, voice intonation, gestures or gait. Mentalizing refers to the ability to infer intentions or beliefs of others, such as whether they are being sincere, sarcastic or deceptive. Social perception refers to the ability to identify social roles, social rules and social contexts from various cues. Individuals with a post-DSM-III diagnosis of schizophrenia have alterations on all three of these aspects of social cognition based on performance-based measures[117], although this notion may not be generalizable to all patients fulfilling the broader ICD-11 definition of schizophrenia or to those with ICD-11 "other primary psychotic disorder".

Attributional bias refers to how individuals typically infer the causes of particular positive and negative events (e.g., having a tendency to attribute hostile intentions to others). Unlike the other social cognitive areas, people with schizophrenia do not consistently show differences in attributional bias compared with healthy individuals[117,118].

Social cognition is relevant to the management of primary psychosis because it is associated with functional outcome[100]. Consistent associations between social cognitive domains and community functioning have been reported in schizophrenia, with mentalizing showing the strongest relationship in one meta-analysis[100]. Further, social cognition explained more variance in community functioning than did nonsocial cognition (16% vs. 6%). Thus, social cognition is a key correlate and determinant of functional outcome in primary psychosis, and can help clinicians to form realistic expectations for how the individual patient might integrate in the community, or how much additional support he/she may need to do so.

Given its relevance for functional outcome, there have been considerable efforts, and some encouraging progress, in developing psychosocial training interventions for social cognition in primary psychosis. These interventions are typically interactive and group-based, and include a variety of visual, auditory and video stimuli depicting social stimuli. Recently, individual computerized interventions have also been developed[119]. One meta-analysis of 16 studies[120] found improvements of large effect sizes in facial affect identification (d=.84), mentalizing (d=.70), and social perception (d=1.29). The impact of these interventions on functional outcome has been encouraging, though not consistent across studies[121].

Beyond psychosocial training interventions, there are considerable efforts to examine the impact of intranasal oxytocin (using single or repeated administration strategies) on social cognitive tasks. Here, however, the results in patients with a diagnosis of schizophrenia have been mixed, with both positive and negative findings[122]. Another approach has been to examine oxytocin as an augmentation during social cognitive training programs, and again the results have been mixed[123].

Measurement of social cognition in primary psychosis has been a daunting challenge. The measurement problems apply to both clinical trials and ordinary practice. Regarding clinical trials, there is no consensus on a battery of social cognition outcome measures, or even a set of social cognitive domains. A highly diverse range of outcome measures have been used in treatment studies, and they often have poor or unknown psychometric properties.

Considering the lack of psychometric information on potential social cognitive endpoints for clinical trials of psychosis, the US National Institute of Mental Health supported two method-development projects. One project focused on evaluation of social cognitive measures that were in current use in psychopathology[124], while the other adapted measures from social neuroscience and evaluated their application to people with psychosis[125]. Both projects produced a rich data set and a series of recommendations for endpoints in clinical trials. Despite these efforts, there is no widely-used battery for measurement of social cognition in clinical trials.

The absence of such standardization means that results from trials vary depending on the specific outcome measure[126]. For example, the majority of studies that found treatment effects for mentalizing used very simple tasks or questionnaires. However, a more challenging and ecologically valid test is The Awareness of Social Inference Test (TASIT)[127], which has good psychometric properties. This test uses video vignettes, and participants are asked to detect lies and sarcasm. Studies using this test have generally failed to find treatment effects. A similar pattern was seen for the domain of social perception. If more challenging and psychometrically stronger measures tend to show smaller or negative findings, this raises questions about the strength of treatment effects for certain domains.

In contrast, other aspects of social cognition, such as facial affect perception, show treatment effects regardless of the specific outcome measure. Attributional bias presents a different measurement issue: there are very few available measures for this domain, and the current ones do not have strong psychometric properties[124].

The situation for the assessment of social cognition in clinical practice is similarly problematic. In contrast to nonsocial cognition, social cognition does not have a long history of clinical evaluation with standardized and highly reliable measures. Partly due to this historical lack of emphasis, it is rarely evaluated in routine cognitive or neuropsychological assessments.

This situation is going to change. Some innovative and interpretable tests of emotion processing are emerging, including an emotion processing battery with a large normative sample, the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)[128]. Also, some social cognitive domains lend themselves to brief assessments that do not require expertise in test administration. For example, there are a large number of tests for facial or vocal emotion perception that are easy to administer and do not depend on language (i.e., could be used cross-nationally)[129].

Nonetheless, at the current time, measurement remains the Achilles' heel of social cognition. Social cognition is an important and functionally meaningful aspect in primary psychosis, but it has not yet moved into broad clinical application.

NEURODEVELOPMENTAL INDICATORS

The neurodevelopmental understanding of primary psychosis has evolved along the decades, from Kraepelin's remarks[130] on the developmental differences in children who as adults would

manifest dementia praecox; to the contributions of Fish[131], who recognized a continuity between infant development and risk of early psychosis; Weinberger[132], who postulated an early genetic or environmental insult to the developing brain interacting with normal adolescent development; and Murray and Lewis[133], who proposed a subtype of schizophrenia being a long-term sequela of obstetric injury.

Subsequently, evidence has accrued with epidemiological research using prospective information, particularly from birth cohorts and population registers, to support wide-ranging manifestations of neurodevelopmental effects in primary psychosis. Indeed, the incidence of primary psychosis peaks between puberty and the mid-twenties, an epoch of renewed grey and white matter changes and a sensitive period for psychosocial development.

Earlier neurodevelopmental indicators in primary psychosis are highly relevant to clinical practice. They include a history of delayed or reduced acquisition of early childhood motor and language skills, atypical age-appropriate social interaction, and lower IQ and school attainment throughout childhood and adolescence[134-137]. Furthermore, soft neurological signs have a prevalence of 50-65% in people with a diagnosis of schizophrenia (compared with 5% in healthy controls)[138]. All these elements offer a window on neurodevelopment, as well as informing clinical management and prognosis.

Soft neurological signs include dysgraphaesthesia (the inability to recognize writing on the skin through touch alone), diminished motor coordination, and problems with complex motor sequencing (such as dysdiadochokinaesia, an impairment in rapid alternating movements). They also encompass persistence of infantile (primitive) reflexes such as the palmomental response (reflex contraction of the mentalis muscle leading to pouting of the lower lip when the palm is scratched), increased blink rate, and a positive glabellar tap (no habituation of blinking when the glabella is tapped).

Soft neurological signs are readily understandable in terms of distributed or circuit dysfunction rather than a localized lesion. They are present from early in development and most likely share the same underlying network-based mechanisms as the pandysmaturation reported in genetically high-risk children[139] and the early motor and language milestone delays seen more broadly in primary psychosis.

Minor physical anomalies (i.e., dysmorphic features representing subtle alterations in the development of somatic structures) have also been observed in some patients with a diagnosis of schizophrenia, with high-arched palate being particularly common (20-25% of patients)[140].

Consideration of neurodevelopmental indicators is important in the clinical assessment of a patient with primary psychosis. Their presence helps to confirm the diagnosis where other phenomenology is scant (e.g., presentations with catatonia or mutism) or where a secondary psychosis is a realistic differential. They can be seen as direct precursors of negative symptoms such as alogia, affective blunting and asociality, and of cognitive alterations. These aspects are challenging to manage clinically, and presage poorer outcome.

The identification of neurodevelopmental markers may support a causal formulation in an individual patient, particularly where there has been obvious obstetric mishap or early trauma such as pre- or neonatal infection. They also illuminate an individual patient's psychosocial life history whereby developmental differences from childhood peers is likely to have created an altered social microenvironment during development and a cascade of abnormal experiences[134], something that needs accommodation in a management plan aiming at functional recovery.

It is also important to assess whether neurodevelopmental indicators are present to such an extent that an alternative diagnosis is more appropriate, such as psychotic phenomena in the context of an autistic spectrum disorder or a learning disability syndrome, particularly where the psychosis itself is similar to a primary syndrome[141] but is treatment resistant[142]. These classical neurodevelopmental disorders may remain undiagnosed into early adulthood and present atypically.

Further investigations, including evaluation by a clinical geneticist, may be required where there are multiple minor physical anomalies or when, collectively, they suggest a specific genetic condition such as velocardiofacial syndrome. Even where the observed picture does not meet diagnostic criteria for a neurodevelopmental disorder, advice from clinicians experienced in these fields can be useful, given the transdiagnostic occurrence of psychotic and neurodevelopmental features[143].

The evaluation of soft neurological signs should be part of the full neurological examination required in every patient with primary psychosis[144], but there are scales intended for both clinical and research practice that can be helpful. The Cambridge Neurological Inventory[145] was developed for the full range of psychiatric conditions and is applicable to primary psychosis. In this inventory, the second part focuses on soft sign examination (primitive reflexes, repetitive sequential motor execution, and sensory integration). The longer Neurological Evaluation Scale[146] focuses on schizophrenia. It includes 26 items, clustered into three subscales (sensory integration, motor coordination, and sequencing of complex motor acts).

The systematic assessment of childhood neurodevelopmental indicators presents a particular challenge in primary psychosis. Effects seen in research using prospective data may be subtle (standing, walking or speech delayed by four to six weeks) and would have been barely noticeable at the time, given the wide range of normal experience, or may simply have been forgotten, even by parents. Contemporary health or school records may be sought, if available. Despite these caveats, inquiry into the developmental history is important.

The Premorbid Adjustment Scale (PAS)[147,148] evaluates the level of functioning in four major areas (social accessibility - isolation, peer relationships, ability to function outside the nuclear family, and capacity to form intimate socio-sexual ties) at each of four periods of the subject's life: childhood (up to 11 years), early adolescence (12-15 years), late adolescence (16-18 years), and adulthood (19 years and beyond). The final section contains items estimating the highest level of functioning that the

subject achieved before becoming ill. The scale is intended to measure only "premorbid" functioning, and its questions have been updated to discount the entire year before the first psychiatric contact, in order to accommodate contemporary focus on early detection and intervention[148]. Ratings are based on reports from family members or clinical records. When it is felt that the patient is reliable, a personal interview may be conducted to complete the ratings. The scoring for each item ranges from "0", corresponding to the healthiest end of the adjustment range, to "6", corresponding to the least healthy end. Asking informants to compare and contrast with the patient's siblings is often helpful.

Overall, consideration of neurodevelopmental indicators can be useful to obtain a more complete characterization of the patient with primary psychosis, help in differential diagnosis, and contribute to the formulation of a more comprehensive and targeted management plan.

SOCIAL FUNCTIONING, QUALITY OF LIFE AND UNMET NEEDS

Impairments of social functioning in schizophrenia have been described since the time of Kraepelin[130]. Social functioning is a broad term, which includes milestones such as marriage or equivalent relationships, social interactions such as friendships, as well as social skills and social motivation. Further, social functioning is related to quality of life, the definition and assessment of which have been complex and occasionally obscured in research on primary psychosis.

Impairments of social functioning in patients with a post-DSM-III diagnosis of schizophrenia have several features. People with this disorder are much less likely than the general population to experience marriage or equivalent milestones[149]. They also have smaller social networks, and are likely to nominate a clinician as the person who knows them best[110]. The generalizability of these findings to all patients fulfilling the broader ICD-11 definition of schizophrenia or to those with ICD-11 "other primary psychotic disorder" remains uncertain.

Social anhedonia is the phenomenon whereby people with schizophrenia experience less pleasure from social interactions and manifest reduced interest in these interactions. In fact, many of them rarely leave their homes, being home as much as 70% or more of the time[150]. It is a complex phenomenon, because there is evidence that individuals with schizophrenia enjoy social activities as much as healthy individuals at the time of the experience, but have challenges in recalling this enjoyment in order to motivate later interactions[151].

Another feature of social functioning in schizophrenia is an impairment in social skills or social competence. Many people with this disorder have reduced ability to interact with others and may make socially inappropriate statements or gestures[152]. These problems make interactions challenging and may reduce the willingness of others to engage with them.

In addition to data on current social functioning, the assessment needs to consider motivation to engage in social activities, the level of social competence, and the individuals' evaluation of their ability compared to objective information (social milestones). Understanding the level of social motivation will be critical for the development of treatment strategies, as social skills training will not improve social outcomes in people who have no plans to engage in social activities[153], and targeted treatment aimed at negative symptoms associated with poor social outcomes is now proven effective[154].

Several social functioning scales are available, and most are very easy to use in practice. The Specific Levels of Functioning (SLOF) has been found to be the rating scale wherein informant reports are most consistently correlated with objective data from performance-based assessments[155]. This 31-item scale has three subscales (vocational, social, and everyday activities). It is easily completed and requires no special training.

The Personal and Social Performance Scale (PSP)[156] also collects data on social and everyday activities. Also amenable to informant report, this scale generates both domain and total scores. The domains are socially useful activities (including work and school), personal and social relationships, self-care, and disturbing and aggressive behavior. Impairments in the four domains are rated on a 6-point scale (from "absent" to "very severe"), with a global score ranging from 0 to 100. As functional impairments in primary psychosis are relatively uncorrelated across domains, consideration of domain scores instead of a total score is highly recommended.

For the critical assessment of motivation to engage in social activities, there are several possibilities. Self-reported measures include the Temporal Experience of Pleasure Scale (TEPS)[157], which captures the level of enjoyment in pleasurable activities (consummatory pleasure) and the anticipation of pleasure in these activities (anticipatory pleasure). A similar assessment of sensitivity to pleasurable activities is the Motivation and Pleasure Scale - Self-Report (MAP-SR)[158]. This scale is designed to be a self-report measure that parallels the widely used negative symptoms assessment by the CAINS[54]. All of these scales capture subjective motivation, which has been found to correlate quite strongly with actual social outcomes measured by an independent rater, bypassing the need for a structured interview procedure.

Problems in social competence are usually treated with social skills training, while recent treatments aimed at motivational impairment have used technology-based interventions such as the Personalized Real-time Intervention for Motivational Enhancement (PRIME)[159]. This is a mobile application which first assesses the participant's level of engagement with others and in activities and then uses those assessment data to make suggestions regarding possible activities to engage in: "Why don't you try to visit someone in your family today?". Cognitive behavioral interventions have shown efficacy for improvement of social skills and concurrent reduction of socially relevant negative symptoms[154].

Quality of life in primary psychosis is multi-faceted and only partially overlapping with social functioning. Objective quality of life indicators include the milestones noted above, as well as employment, independence in living, and other elements of main-

tenance of normal adult autonomy. Subjective quality of life is the report of both activities performed and the individuals' subjective response to these activities. It has been widely confirmed that overlap between objective and subjective quality of life indices is reduced in people with schizophrenia, with evidence of under-estimation of level of impairment found objectively[160,161].

In terms of subjective quality of life, several scales are readily available. It is important to capture patient quality of life reports, even if divergent from objective information, because patients' motivation to engage in multiple different treatments will be based on their perception of their current level of functioning.

The World Health Organization Quality of Life Scale (WHO-QOL)[162] has been widely used to assess subjective quality of life. This scale has the benefit of being self-administered. It examines quality of life in the domains of physical and mental health, social relationships, and the environment.

A rater-administered scale, the Quality of Well-Being scale (QWB)[163], captures subjective illness burden and has the advantage of providing norms across different illnesses, including psychiatric and physical conditions. This is a more challenging assessment which requires training to administer.

A main driver of quality of life in persons with primary psychosis is represented by the dimension of unmet needs[164]. Unmet needs are frequently found in the areas of daytime activities, information, company, intimate relationships and sexual expression. In many parts of the world, housing, employment and social benefits also represent frequent unmet needs in people with primary psychosis[165].

Including these elements in the clinical assessment framework is important for several reasons. First, a perspective of needs is humanizing and normalizing. There is, in fact, a widely recognized universal hierarchy of human needs as defined by Maslow[166]: physiological, safety, love and belonging, esteem, and self-actualization needs. Second, the concept of need recognizes the service user's experience and preference, given that assessment requires his/her perspective on what is "unmet".

Assessment of needs thus becomes an active process of exploration, listening and understanding on the part of the clinician, often requiring a degree of negotiation between clinician and patient, which in turn will enhance the likelihood of shared decision-making. This is important, as better staff-patient agreement on needs makes a significant additional contribution in predicting treatment outcomes[167], and staff with an active and shared decision-making style has more impact on reducing unmet needs over time[168].

Third, the assessment of needs automatically takes into account the level of contextual influences, such as the impact of friends, family and informal help, in making a need met or unmet. This enhances the sensitivity of the mental health service to the role of informal carers and other resources in the network. Finally, there is evidence that systematic monitoring of patient needs may result in better outcomes and is cost-effective[169-171].

The Camberwell Assessment of Need (CAN)[172,173], available in 26 languages, is a widely used and practical instrument to assess needs in clinical care. Its reliability and validity have been tested extensively. It is comprehensive, assessing a full range of 22 health and social needs, including housing, food, cleaning, self-care, daily activities, physical health, psychotic symptoms, treatment or illness information, psychological distress, personal security, social security, security of others, alcohol, drugs, social relationships, emotional relationships, sexual life, care of children, education, financial tasks, use of telephone/computer, and use of public transportation. Clinicians can choose to add further needs, for example religion/spirituality. This instrument separately assesses the perspective of staff, service users and family members, identifying areas of agreement and disagreement about whether a need is present, which supports negotiation and shared decision-making.

The assessment of the patient's practical needs is essential for the formulation of a comprehensive management plan. For patients who express an interest in supported employment, the Individual Placement and Support (IPS) model has been found to be significantly more effective than other types of vocational assistance in many randomized trials conducted internationally[174]. Among the basic principles of the IPS model are eligibility based on client's choice, focus on competitive employment, integration of mental health and employment services, attention to the client's preferences, and individualized job supports[174].

CLINICAL STAGING

Staging was developed in clinical medicine as a strategy to add precision to diagnosis and treatment selection and also to prognosis and prediction of outcome[175,176]. A transdiagnostic approach is essential for staging in psychiatry. This approach acknowledges the fluid and dynamic nature of the onset and early stages of mental ill-health, during which microphenotypes ebb and flow, and either fade or evolve into a more stable syndrome or more commonly syndromes (Figure 1). Primary psychosis is one of these syndromes, one that typically emerges from earlier stages which already display a need for care, and attracts additional comorbid syndromes and functional impairment[177].

While the idea of staging had been raised initially for common mental disorders[178], the early intervention paradigm in psychosis created the ideal conditions for clinical staging to be formulated. First episode psychosis was the fulcrum around which this began, and an evidence-based case was steadily made that the content of treatment for such cases was very different from what was appropriate for later stages of illness.

An earlier clinical stage, the ultra/clinical high risk state (corresponding to stage 1b in Figure 1), was defined, covering the period prior to the threshold for a first episode of psychosis being reached, and this has become an intense focus for research and intervention[179]. The validity of this earlier stage was supported by its manifestly different treatment needs, and ultimately overwhelming evidence that progression could be delayed at least, and early trajectories of illness significantly improved[180,181]. While some critics remain unconvinced[182], the mindset of the psychosis field has moved from deterministic "doomed from

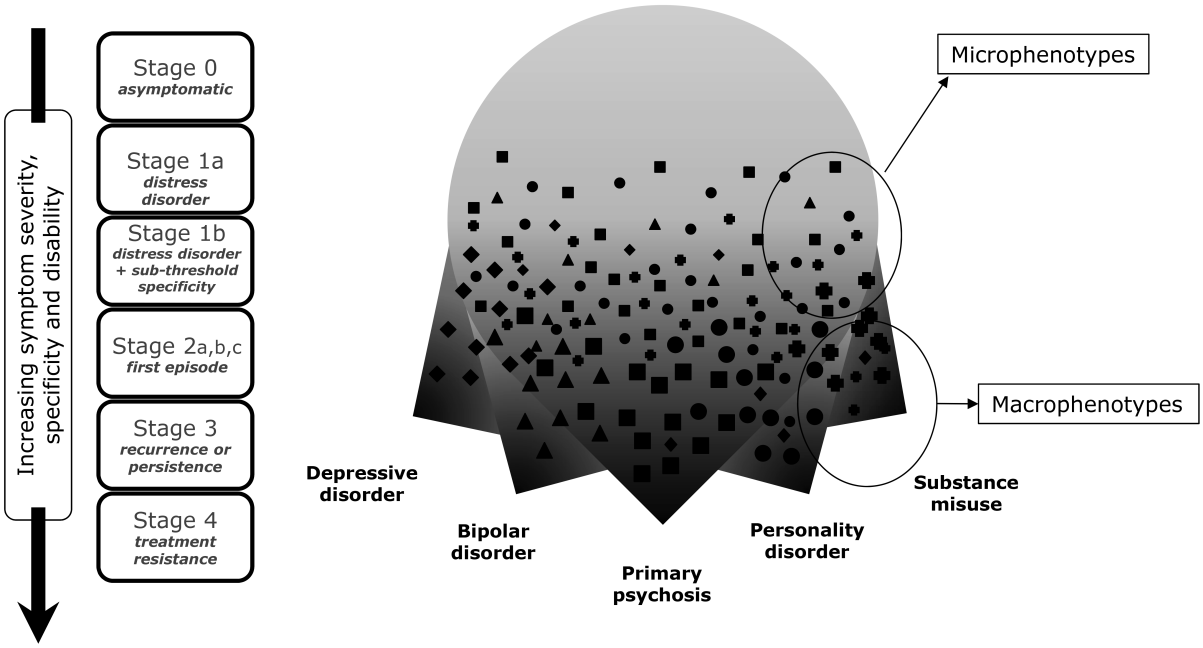

Figure 1 Clinical staging model showing the emergence of undifferentiated microphenotypes that may progress to macrophenotypes such as primary psychosis

the womb" thinking to a more preventive, recovery-oriented approach[180,183].

In this earlier clinical stage, in which psychotic symptoms are present though still attenuated, but there is a need for care, the treatment consists of psychosocial interventions influenced by CBT, and a focus on treatable comorbid syndromes such as anxiety and depression, alleviating stress, strengthening coping and minimizing illicit drug use. At this stage, antipsychotic medications are not indicated.

When new perceptual experiences and/or delusional ideas cluster and persist, reaching a threshold of frequency and severity that causes distress and functional impairment, a diagnosis of first episode psychosis (stage 2) can be made.

Patients with first episode psychosis respond much better to all treatments if the duration of untreated psychosis (DUP) is reduced to a minimum. There is varying evidence on the exact window of time, but some of it suggests that delays of even a few weeks may make a significant difference to treatment response[184,185]. This suggests that first episode psychosis might be better considered as a stage with substages within it.

In fact, with a much shorter DUP now achievable in early intervention services, it may be possible for a small subgroup of patients to remit without antipsychotic medication if provided with intensive psychosocial interventions alone[186], although further evidence is needed in this respect. This might be termed stage 2a.

In all other cases of first episode psychosis (stage 2b), research evidence indicates that low doses of antipsychotic medications are often effective and must be rigorously adhered to if adverse experiences are to be minimized and engagement maximized[187]. Shared decision-making has a crucial place here. The imperative to prevent weight gain and metabolic consequences means that medications least likely to produce these effects must be first line.

A subgroup of patients who fail to respond to dopamine antagonists and reveal early treatment resistance can be reclassified as a further substage of stage 2 (stage 2c), or alternatively as having rapidly progressed to stage 4. Here the benefit-risk ratio changes sharply and, while clozapine has a number of adverse effects which mean it should not be used as first line, the evidence strongly mandates its use if early treatment resistance or stage 4 is reached[188].

Psychosocial treatments, notably supported vocational programmes such as IPS and family interventions, have to be adapted to the stage of illness, and are much more effective at stage 2 [189].

Beyond the first episode (stage 2), patients may enter stage 3 (recurrence or persistence) or 4 (treatment resistance). Stage 3 intervention involves the prevention of relapse and efforts to treat comorbidity and persistent subthreshold or residual symptoms of psychosis and other associated syndromes. Long-acting injectable antipsychotics can be seen as a preventive strategy. However, dose reduction and even discontinuation are possible for a subgroup of patients[190], so a personalized approach with substages and subgroups reflects a heterogeneity within stage 3.

Late stage 3 patients who appear to have stabilized, but with continuing symptoms and functional impairment, can be offered a different suite of psychosocial interventions which may greatly improve their quality of life. This may involve meaningful activity, including part-time work, strength-based strategies, social engagement within community to combat loneliness, family sup-

port, financial support, and expert medical care to respond to the greatly increased risk of medical illnesses.

For stage 4 (treatment resistant) patients, the use of clozapine, as mentioned above, is mandated.

A contributing life is possible for most people with primary psychosis. The "soft bigotry of low expectations" is a consequence of poorly resourced systems of care and antiquated diagnostic thinking, which is not informed by the opportunities that new models of care and high fidelity implementation can now deliver. Such approaches, which of course need to be supported by scientifically valid data, depend on congruent mindsets and conceptual frameworks, and a much more educated and supportive wider community.

ANTECEDENT AND CONCOMITANT PSYCHIATRIC CONDITIONS

The diagnosis of schizophrenia was previously considered in a hierarchical framework, wherein comorbid psychiatric conditions were viewed as diverse manifestations of the psychotic process and were not considered or addressed. Antipsychotic medications were expected to impact on a wide array of psychopathology, whereas they largely target only psychotic symptoms.

We now recognize that the majority of persons with primary psychosis have other antecedent or concomitant psychiatric syndromes or subthreshold conditions. This is unsurprising given the large overlap of common gene variants for multiple psychiatric conditions and the association of many environmental exposures with diverse psychiatric disorders. Addressing comorbid conditions, even those that are subthreshold with respect to categorical diagnoses, and considering antecedent conditions in the treatment plan, can significantly improve the patient's functional outcome and his/her quality of life.

In some settings, the Structured Clinical Interview for DSM-5 (SCID-5)[191] or other semi-structured assessments are employed to explore other psychopathological domains. However, these instruments are designed to detect categorical diagnoses, rated only as present or absent, and do not identify subthreshold conditions which might nonetheless inform clinical approaches. Continuous scales can detect symptoms and be useful in monitoring treatment. DSM-5's Section III includes a cross-cutting symptom measure[1] which may be used as a screening tool to identify the presence of other symptom domains in a patient with a diagnosis of primary psychosis.

Depressive symptoms are common even in persons with non-affective psychoses. They are highly confusable with negative symptoms, particularly social withdrawal, anhedonia, avolition, and reduced emotional expression. So, information on enduring versus episodic presentations of such symptoms, as well as on alterations in appetite, sleep and concentration, and the presence of guilt and hopelessness, is essential to elicit. The Calgary Depression Scale for Schizophrenia[69] can be used to disentangle negative and depressive symptoms.

Persisting depression despite antipsychotic treatment limits recovery and well-being and is associated with increased suicide risk[192]. Adjunctive antidepressant medications may be needed. On the other hand, subsyndromal or premorbid manic symptoms may suggest the practicability of a lithium trial, especially when there is a family history of bipolar disorder.

Social anxiety is also highly prevalent in primary psychosis. It is likewise distinct from negative symptoms and predicts poor functioning. As social anxiety is readily addressed through psychotherapy or medication, it should not be overlooked or confused with paranoia. The Liebowitz Social Anxiety Scale[193] can be used for this purpose.

The common finding of antecedent obsessive-compulsive disorder (OCD) or traits in persons with primary psychosis is notable, as this subgroup demonstrates an earlier age of psychosis onset, worse psychotic and negative symptoms, and more depressive symptoms and suicide attempts, resulting in higher hospitalization rates and a worse prognosis overall[194]. This component can be explored in patients with a diagnosis of primary psychosis by using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[195].

The treatment of comorbid OCD and psychosis is complex. Newer atypical antipsychotics are sometimes associated with *de novo* occurrence or worsening of OCD phenomena that can be managed by medication changes, but persons with premorbid and persisting OCD require other interventions, including CBT and, if that is not ameliorative, adjunctive antidepressant treatment targeting the OCD symptoms.

Post-traumatic stress disorder (PTSD) is commonly comorbid with primary psychosis, requiring specific interventions and possibly heralding treatment resistance. Treatment-refractory psychotic symptoms with relatively preserved intellectual function are also reported in persons who experienced premorbid eating disorders several years before psychosis was manifest, found to be as many as 10% of schizophrenia cases in a recent series[196]. These cases and those with PTSD may require higher doses of antipsychotics. Attention-deficit/hyperactivity disorder (ADHD) in childhood also confers a greater risk of subsequent psychosis, but does not appreciably alter the illness expression[197].

Psychotic symptoms frequently present in association with substance use, particularly chronic cannabis abuse, but also use of amphetamines, cocaine, hallucinogens, opioids, phencyclidine, sedatives/hypnotics and alcohol. If the hallucinations and delusions exceed those that are typically observed in the setting of substance intoxication or withdrawal, then a diagnosis of substance induced psychosis will have to be considered.

Many individuals who are already at high risk for psychosis use substances, and their psychotic symptoms do not abate when intoxication or withdrawal is resolved, indicating a primary psychotic disorder. Evidence of prior psychiatric symptoms can shed light on the differentiation of substance induced versus primary psychosis.

Persons with psychosis have a more than 4-fold increase in substance use compared to the general population, with an even greater relative risk for nicotine addiction[198]. Interventions for substance use and abuse are frequently essential components of

the treatment plan.

Psychotic symptoms occurring in the context of global developmental delay, communication disorders of childhood onset, or autism spectrum disorder are not considered to be primary psychotic disorders, unless prominent delusions or hallucinations emerge that persist for at least one month, or for a lesser duration if they are successfully treated. Psychotic symptoms in persons with developmental disorders appear to be resistant to antipsychotic treatment[142], possibly having distinct underpinnings. Additional studies are needed that may define the characteristics of those with developmental disorders who do respond to different medications for precision treatment approaches.

Finally, although the vast majority of persons with primary psychosis are far more likely to be victims than aggressors, there is a small increase in the risk for antisocial traits among these persons. This comorbidity is rarely considered, but it should be assessed and inform treatment planning. Antisocial traits are not revealed by prior contact with the criminal justice system, which is sadly quite common among persons with psychosis. A history of antisocial traits in childhood and demonstrated callous indifference towards others can be elicited using the Hare Psychopathy Checklist-Revised[199].

PHYSICAL COMORBIDITIES

People with primary psychosis suffer excess morbidity and mortality from physical conditions, particularly cardiometabolic diseases, leading to a drastically reduced life expectancy[11]. Although this is partly due to the metabolic side effects of antipsychotic medication, unhealthy lifestyle behaviors further increase the risk of physical complications/disorders. Despite numerous calls to take their physical health seriously, the screening, assessment and management of physical health aspects in people with primary psychosis remain poor, even in high-income countries. Physical health improvement in these patients is therefore essential, and physical health considerations should be paramount in the choice of antipsychotic medication[11,200-203].

One third of people with primary psychosis develop metabolic syndrome[204], characterized by the simultaneous occurrence of several metabolic abnormalities (abdominal obesity, glucose intolerance or insulin resistance, dyslipidemia and hypertension)[201]. Meta-analytic data show that, compared with the general population, these people have a 1.9 times higher risk of developing the syndrome[204].

Primary psychosis is also a risk factor for cardiovascular diseases and type 2 diabetes mellitus[205,206]. According to a large-scale meta-analysis, a diagnosis of schizophrenia increases the risk for coronary heart disease by 1.5-1.6 times[207]. The risk for type 2 diabetes mellitus is two times higher in people with schizophrenia compared to the general population[206].

As the individual components of metabolic syndrome are critical in predicting the occurrence of cardiovascular diseases, type 2 diabetes mellitus, cancer and other related diseases, they should be checked at baseline, taken into account in the choice of medication, and measured regularly during treatment[208]. Among second-generation antipsychotics, clozapine and olanzapine are associated with the highest cardiometabolic risks, while the lowest risk is with aripiprazole, ziprasidone, lurasidone and amisulpride[207].

Clinicians should monitor the weight of each patient at every visit. Central/abdominal obesity correlates more strongly with insulin resistance, and places people with primary psychosis at higher risk for developing type 2 diabetes mellitus and cardiovascular diseases, than does total body weight or body mass index. Waist circumference, therefore, is the best measurement to assess these risks, and can easily be done with a simple tape measure placed around the waist. This parameter should be measured at midpoint between the last rib and the iliac crest. Cutoff points for increased obesity-related health risks are 94 cm for men and 90 cm for women (these cutoff values, however, are somewhat lower for Asians and South and Central Americans)[208].

Hypertension increases the risk for a variety of cardiovascular diseases. Although differences in the definition of hypertension between guidelines exist, any systolic blood pressure >120 mmHg is associated with an increased cardiovascular risk. Blood pressure monitoring, therefore, should become part of the routine health assessment in patients with primary psychosis. A checklist for accurate measurement of blood pressure is provided by the American College of Cardiology/American Heart Association (ACC/AHA)[209]. Importantly, repeated measurements separated by 1-2 min intervals, as well as out-of-office-based measurements, are required to confirm the diagnosis of elevated blood pressure/hypertension. At the first visit, blood pressure should be recorded at both arms. Thereafter, one should use the arm that gives the higher reading[209].

It is also important to calculate and manage the overall cardiovascular risk of a patient. Several institutions and consensus health panels, including the World Health Organization (WHO) and the Joint British Societies (JBS), have published online tools to calculate patients' cardiovascular disease risk, based on several clinical parameters such as age, gender, blood pressure, smoking status, total cholesterol, and presence or absence of diabetes mellitus[210-212]. The value of such predictions is to help communicate risk, so that patients can receive advice (and treatment if necessary) appropriate to their risk level.

Identifying and managing all modifiable cardiovascular risk factors in people with primary psychosis – such as smoking, an unhealthy diet, obesity, sedentary lifestyle, alcohol consumption, diabetes mellitus, and dyslipidemia – are as important as managing hypertension in lowering overall cardiovascular risk[213,214]. Evidence has shown that people with schizophrenia have significantly higher rates of current smoking, heavy smoking, and nicotine dependence, and have significantly higher food intake and poorer diet quality than the general population[203]. Moreover, more than half of people with schizophrenia (55%) do not meet physical activity guidelines and are sedentary for more than 8 hours per day[203,215]. One in five patients have or have had alcohol use disorder[203].

As a general rule, every patient should have an electrocardio-

gram measurement before prescribing antipsychotic drugs that have been associated with QT prolongation. Moreover, these drugs should not be prescribed for patients with known heart disease, a personal history of syncope, a family history of sudden cardiac death at an early age (especially if both parents had sudden cardiac death), or congenital long QT syndrome[208].

Regardless of age and presence of other risk factors, periodic monitoring of patients with primary psychosis to prevent hyperglycemia is critical, and testing should be considered early in the course of treatment. Finger prick tests, giving an instant reading or snapshot of the glucose level in the blood, should be carried out at baseline, after three months to capture early cases of hyperglycemia, and annually thereafter[208]. These monitoring intervals are, however, suggestions which need to be modified with regard to the administered antipsychotic. Ideally, blood glucose should be assessed in the fasting state, because this is the most sensitive measurement for the detection of developing glucose abnormalities. Conventional tests for screening hyperglycemia are the fasting plasma glucose test, the oral glucose tolerance test, and the glycosylated hemoglobin (HbA1c) test. As adherence in this patient population may be an issue, the HbA1c test may be preferable to a fasting glucose level as a screening test[216].

Lipid parameters, especially triglycerides and high density lipoprotein (HDL)-cholesterol, should also be assessed at baseline and at three months, with 12-monthly assessments thereafter. More frequent screening is unnecessary, unless in case of abnormal values[206]. Fasting is not routinely required for the determination of a lipid profile.

Individual lifestyle counseling and psychoeducation interventions focused on promoting a healthy lifestyle should be considered as first-line strategies for the prevention and management of physical comorbidities in patients with primary psychosis[203,216-218]. Patients should be advised to engage in at least 30 min of moderate-intensity physical activity for a minimum of five days per week[215]. An e-learning tool from the National Centre for Smoking Cessation is now freely available online for clinicians to acquire core knowledge and skills to deliver effective behavioral support for smoking cessation[203].

When lifestyle interventions for physical comorbidities are not effective, medication may be indicated[208]. Metformin is the leading pharmacological option for managing weight gain during antipsychotic treatment, and has the additional advantage of reducing the incidence of type 2 diabetes in patients with hyperglycemia. Growing evidence also suggests that metformin has cardioprotective effects beyond its hypoglycemic effects[219]. Bupropion and varenicline have proven their effectiveness for smoking cessation in individuals with primary psychosis[220,221].

In cases where physical health problems – such as hyperglycemia, hyperlipidemia or hyperprolactinemia – are secondary to antipsychotic medication, dose reduction or switching to an antipsychotic with a lower risk profile should be considered, if safe and feasible[202,208]. Patients treated with clozapine need a special monitoring, because the adverse drug reactions related to physical health that can be induced by this medication (agranulocytosis, myocarditis and cardiomyopathy, cardiometabolic diseases) are a major concern[202].

Prevention of physical health problems in people with primary psychosis by promoting a healthy lifestyle is likely to be more efficient than intervening after significant changes in clinical or biological markers are found during cardiometabolic screening[222]. 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 physical comorbidities[223], although its feasibility and clinical utility in patients with primary psychosis remains to be proved.

FAMILY HISTORY

In schizophrenia spectrum psychosis, family history of the disorder is one the strongest known risk factors. According to a meta-analysis, having an affected parent is associated with a 7.5-fold higher risk for schizophrenia in the offspring[224].

Only a minority of people with a diagnosis of schizophrenia, however, have a positive family history of that disorder. A simulation study of complex polygenic diseases estimated that 83-90% of persons with schizophrenia in typical families (with an average of two children) do not have any affected first-, second-, or third-degree relatives[225]. This large proportion of sporadic cases is expected under the polygenic model, considering the low prevalence rate of the disorder[225].

The clinical assessment of family history in a patient with primary psychosis should not only focus on schizophrenia. Clinically diagnosed schizophrenia may be associated with the presence of several different mental disorders in first-degree relatives, and more schizophrenia in the population can be attributed to a family history of a non-schizophrenia disorder than to a family history of schizophrenia itself[226]. These findings echo those of molecular genetic studies, showing that two thirds of genetic associations are common to schizophrenia, bipolar disorder and major depressive disorder, and overlaps also exist with genetic variants contributing to autism, ADHD and intellectual disabilities[227,228]. Therefore, the clinical assessment of family history in patients with primary psychosis should consider the entire spectrum of mental disorders. Given the high lifetime rates of mental disorder, a positive family history, broadly defined, may be expected in a sizeable proportion of patients.

The clinical interpretation of the presence of family history is complex and goes beyond "genetic load". Schizophrenia polygenic risk scores appear to mediate less than 20% of the effect of family history[229]. This is likely in part explained by the fact that particularly parental family history also reflects environmental influences, such as higher rates of birth and pregnancy complications[230,231], growing up in an unfavorable home environment[232], out-of-home placement[233], elevated divorce rate, alterations in parental communication[234], and poor school performance[235]. The sizeable impact of growing up with a parent with severe mental illness on psychological and social development has been recently reviewed[236]. Therefore, a positive family history should be accompanied by an examination of the devel-

opmental impact of parental psychopathology and the clinical needs associated with this.

Family history is also of direct clinical relevance, as the first episode of primary psychosis typically occurs when patients are still dependent on and/or living with their parents. The presence of parental psychopathology may indicate reduced family resilience and increased need for family support[236].

In a patient with primary psychosis, the family history of mental disorders can be assessed using either structured interviews or screening instruments. Most structured interviews, such as the Family Interview for Genetic Studies[237] and the Diagnostic Interview for Genetic Studies[238], can take several hours to complete. In clinical practice, shorter questionnaires or screens are more suitable for use.

The Family History Screen (FHS)[239] collects information on 15 lifetime mental disorders as well as on suicide attempts. It is administered to a family informant, who reports about himself/herself and other biological relatives (parents, siblings and offspring). The screen starts with general questions about symptoms, treatment and impairment, followed by more specific questions about psychopathology. The FHS takes about 5 to 20 min to administer, as each question is posed only once about all family members as a group.

Family history needs to be re-assessed over time, as not all relatives of the index patient may have passed through their period of risk for each mental disorder. Also, new information may arise that previously had remained undetected due to recall difficulties or lack of knowledge.

There is some evidence that a family history of psychosis may affect prognosis. For example, this history was associated with worse outcomes of the disorder in several meta-analyses, especially regarding negative symptoms[240] and occupational and global outcome[241]. Effect sizes, however, were relatively small. Younger age of onset has also been associated with family history[240], which is clinically relevant since this variable is associated with poorer clinical and social outcome[242]. There is no evidence that gender moderates the influence of family history on outcome. However, it has been noticed that, although men typically display more negative symptoms than women, this may not be the case among those with a family history[242].

In the recent Swedish National Register and Genomic Study [243], family history was found to be associated with a higher risk for treatment resistance in patients with schizophrenia. In a subset of cases with genomic data, there was no significant association between the genetic risk scores of four mental disorders and treatment resistance. However, further research is needed to explore if genetic risk scores are associated with clinical outcome, alone or when combined with family history data.

In summary, broadly defined family history of mental illness may impact psychosocial development of patients and alter family resilience in a clinically relevant fashion. Family history can be reliably assessed in patients with primary psychosis in routine clinical practice using short screening instruments. The presence of a family history of the disorder is associated with an earlier age at onset and may have an effect on outcome.

OBSTETRIC COMPLICATIONS

Obstetric complications are among the best replicated environmental risk factors for psychosis in the schizophrenia spectrum. They include a number of different variables which present a hazard to the normal development of the baby's brain.

The significance of the association between birth complications and schizophrenia was established by the work of Scandinavian researchers[244,245] from the 1970s onwards. Indeed, their findings contributed to the thinking behind the formulation in 1987 of the neurodevelopmental model of schizophrenia[133,246].

The topic was comprehensively reviewed by Cannon et al[247]. Their meta-analysis of prospective population-based studies revealed that three groups of complications were significantly associated with later schizophrenia: a) complications of pregnancy (bleeding, diabetes, Rh incompatibility, pre-eclampsia); b) abnormal foetal growth and development (low birthweight, congenital malformations, reduced head circumference), and c) complications of delivery (uterine atony, asphyxia, emergency caesarean section). However, estimates of effect sizes were generally less than 2.

Very recently, Davies et al[248] carried out a meta-analysis of pre- and perinatal factors for psychosis as a whole, largely confirming Cannon's findings. Both meta-analyses concluded that foetal hypoxia and anoxia-related factors, where the developing brain is deprived of oxygen, are among those most consistently implicated.

In clinical practice, one should always enquire of patients if they know whether they were subject to any obstetric events. A minority of patients may know about this, particularly if the events were severe or life-threatening (e.g., prematurity, emergency caesarean section, being "blue" or in an incubator). However, more likely than not, the patient will not know about this aspect of his/her life.

This lack of information cannot be taken as meaning that such events did not occur. Therefore, wherever possible, it is wise to ask a parent, particularly the mother, about pregnancy and the patient's birth. The evidence is that mothers remember major events that occurred (e.g., pre-eclampsia, forceps delivery), although they may have forgotten more minor events (e.g., antenatal haemorrhage)[249]. Fathers are much less reliable.

The Lewis-Murray checklist[246,250] can be used for rating information obtained from maternal interviews. It covers 16 complications: rubella and syphilis during pregnancy, Rh incompatibility, antepartum haemorrhage, severe pre-eclampsia, premature rupture of membranes, labour >36 hours, complicated twin birth, cord prolapse, gestational age <37 weeks or >42 weeks, emergency caesarean section, breech or abnormal presentation, mid to high forceps, birth weight ≤2 kg, incubator >4 weeks. Each of these complications is rated. Thresholds are given rating them as "definite" or "equivocal"[250].

If it is very important to establish the facts and mother is vague, then the ideal approach is to obtain the original birth records. The Lewis-Murray checklist can be applied to these. However, the McNeil-Sjöström scale[251] is more comprehensive and was specifically designed for use with birth records. It takes longer to complete but gives much more detailed information. Therefore, it

is generally used in research rather than clinical practice.

Prospective studies have examined the overall long-term consequences to babies of being exposed to obstetric complications[252,253]. These have demonstrated that early brain hazards, especially those which cause periventricular haemorrhage, are associated to vulnerability not only to psychosis but also to neurodevelopmental disorders such as ADHD and autism. Cognitive problems are common (including lower IQ), as well as neurological deficits ranging from soft signs to cerebral palsy. Neuroimaging studies have shown that, when babies who suffered periventricular bleeds reach adult life, they show an excess of brain structural abnormalities such as ventricular enlargement and cortical thinning, as well as dopaminergic abnormalities, reminiscent of those found in patients with schizophrenia[253,254].

If one elicits a history of a major obstetric event, then what relevance does this have to the patient? It may have none, as the vast majority of babies exposed to such events develop entirely normally; the psychosis may be coincidental. However, the event is particularly likely to be significant if the patient has shown evidence of soft neurological signs or developmental problems in childhood (e.g., late milestones, lower IQ than siblings, childhood psychiatric or behavioral problems, especially ADHD).

Should any of these be present, then further investigation is warranted. In particular, structural magnetic resonance imaging (MRI) may be useful to ascertain if there is any evidence of early brain damage: larger ventricles, small hippocampi or cortical thinning may point to significance. Neuropsychological testing may be useful to establish overall intellectual functioning or any specific alterations. For some unknown reason, the male foetus or baby is more susceptible to long-term neuropsychiatric consequences of early brain insults.

Does the presence of an obstetric event which seems to be significant make any difference to the patient's care? Not directly, but it does obviously contribute to the characterization of the individual case. It may have caused developmental delays in childhood as well as other behavioral problems long before the onset of the psychosis; it may also explain cognitive alterations and MRI abnormalities. Furthermore, it may help parents to understand why their son or daughter has developed the psychosis, and prevent them worrying about whether they may have caused the illness through some fault in their parenting.

Of course, one should keep in mind that risk factors for psychosis seldom act alone, and obstetric events may be a contributory cause acting on top of genetic predisposition or together with other environmental risk factors such as migration or cannabis use.

EARLY ENVIRONMENTAL EXPOSURES

Epidemiological evidence suggests that an adverse environment during the neurodevelopmentally sensitive period is associated with an increased risk for primary psychosis in later life. The meta-analytical effect size estimates of primary psychosis risk vary for the different exposures, that include childhood adversities (e.g., parental death, abuse, neglect and bullying) as well as urban environment, migration and ethnic minority (that are likely to act through increased socio-environmental adversities)[255-257].

The effects of early exposures appear to be complex, dynamic and interactive[258]. Childhood adversity represents the epitome of the complex etiology of primary psychosis. For instance, childhood sexual abuse, in addition to primary psychosis, is associated with a wide range of mental and physical health outcomes, from obesity to depression to substance misuse[259], which are also individually linked to increased risk for psychosis and poor outcomes among individuals with psychosis.

The detrimental impact of childhood adversities also appears to be additive[260]. In this regard, there may be various causal and non-causal paths between childhood adversities and primary psychosis, such that the link between adversities and psychosis may also be partly dependent on the widespread detrimental impact on well-being. Further, evidence suggests a gene-environment interplay, as the association between childhood adversities and primary psychosis increases as a function of high genetic vulnerability[261].

A recent meta-analysis shows that childhood adversity is associated with poorer treatment outcomes among individuals diagnosed with psychotic disorders (OR=1.51, 95% CI: 1.08-2.10)[262]. Childhood adversity is also linked to reduced service engagement and medication adherence[263]. Notwithstanding the scarcity of higher-quality evidence from prospective studies in large samples, these findings indicate that it is important to acknowledge the presence of childhood adversity when forecasting the course of illness and formulating a management plan. Therefore, childhood adversity should be routinely assessed in individuals with primary psychosis.

However, the assessment of childhood adversities is challenging, even for an experienced mental health practitioner. First, the retrospective collection may be prone to recall bias. Second, acknowledging subjective experience, including perception and meaning assigned to adversity, is as much important as, if not more important than, the objective evaluation of an adverse event. Third, sociocultural background and personality influence appraising, reporting and disclosing of early adversities, and should therefore be considered during the assessment. Finally, a thorough assessment, taking into account the timing, duration, severity, frequency and type of childhood adversity, will yield better results, but may be considered time-consuming in a hectic clinical setting.

Of numerous self-report and clinician-rated instruments for screening or more definitive appraisal of exposure to childhood adverse events, the Childhood Trauma Questionnaire (CTQ)[264] and the Childhood Experiences of Care and Abuse (CECA)[265] are the most commonly used.

The CTQ is a self-report instrument, supported by robust psychometric data collected from different populations in diverse settings across the world. A total of 70 items (28 items for the CTQ-Short Form) are rated on a 5-point Likert scale (from "1 - never" to "5 - very often"), to assess five domains of childhood adversity: emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse.

With easy and quick administration (10 to 15 min), the CTQ

may serve as a useful screening tool that covers a relatively broad range of childhood adversities. This simple questionnaire can be integrated into routine electronic health records to provide a basic perspective of the history of early exposures[266].

The CECA offers the most detailed and contextualized formal assessment of childhood adversities, measuring the frequency, pervasiveness and intensity of physical and sexual abuse, maternal and paternal antipathy, and neglect. However, this tool requires at least an hour-long interview and a specific training of the interviewer.

The Retrospective Bullying Questionnaire measures the frequency, intensity and duration of physical, emotional and relational victimization during elementary and middle/high school period[267].

It should be noted that these instruments have been designed to collect information in a research context, and evidence on their clinical utility remains limited[268]. Further, childhood adversities, although largely unvarying in essence, may change in form over time (e.g., cyberbullying). These emerging forms of early adversities need to be addressed as well.

A meta-analysis of 12 studies showed that trauma-focused CBT (e.g., gradual imaginal exposure, cognitive restructuring) and eye-movement desensitization reprocessing therapy result in a small improvement in positive symptoms immediately after treatment (g=0.31, 95% CI: 0.55-0.06), but not at follow-up, while having no effect on negative, depressive or anxiety symptoms[269]. A more inclusive systematic review failed to show converging high-quality evidence for the effectiveness of trauma-informed psychotherapeutic interventions in patients with psychotic symptoms[263].

Given the limited benefit of current trauma-focused psychotherapeutic interventions, and the need for further studies with low risk of bias, these interventions cannot be routinely recommended for patients with primary psychosis who present with a history of early adversities, particularly in a limited resource mental health setting. However, they should certainly be considered on a case-by-case basis.

Trauma-focused psychotherapies should be tailored to the needs of individuals with primary psychosis. Randomized controlled trials are required to find the optimal duration and intensity for an effective intervention. Further, research is needed to help inform health care strategies to identify individuals most likely to benefit from these interventions.

From a public health perspective, early adversities are modifiable factors contributing to the global burden of mental disorders, including primary psychosis. Therefore, the ultimate goal should be to promote a nurturing environment for optimal childhood development[270].

RECENT ENVIRONMENTAL EXPOSURES

Major stressful life events, i.e. situations that bring about a very significant positive or negative change in personal circumstances and/or involve an element of threat, may operate close to the onset or relapse of psychosis.

A meta-analysis reported an association of major stressful life events with psychotic disorder and subclinical psychotic experiences, with an odds ratio of around 3[271]. However, the methodological quality of the majority of included studies was low. Moreover, a part of the association may be explained by a shared underlying genetic propensity, increasing the risk for psychosis as well as exposure to major life events[272].

From a clinical point of view, stressful life events may be particularly important when preceded by childhood adversity. A study found that 47% of the effect of childhood abuse was mediated by adverse events in adulthood, particularly events involving violence[273]. Moreover, some studies reported that exposure to childhood adversity may also increase the impact of stressful life events[274], suggesting stress sensitization.

For assessment purposes, the semi-structured interview Life Events and Difficulties Schedule (LEDS) is considered the gold standard, as it takes account of factors such as timing, severity and independence of events[275]. It is, however, time-consuming to administer and rate. Alternatively, questionnaires such as the Social Readjustment Rating Scale (SRRS)[276], the Psychiatric Epidemiology Research Interview (PERI) Life Events Scale[277], and the Questionnaire of Stressful Life Events (QSLE)[278], can be used.

In addition to stressful life events, the subjective feeling of being overwhelmed by, or unable to control, the demands of the environment seems to be a further factor linking stress experience to psychosis. At the population level, a study among 177,000 individuals found consistent evidence for a link between perceived stress and psychotic experiences[279]. Data again suggest that the impact of perceived stress is stronger in individuals previously confronted with childhood adverse events[280].

While it should be appreciated that perceived stress is not an independent environmental factor, but arises in interaction with the subjective experience of the individual, its assessment may be of considerable clinical relevance, given its close correlation with[279], as well as future prediction of[281], psychotic symptom levels. This can be done using instruments such as the Perceived Stress Scale[282] or the Psychological Stress Index[283].

Ecological momentary assessments, which measure symptoms, feelings and context multiple times per day during the course of several days, may even be more suited to assess daily life stress and the person's sensitivity to it[284]. Novel e-health approaches, such as apps, may help to implement these assessments in standard clinical practice[284].

There are evidence-based approaches that can help to reduce the impact of both stressful life events and daily life stress in psychotic patients, such as CBT for psychosis (CBTp), physical exercise, mindfulness, and acceptance and commitment therapy.

Another environmental exposure exerting its effect close to the onset or relapse of psychosis is the use of illegal substances, particularly cannabis. Meta-analyses report a 2- to 3-fold increased risk of psychosis in frequent users, with clear evidence for a dose-response relationship[285]. This risk may be higher at a younger age at onset of use, in case of a family history of psychosis, or when cannabis strains with high levels of tetrahydrocannabinol are consumed[286]. Individuals with a history of severe

childhood exposure to traumatic events also seem to be more sensitive to the psychosis-inducing effects of cannabis[286].

A systematic review concluded that around one third of psychotic patients had clinically significant cannabis use at their first episode, and the time between first use and the first psychotic break was on average about six years. During the first ten years after the first episode, around half of the previous users quit smoking cannabis. Those who continue to use it have higher relapse rates, longer hospital admissions and more severe psychotic symptoms than individuals who discontinue use or are non-users[287]. Part of this effect may be mediated by worse medication adherence in cannabis users[288]. Importantly, quitting cannabis use may improve psychotic symptoms to the level of non-using patients[288].

Cannabis use can be assessed using the most updated version of the Cannabis Experience Questionnaire[289]. Unfortunately, treatment of cannabis use in patients with psychotic disorders remains a challenge: a meta-analysis indicated no evidence of effect on frequency of use for any intervention, but there was some evidence for a decrease of quantity of use and positive symptoms associated with motivational intervention, either with or without CBTp[290]. There is, as yet, no compelling evidence to suggest that pharmacological substitution is effective.

PROTECTIVE FACTORS / RESILIENCE

In primary psychosis, personal and social protective factors and the individual's levels of resilience can be mediators of the relationship between illness factors, such as cognitive impairment and negative symptom severity, and outcomes such as work and school functioning.

Protective factors include good coping capacity and problem solving skills, higher education, social and emotional support, participation in community activities, and economic/financial security[40,291-294]. Resilience refers to the ability to positively adapt to psychosocial adversity. Aspects of resilience include positive self-image, self-control, cognitive flexibility, social competence, emotional self-regulation, self-efficacy, and optimism[293,295-298].

Given that no protective factor or aspect of resilience emerges as a "primary" contributor to functioning in persons with psychosis, consideration of several factors is important for understanding their relative contribution[296,299]. Some factors can have a direct effect on functioning, while others act as mediators of the relationship between one illness factor and daily functioning. For example, positive coping and resilience partly mediate the relationship between negative symptoms and disability in primary psychosis[99,100,298].

The assessment of protective factors and characteristics of resilience in an individual with primary psychosis is an important step in the formulation of a targeted management plan. The number of protective and resilience variables is relatively large. Individual patients might be deficient in some, but not all factors. Although there is no one gold-standard assessment for protective factors or characteristics of resilience, there are several tools from which the clinician can choose. The analysis of total scores or individual items from these assessment measures can be used to personalize the treatment approach.

The Brief Cope (BC)[300] is a self-report 14-subscale/28-item questionnaire composed of two items per subscale. A higher score indicates greater use of a specific coping strategy. The BC contains items assessing "adaptive" coping (e.g., "I've been taking action to try to make the situation better" and "I've been getting emotional support from others"), and "maladaptive" coping (e.g., "I've been using alcohol or other drugs to make myself feel better" and "I've been criticizing myself").

The Simplified Coping Style Questionnaire (SCSQ)[301] is a 20-item self-report questionnaire with two categories: positive coping styles (items 1-12) and negative coping styles (items 13-20). The SCSQ items assess "appraisal" coping (e.g., "I try to see the positive side of the situation") and "behavioral methods" of coping (e.g., "I make compromises"). The participants can rate each item from "0 - never" to "3 - often", based on the frequency with which they used a given strategy when addressing a stressful situation or problem. This scale can be used to identify the coping style most often adopted by the patient. Low scores on specific items or low total scores indicate that an intervention to improve coping skills is needed.

The Social Network Questionnaire (SNQ)[302] can be used to assess structural and qualitative aspects of patients' social network. This self-administered questionnaire includes 15 items rated on a 4-point scale (from "1 - never" to "4 - always"), organized into four factors: quality and frequency of social contacts, practical social support, emotional support, and quality of an intimate relationship. If family tension and criticism is high and family support is a potential protective factor that needs to be improved, then empirically-based approaches such as family psychoeducation and family therapy would be indicated.

Resilience can be assessed using the Resilience Scale for Adults (RSA)[303], a 33-item self-administered scale that examines intra- and inter-personal factors thought to facilitate adaptation when a patient is facing psychosocial adversity. Items are organized into six factors: perception of self, perception of the future, structured style, social competence, family cohesion, and social resources. The RSA total score can be used as a global index of resilience, with higher scores reflecting higher resilience.

The Connor-Davidson Resilience Scale (CD-RISC)[304] is a 25-item, 5-point Likert-type scale ranging from "0 - not true at all" to "4 - true all the time". Patients rate each item based on how they felt over the previous month. The total score ranges from 0 to 100, with higher scores representing greater resilience. The 3-factor structure comprises tenacity, strength and optimism, all of which have adequate internal reliability.

The Recovery Style Questionnaire (RSQ)[305], a 39-item self-report measure, is designed to assess two distinct recovery styles, termed "integration" and "sealing over". Integration (i.e., trying to understand and put one's illness into perspective) has been associated with better outcomes, lower levels of depression, and better self-evaluation, as compared to a "sealing over" style, in

which individuals try to cover-up, deny, or downplay the seriousness of a psychotic episode.

The relationship of protective factors and resilience to real-life functioning highlights the importance of working in collaboration with patients when defining life goals and designing treatment programs. A resilience-promoting mental health service should offer hope, optimism, empowerment, a focus on identity (the process of having to reinvent oneself after the onset of psychosis) and meaning (relationship with symptoms, illness and others)[306], and foster the ability to absorb suffering[307,308]. Peer-run recovery colleges aim to facilitate these processes[309].

INTERNALIZED STIGMA

Internalized stigma has been defined as "the devaluation, shame, secrecy and withdrawal triggered by applying negative stereotypes to oneself"[310].

Surveys of people with schizophrenia have found that such experiences are either common or usual. A cross-national study in 14 European countries reported that 43% of patients with this diagnosis had moderate or high levels of internalized stigma[311]. In a study conducted in rural settings in China, internalized stigma was found among 95% of people with severe mental illness[312].

A wide range of factors have been associated with the experience of internalized stigma. Perhaps the most consistent finding is the close link with low self-esteem. Higher internalized stigma was also shown to be connected to lower quality of life and lower levels of social functioning. There is evidence, as the name implies, that internalized stigma is associated with, and may often be a consequence of, experienced discrimination by others. There are also clinical associations, with connections between internalized stigma and symptoms of depression. A further implication of this line of reasoning is that higher internalized stigma may confer a greater risk of suicidality.

Further contextual and environmental factors also appear to play a role in internalized stigma, including how mental disorders are portrayed in the media, as well as cultural explanatory models of mental illness, with supernatural accounts being found to be more common among people with higher rates of internalized stigma. This stigma is also positively associated with psychiatric symptom severity and negatively associated with treatment adherence[313].

Several important sequelae of internalized stigma have been identified. Higher rates are associated with lower rates of help-seeking, and this may be especially the case among some minority ethnic groups and among older people. A mediation analysis has suggested that help-seeking may be especially impaired among people with both higher levels of internalized stigma and depression[313].

Internalized stigma can also be a potent barrier to seeking employment, as the anticipation of rejection deters people from applying for work[314]. More broadly, the literature suggests that internalized stigma is a powerful obstacle to recovery among people with severe mental illness, and can impair forming intimate partner relationships and social functioning.

For formal assessment of internalized stigma, the most commonly used measure is the Internalized Stigma of Mental Illness (ISMI) scale[315]. This scale was developed in collaboration with people with mental disorders, and contains 29 items with a score from "1 - disagree" to "4 - strongly agree". It has high internal consistency and test-retest reliability. Construct validity was supported by comparisons against scales measuring related constructs with the same methodology.

The ISMI score has positive correlations with measures of depressive symptoms, and negative correlations with measures of self-esteem, empowerment and recovery orientation[315,316]. There are now versions available in 47 languages, and adaptations for people with various mental disorders as well as for their parents and caregivers, and for people of different ethnicity. Evaluations of these versions of the scale have shown their reliability and validity across a wide range of languages and cultures, although not all psychometric properties have been assessed in all the scale versions.

Internalized stigma has several key implications for clinical practice. First, mental health practitioners need to recognize that internalized stigma among patients with a diagnosis of primary psychosis, in particular schizophrenia, is likely to be common and may be disabling. It is therefore necessary to ask patients directly about their understanding of their diagnosis of psychosis and their views about the implications of having such a condition. This will often lead to a detailed discussion to help the patient correct common misunderstandings, for example that psychosis is always a chronic and progressively disabling condition, or that psychosis means never being able to work or marry. Such discussions are often also necessary with family members to convey a realistic prospect of recovery from a psychotic episode, with an emphasis upon supporting advocacy, self-esteem and empowerment[317].

The verified presence of internalized stigma may have significant implications for the formulation of the management plan. Stigmatizing contacts with health professionals can worsen internalized stigma, and therefore interventions to reduce stigma among health care staff will contribute to reduction in internalized stigma. Advocacy groups and peer support may act to reduce the stigma[318]. There are now well-established methods to reduce experienced stigma[319], and there is emerging evidence that group therapeutic interventions can have a favorable impact, with psychoeducation being the most effective intervention element[320].

DISCUSSION

The current practice of the management of patients with primary psychosis worldwide is often characterized by an oversimplification at several different levels.

The first level is that of diagnosis. Most treatment research and practice guidelines focus on schizophrenia, but this condition, as defined by the DSM-III and its successors, accounts for only less than one half of cases of primary psychotic disorder, and about one quarter of all cases of psychosis[5]. So, it is not appropriate to

generalize to all patients with primary psychotic disorder what research has documented in people with a post-DSM-III diagnosis of schizophrenia (i.e., concerning neurocognition, social cognition and social functioning), nor is it correct to regard all patients with "psychosis" (a term that is often used today as a synonym for either schizophrenia or primary psychosis) as having the same treatment needs.

Furthermore, even if the diagnosis is made according to one of current diagnostic systems, which is not the case in many clinical settings worldwide[321], we cannot ignore that the definitions of all primary psychotic disorders, and in particular that of schizophrenia, differ in some significant respects between the DSM-5 and the ICD-11, so that the research evidence collected in samples of patients with a post-DSM-III diagnosis of schizophrenia is not necessarily generalizable to all patients receiving this diagnosis according to the ICD-10 or ICD-11.

A second level of oversimplification is that of psychopathological evaluation. It is widely acknowledged that schizophrenia, however diagnosed, is a heterogeneous entity. Both the DSM-5 criteria and the ICD-11 clinical description of that syndrome are polythetic, so that a patient presenting with only positive symptoms, minimal social and neurocognitive impairment and an episodic course, with little or no residual symptomatology in the intervals between the episodes, will receive the same diagnosis as a patient with prominent positive, negative and disorganization symptoms, a significant social and neurocognitive impairment and a continuous course. In the absence of a more focused clinical assessment beyond the mere diagnosis, these patients are likely to receive the same management, although their treatment needs may be very different.

Moreover, treatment needs in a given patient may change significantly depending on the current stage of the illness. Nonetheless, clinical staging is very rarely applied in ordinary practice, as is a detailed assessment of the course of the illness up to that moment.

A third level of oversimplification is that of history taking. The fact that schizophrenia (or "psychosis") is clearly a heterogeneous condition, with a multitude of underlying genetic and environmental vulnerability and protective factors, which are involved to a different degree in the individual patient, should prompt a comprehensive assessment of the history of each patient, with respect to the best validated of those vulnerability factors, such as family history, history of obstetric complications, early and recent environmental exposures, as well as to the personal and social protective factors that have been supported by research evidence. This assessment can influence in several respects the choice and the modulation of the various components of the management plan. Unfortunately, it is very rare that this evaluation is implemented in ordinary clinical practice.

A fourth level of oversimplification can be identified in the choice of the treatment modality. Although every clinician and researcher would agree that the management of schizophrenia (or "psychosis") must be "integrated" and consist of several components, the reality in many clinical contexts worldwide is that the patient will just receive an antipsychotic medication plus some psychosocial support that will likely not be evidence-based. CBT is very seldom used in the vast majority of clinical settings worldwide, although there is evidence to support its efficacy in primary psychosis[7].

The fifth level of oversimplification is that of the choice of the specific intervention within a given treatment modality. In the case of pharmacotherapy, although there seem to be differences among the various available drugs with respect to their efficacy on positive and negative symptoms[29], it is true that these differences are not so clear at the moment as to guide the choice of medication in the individual patient. However, it is also true that there are major differences among the available drugs in terms of tolerability, which makes the characterization of the individual patient with respect to physical health and physical comorbidities absolutely needed in order to guide the choice of medication[207,322]. Unfortunately, this is a principle upon which all clinicians would agree, but which is not consistently translated into routine clinical practice worldwide[11].

Concerning psychosocial interventions, a significant body of research has accumulated in the past few decades, and we have a somewhat clear idea of what "works" in populations of patients with schizophrenia (or "psychosis")[323], and also, to some extent, of the features in the individual patient that could guide the choice and tailoring of a given intervention (see, for instance, the section on social functioning of the present paper). The reality, however, is that the psychosocial intervention in patients with schizophrenia (or "psychosis") is often stereotyped (i.e., not adapted to the characteristics and needs of the individual patient in the specific stage of his/her illness) and not evidence-based (the social skills training, cognitive remediation and family interventions that are validated by research are certainly not the most frequently used worldwide).

The sixth level of oversimplification can be recognized in the translation into ordinary practice of some principles upon which the vast majority of clinicians and researchers would agree: that the management of primary psychosis should be recovery-oriented; that it should take into account the patient's practical needs; and that the management plan will have to be agreed upon between the clinician(s) and the patient. It is indeed not common that a resilience-promoting therapeutic environment and a focus on empowerment, identity, meaning and resilience is ensured in ordinary practice; that patients' needs in terms of employment, housing, self-care, social relationships and education are taken into account in the management plan; and that negotiation and shared decision-making are really implemented[13].

So, it could be argued that the availability of biological markers which can guide us in the choice of the most appropriate medication in an individual patient, so frequently emphasized in the literature, is only one of the unmet needs that we have today concerning the management of patients with primary psychosis. Further unmet needs are: a) an approach to management that considers the various treatment modalities found to be effective by research, and that incorporates the general principles of care agreed upon by the vast majority of clinicians; and b) the personalization of management on the basis of a clinical char-

acterization of the individual patient beyond the mere diagnosis, which might become more systematic through the development of standardized decision tools.

The present paper represents an attempt to address these latter unmet needs. We describe the salient domains to be covered in the clinical characterization of the individual patient with primary psychosis aimed at personalization of management. We identify, within each domain, simple assessment instruments that can already be considered for use in ordinary clinical practice, and that can be included in comprehensive batteries of measures to be tested in large observational studies in order to guide the development of standardized decision tools[15]. Finally, we encourage a clinical practice taking into account all the available treatment modalities validated by research evidence, addressing the patient's practical needs, and offering a focus on identity, meaning and resilience.

One could argue that clinicians do not like to use standardized assessment instruments in their routine practice, and that they often do not even use formal diagnostic systems in that practice. However, as we already pointed out in the paper on the clinical characterization of the patient with a diagnosis of depression[14], our experience with the above diagnostic systems is very telling in this respect. Although those systems are seldom formally used in routine practice, several elements of their description of major mental disorders have been incorporated by most clinicians in their personal prototypes of those disorders, so that the reliability of psychiatric diagnosis has become today, although certainly far from optimal, much better than it was in the 1970s. Something similar may happen with respect to the clinical characterization of the patient with psychosis or depression: although only a minority of clinicians will formally adopt the standardized decision tools to be developed, it is likely that many of them will incorporate several elements of those tools in their ordinary practice, which may make the patient characterization more reliable and clinically useful than it is today.

Although group-based comparisons constitute the scientific basis underlying academic psychiatry and psychology, the fact remains that individual patients are more likely to "escape" group-based predictions than to behave in accordance. Clinicians are faced with individuals with largely unique combinations of symptoms, unique needs and unique treatment responses. Leaving this individual heterogeneity unaccounted for exposes patients and carers to disappointment and confusion as group-based predictions do not materialize.

Furthermore, the assessment and management of primary psychosis is not a linear guideline affair, but an iterative process of "finding it out together", requiring a solid therapeutic relationship characterized by genuine interest and curiosity, a caring attitude, and the ability to project trust and stimulate motivation. There is evidence that shared decision-making results in a better patient-clinician relationship and better outcomes in mental health settings[162,163,324]. Quality of care is something dynamic, plural and relational, which is established in a continuing collaborative process between patient and clinician.

We hope that the present paper will contribute to make the management of the patient with primary psychosis, in the real world, less stereotyped and more personalized, in the broadest sense of this latter word. We are open to comments and additions, which may be incorporated in a future updated version of the article.

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An organization- and category-level comparison of diagnostic requirements for mental disorders in ICD-11 and DSM-5

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In 2013, the American Psychiatric Association (APA) published the 5th edition of its Diagnostic and Statistical Manual of Mental Disorders (DSM-5). In 2019, the World Health Assembly approved the 11th revision of the International Classification of Diseases (ICD-11). It has often been suggested that the field would benefit from a single, unified classification of mental disorders, although the priorities and constituencies of the two sponsoring organizations are quite different. During the development of the ICD-11 and DSM-5, the World Health Organization (WHO) and the APA made efforts toward harmonizing the two systems, including the appointment of an ICD-DSM Harmonization Group. This paper evaluates the success of these harmonization efforts and provides a guide for practitioners, researchers and policy makers describing the differences between the two systems at both the organizational and the disorder level. The organization of the two classifications of mental disorders is substantially similar. There are nineteen ICD-11 disorder categories that do not appear in DSM-5, and seven DSM-5 disorder categories that do not appear in the ICD-11. We compared the Essential Features section of the ICD-11 Clinical Descriptions and Diagnostic Guidelines (CDDG) with the DSM-5 criteria sets for 103 diagnostic entities that appear in both systems. We rated 20 disorders (19.4%) as having major differences, 42 disorders (40.8%) as having minor definitional differences, 10 disorders (9.7%) as having minor differences due to greater degree of specification in DSM-5, and 31 disorders (30.1%) as essentially identical. Detailed descriptions of the major differences and some of the most important minor differences, with their rationale and related evidence, are provided. The ICD and DSM are now closer than at any time since the ICD-8 and DSM-II. Differences are largely based on the differing priorities and uses of the two diagnostic systems and on differing interpretations of the evidence. Substantively divergent approaches allow for empirical comparisons of validity and utility and can contribute to advances in the field.

Key words: ICD-11, DSM-5, diagnosis, classification, mental disorders, neurodevelopmental disorders, primary psychotic disorders, mood disorders, anxiety and fear-related disorders, disorders specifically associated with stress, disorders due to substance use, personality disorders, neurocognitive disorders

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The International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) have separate and intertwining histories that can be traced back to the mid-20th century, with both the World Health Organization (WHO) and the American Psychiatric Association (APA) having a "legitimate historical claim to the intellectual foundations of modern classifications of mental disorders"[1,p.78].

The harmonization of the two classifications reached its peak with the ICD-8[2] and DSM-II[3], which were nearly identical, as a result of the close collaboration between the two sponsoring organizations in their development. The introduction to the DSM-II indicates that this reflected "the growth of the concept that the people of all nations live in one world; with the increasing success of the World Health Organization in promoting its uniform International Classification of Diseases, already used in many countries, the time came for psychiatrists of the United States to collaborate"[3, p. vii].

Although there were parallel developments on both sides of the Atlantic[1,4], the DSM-III[5] is widely credited with introducing an empirical approach to mental disorder diagnosis that was neutral with respect to causality and included explicit diagnostic criteria originally developed for research.

An early question for the DSM-III Task Force was whether to participate in the development of the ICD-9[6], already underway at that time. According to R. Spitzer, the chair and driving force of the DSM-III, the Task Force believed that, despite the value of a single international classification system, it was more important that psychiatric classification benefit from new developments in the US: "We were relatively unconcerned by frequently having a different definition of a DSM category than of a corresponding ICD-9 category. We believed it was a small price to pay for our ability to be innovative." [7, p.353]. Although the DSM-III was intended primarily for use in the US, it was translated into 13 languages[8] and had substantial international impact[9].

There was considerable collaboration between the developers of the ICD-10[10] and DSM-IV[11]. Beginning In 1978, the US Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) sponsored a 16-year collaboration with the WHO and APA that

was instrumental to the development and harmonization of those diagnostic systems[12]. Both the WHO and APA agreed that, for the purpose of international collaboration and research, differences between the two systems should be minimized.

To evaluate the success of the ICD-10/DSM-IV harmonization effort, M. First conducted a detailed analysis[13] of the 176 criteria sets included in both the DSM-IV and the ICD-10 Research Diagnostic Criteria[14], which was the version of the ICD-10 most similar to the DSM-IV. This analysis revealed that the two sets of criteria were identical for only one disorder (transient tic disorder). In contrast, 21% of the criteria sets had conceptually based differences that appeared to be intentional, and 78% had differences reflecting dissimilar ways of operationalizing the same diagnostic construct, which often appeared to be arbitrary or unintentional.

Both the ICD-10 and DSM-IV have had substantial impact on global psychiatric practice and research. While the DSM-IV was used much more often in research around the world[1], a study of nearly 5,000 psychiatrists in 44 countries conducted by the World Psychiatric Association and the WHO indicated that, for a substantial majority of psychiatrists outside the US, the ICD-10 is the classification most used in daily clinical practice[15]. A subsequent study[16] indicated that the version of the ICD-10 most used in clinical practice is the Clinical Descriptions and Diagnostic Guidelines (CDDG)[17], developed by the WHO Department of Mental Health and Substance Use for "general clinical, educational and service use"[17,p.1] by psychiatrists and other mental health professionals.

As with the ICD-10 and DSM-IV, the ICD-11 classification of mental disorders and the DSM-5[18] were developed during overlapping time periods, and both the WHO and APA again noted the desirability of harmonization. Several aspects of the ICD-11 and DSM-5 development processes promoted this goal. An ICD-DSM Harmonization Group was appointed and met several times, with discussions primarily focused on the organization of the groupings in the classifications (referred to as the "metastructure"[19]). The DSM-5 leadership attended meetings of the ICD-11 Advisory Group, and the leadership of the ICD-11 group attended DSM-5 Task Force meetings. Most ICD-11 Working Groups included experts who were also members of the corresponding DSM-5 Workgroups.

The stated task of ICD-11 Working Groups included an evaluation of the DSM-5 proposals in their area of work and whether these were suitable for global application (because the ICD-11 Working Groups had just started their work as the DSM-5 development process was drawing to a close, there was no similar opportunity for the DSM-5 Workgroups to examine drafts of the ICD-11 material). While there was no prohibition against ICD-11 proposals deviating from the DSM-5, the expectation was that such deviations be intentional rather than arbitrary or accidental, and that the Working Groups be able to articulate a rationale for the differences.

The purpose of the present analysis is to evaluate the success of these harmonization efforts, as well as to provide a guide for practitioners, researchers and policy makers describing the important differences between the two systems. We compared the version of the ICD-11 intended for use by mental health professionals in clinical settings (the ICD-11 CDDG[20]) with the DSM-5 in terms of the degree to which the two systems are harmonized at both the organizational and the disorder-by-disorder level.

HARMONIZATION AT THE ORGANIZATIONAL LEVEL

The ICD-DSM Harmonization Group was mostly focused on harmonizing the organization of the diagnostic groupings in the classifications, or "metastructure". As can be seen in Table 1, this effort was largely successful. The initial chapters (through Dissociative Disorders) are almost completely harmonized, except for the absence of an overarching Mood Disorders grouping in the DSM-5, and Catatonia being a separate grouping in the ICD-11. From Feeding and Eating Disorders onward, there are differences both in the ordering of the diagnostic groupings and in granularity. For example, Disorders of Bodily Distress and Bodily Experience, Factitious Disorders, and Psychological and Behavioural Factors Affecting Disorders or Diseases Classified Elsewhere, each of which is a separate diagnostic grouping in the ICD-11, are all subsumed by the Somatic Symptom and Related Disorders grouping in the DSM-5.

Moreover, some DSM-5 diagnostic groupings correspond to groupings located in parts of the ICD-11 outside the chapter on Mental, Behavioural and Neurodevelopmental Disorders (Chapter 6). In the ICD-11, Sleep-Wake Disorders is a separate chapter (Chapter 7) that combines entities previously located across the ICD-10 chapters on Mental and Behavioural Disorders, Diseases of the Nervous System, and Diseases of the Respiratory System. The new ICD-11 chapter on Conditions Related to Sexual Health (Chapter 17) contains Sexual Dysfunctions and the Gender Incongruence grouping, which corresponds to the DSM-5 Gender Dysphoria grouping. There are significant differences between the ICD-11 and DSM-5 with regard to these sexual health conditions, which have been reviewed in this journal[21].

There are also some differences regarding the placement of certain disorders in diagnostic groupings, reflecting differences in perspectives and underlying organizational principles in the ICD-11 and DSM-5. In the ICD-11, Hypochondriasis is defined as a preoccupation with or fear about the possibility of having a serious, progressive or life-threatening illness, accompanied by either repetitive and excessive health-related behaviours, such as repeatedly checking the body for evidence of illness, or maladaptive avoidance behaviour. It is included in the grouping of Obsessive-Compulsive and Related Disorders based on shared phenomenological features (repetitive thoughts about having an illness, and repeated and excessive behaviours driven by the preoccupation)[22], high rates of co-occurrence and tendency to run in families with the other disorders of the grouping[23], and a similar response to treatments[24]. The presence of somatic symptoms is not an essential feature of Hypochondriasis in the ICD-11, although they may occur transiently and be a focus of considerable

Table 1 Comparison of the ICD-11 vs. the DSM-5 metastructure

ICD-11	DSM-5
Neurodevelopmental Disorders	Neurodevelopmental Disorders
Schizophrenia and Other Primary Psychotic Disorders	Schizophrenia Spectrum and Other Psychotic Disorders
Catatonia	
Mood Disorders	Bipolar and Related Disorders
	Depressive Disorders
Anxiety and Fear-Related Disorders	Anxiety Disorders
Obsessive-Compulsive and Related Disorders	Obsessive-Compulsive and Related Disorders
Disorders Specifically Associated with Stress	Trauma- and Stressor-Related Disorders
Dissociative Disorders	Dissociative Disorders
Feeding and Eating Disorders	Feeding and Eating Disorders
Elimination Disorders	Elimination Disorders
Disorders of Bodily Distress and Bodily Experience	Somatic Symptom and Related Disorders (not in the same order as ICD-11; placed before Feeding and Eating Disorders)
Disorders Due to Substance Use and Addictive Behaviours	Substance-Related and Addictive Disorders
Impulse Control Disorders	Disruptive, Impulse-Control, and Conduct Disorders
Disruptive Behaviour and Dissocial Disorders	
Personality Disorders and Related Traits	Personality Disorders (not in the same order as ICD-11; placed after Neurocognitive Disorders)
Paraphilic Disorders	Paraphilic Disorders (not in the same order as ICD-11; placed after Personality Disorders)
Factitious Disorders	Not a separate grouping but included in Somatic Symptom and Related Disorders
Neurocognitive Disorders	Neurocognitive Disorders
Mental or Behavioural Disorders Associated with Pregnancy, Childbirth and the Puerperium	Not a separate grouping; perinatal specifiers available for specific disorders
Secondary Mental or Behavioural Syndromes Associated with Disorders or Diseases Classified Elsewhere	Not a separate grouping but included within the disorder groupings with which they share phenomenology
Psychological and Behavioural Factors Affecting Disorders or Diseases Classified Elsewhere	Not a separate grouping but included in Somatic Symptom and Related Disorders
Sleep-Wake Disorders (Chapter 7)	Sleep-Wake Disorders (within mental disorders; placed after Elimination Disorders)
Sexual Dysfunctions (placed in Chapter 17, Conditions Related to Sexual Health)	Sexual Dysfunctions (within mental disorders; placed after Sleep-Wake Disorders)
Gender Incongruence (placed in Chapter 17, Conditions related to Sexual Health)	Gender Dysphoria (within mental disorders; placed after Sexual Dysfunctions)

preoccupation when they occur[22]. On the other hand, the DSM-5 classifies cases of Hypochondriasis as either Somatic Symptom Disorder or Illness Anxiety Disorder (both of which are located in the Somatic Symptom and Related Disorders grouping) depending on whether or not the person's excessive concerns are related to somatic symptoms that the person is currently experiencing. Analogously, Functional Neurological Symptom Disorder is included in the Somatic Symptom and Related Disorders grouping in DSM-5, whereas its ICD-11 counterpart (Dissociative Neurological Symptom Disorder) is included in the Dissociative Disorders grouping, reflecting the fact that the ICD-11 conceptualizes the neurologic-like symptoms as being the result of a dissociative process ("involuntary disruption or discontinuity in the normal integration of motor, sensory or cognitive functions").

The ICD-11 also differs from the DSM-5 in its placement of Secondary Mental or Behavioural Syndromes Associated with Disorders or Diseases Classified Elsewhere, which correspond to Mental Disorders Due to Another Medical Condition in the DSM-5. By ICD-11 convention, these syndromes are all placed together in a single etiology-based diagnostic grouping. The DSM-5, instead, distributes these conditions to the various diagnostic groupings with which they share the symptomatology (e.g., Psychotic Disorder Due to Another Medical Condition is included in the Schizophrenia Spectrum and Other Psychotic Disorders grouping), giving priority to facilitating differential diagnosis. It should be noted that the ICD-11 for the first time allows the same disorder to be listed in multiple diagnostic groupings at the same time, with one of the appearances denoted as primary. There-

fore, the "secondary" disorders in ICD-11 are also cross-listed in the respective symptomatic groupings.

HARMONIZATION AT THE DISORDER LEVEL

The current analysis focused primarily on the examination of differences between the ICD-11 CDDG and the DSM-5 diagnostic criteria at the disorder level, following a systematic methodology.

The disorders in the ICD-11 CDDG and the parallel disorders in the DSM-5 were first reviewed to identify those that appear in both diagnostic systems. Disorders in the DSM-5 that correspond to disorders that are now included in other chapters of ICD-11 (Sleep-Wake Disorders, Sexual Dysfunctions, and Gender Incongruence) were excluded from the comparison. Other and Unspecified categories were also excluded from the analysis.

For each disorder that appears in both the ICD-11 and DSM-5, the two principal authors (MBF and GMR) compared the Essential Features section[20] of the ICD-11 CDDG to the DSM-5 diagnostic criteria, and rated the extent of agreement according to four designations.

A rating of "major difference" was assigned if there were either: a) significant conceptual differences between the ICD-11 and DSM-5 diagnostic requirements, or b) cases in which the two systems were likely to identify different individuals as having the disorder. A rating of "minor definitional difference" was assigned if both the ICD-11 and DSM-5 were describing the same diagnostic entity on a conceptual level, but differed in how an aspect of the disorder was defined. A rating of "minor difference due to degree of specification" was assigned if both the ICD-11 and DSM-5 were identifying essentially the same diagnostic entity on a conceptual level, but differed in the specificity of operationalization. A rating of "essentially identical" was assigned if the definitions were entirely identical or the differences in wording were judged to be so inconsequential that exactly the same group of individuals was likely to be identified.

MBF and GMR assigned their ratings independently and then discussed divergent ratings in order to achieve a consensus. These ratings were not based on empirical evidence, as there has been only a small number of studies comparing the ICD-11 CDDG and DSM-5 criteria for a particular disorder in terms of whether they are identifying the same people or yield similar prevalence estimates[25,26]. Rather, these ratings reflected the judgement of the two principal authors. Differences in available qualifiers (specifiers in the DSM-5) and their definitions were not covered in the current analysis. When a single disorder in one system corresponded to more than one disorder in the other system, the disorders were counted as a single diagnostic entity.

A total of 26 disorders appear in one system but not in the other, with 19 disorders included in the ICD-11 but not in the DSM-5, and seven disorders included in the DSM-5 but not in the ICD-11 (see Table 2). Of those that are in the ICD-11 but not in the DSM-5, eleven are newly added disorders, the rationale for the inclusion of most of which has been previously described in this journal[27].

The main reason why these disorders appear in the ICD-11 but not in the DSM-5 is the difference in the criteria for inclusion of a new disorder based on the priorities of the sponsoring organizations. The WHO tended to prioritize public health needs in its decisions[28]: if there was convincing empirical evidence for the existence of a particular condition and that it was a legitimate focus of health care services, it was consistent with the purpose of the ICD-11 to include it in the classification. From the APA's perspective, in contrast, concerns about the proliferation of new psychiatric diagnoses going back to the DSM-IV[29] resulted in the requirement for a considerable degree of supporting empirical evidence in order for a diagnosis to be added. This requirement became so stringent in the DSM-5[30] that only a few proposed diagnoses were ultimately approved for inclusion.

Diagnoses added to the DSM-5 that are not in the ICD-11 include Social (Pragmatic) Communication Disorder and Disruptive Mood Dysregulation Disorder. There continues to be controversy about the empirical support for their designation as separate diagnostic categories[31,32], and the ICD-11 Working Groups viewed the available evidence as insufficient to justify their inclusion in the ICD-11.

The 103 disorders appearing in both the ICD-11 and DSM-5 were rated regarding the extent and nature of the differences in their diagnostic requirements in the two systems. Based on the consensus assessment, disorders rated as having major differences between the two systems (20 diagnostic entities, or 19.4% of those rated) are shown in Table 3. Disorders rated as having minor definitional differences (42 disorders; 40.8%) are listed in Table 4, and those with minor differences due to greater degree of specification in the DSM-5 (10 disorders; 9.7%) are shown in Table 5. Those rated as essentially identical (31 disorders; 30.1%) are listed in Table 6. The following sections of this paper focus on the major differences between the ICD-11 and DSM-5 and some of the most important instances of minor differences, including the rationale and related evidence.

Neurodevelopmental Disorders

Developmental Language Disorder / Language Disorder plus Social (Pragmatic) Communication Disorder

The ICD-11 CDDG for Developmental Language Disorder and the DSM-5 criteria for Language Disorder require deficits in the acquisition and use of language skills (e.g., limited sentence structure, reduced vocabulary), but the ICD-11 also includes "the ability to understand and use language in social contexts, for example making inferences, understanding verbal humour and resolving ambiguous meaning (i.e., pragmatics)". Individuals with deficits primarily in this area would receive the diagnosis of Developmental Language Disorder with the qualifier "impairment of mainly pragmatic language".

Individuals with these same deficits, but without the additional features characteristic of Autism Spectrum Disorder, are

Table 2 Mental disorders included in one system but not the other

ICD-11	DSM-5
Developmental Language Disorder with impairment of mainly pragmatic language	**Social (Pragmatic) Communication Disorder***
Schizophrenia or Other Specified Primary Psychotic Disorder	**Schizophreniform Disorder**
Acute and Transient Psychotic Disorder	Brief Psychotic Disorder
Catatonia Induced by Substances or Medications*	Other Substance-Induced Disorder
Mixed Depressive and Anxiety Disorder	Other Specified Depressive Disorder or Other Specified Anxiety Disorder
Olfactory Reference Syndrome*	Other Specified Obsessive-Compulsive and Related Disorder
Complex Post-Traumatic Stress Disorder*	Post-Traumatic Stress Disorder or Adjustment Disorder (if stressor does not qualify for Post-Traumatic Stress Disorder) or Other Specified Trauma and Stressor-Related Disorder
Prolonged Grief Disorder*	Other Specified Trauma and Stressor-Related Disorder; included among Conditions for Further Study as Persistent Complex Bereavement Disorder°
Trance Disorder	Other Specified Dissociative Disorder
Possession Trance Disorder	Dissociative Identity Disorder or Other Specified Dissociative Disorder
Partial Dissociative Identity Disorder*	Dissociative Identity Disorder (for cases with dissociative amnesia), or Other Specified Dissociative Disorder (for cases without dissociative amnesia)
Body Integrity Dysphoria*	Other Specified Mental Disorder
Episode of Harmful Substance Use*	Unspecified Substance-Related Disorder
Other Specified Disorders Due to Use of Hallucinogens	**Hallucinogen Persisting Perception Disorder**
Nicotine Intoxication	Other Tobacco-Induced Disorder
Volatile Inhalant Withdrawal	Other Inhalant-Induced Disorder
Gaming Disorder*	Other Specified Mental Disorder; included among Conditions for Further Study as Internet Gaming Disorder
Compulsive Sexual Behaviour Disorder*	Other Specified Disruptive, Impulse-Control, and Conduct Disorder
Oppositional Defiant Disorder, with chronic irritability-anger	**Disruptive Mood Dysregulation Disorder***
Paraphilic Disorder Involving Solitary Behaviour or Consenting Individuals	**Fetishistic Disorder** **Transvestic Fetishistic Disorder** **Sexual Masochistic Disorder**
Amnestic Disorder	Major Neurocognitive Disorder
Secondary Neurodevelopmental Syndrome*	Other Specified Neurodevelopmental Disorder
Secondary Dissociative Syndrome	Other Specified Dissociative Disorder
Secondary Impulse Control Syndrome*	Other Specified Disruptive, Impulse Control, and Conduct Disorder, or Personality Change Due to Another Medical Condition

Bold prints indicate that the disorder is included in the corresponding diagnostic system, whereas non-bold prints indicate the closest available category in the other system. Asterisks indicate newly added disorders. °Prolonged Grief Disorder is going to be included in the DSM-5-TR.

diagnosed in the DSM-5 as having Social (Pragmatic) Communication Disorder. These individuals previously received, according to the DSM-IV, the diagnosis of Pervasive Developmental Disorder Not Otherwise Specified, but this category has been eliminated from the DSM-5[33].

Although the ICD-11 Working Group considered adding the category of Social (Pragmatic) Communication Disorder, it concluded that there was insufficient evidence of a disorder in social communication separable from Autism Spectrum Disorder on the one hand and Developmental Language Disorder on the other[32,34].

Autism Spectrum Disorder

The ICD-11 CDDG and the DSM-5 criteria for Autism Spectrum Disorder are similar in their conceptualization of autism as a broad category ("spectrum") comprising many different presentations, and in their specific phenomenological requirements of: a) persistent deficits in social communication/social interaction; and b) restricted, repetitive and inflexible patterns of behaviour, interests or activities. However, although they are intended to identify the same people, there are some differences in diagnostic requirements.

Table 3 Disorders or diagnostic entities with major differences between the two diagnostic systems

Developmental Language Disorder in ICD-11 / Language Disorder *plus* Social (Pragmatic) Communication Disorder in DSM-5
Schizophrenia in ICD-11 / Schizophrenia *plus* Schizophreniform Disorder in DSM-5
Schizoaffective Disorder
Acute and Transient Psychotic Disorder in ICD-11 / Brief Psychotic Disorder in DSM-5
Mixed Episode in ICD-11 / Mood Episode with Mixed Features in DSM-5
Dysthymic Disorder in ICD-11 / Persistent Depressive Disorder in DSM-5
Hypochondriasis (in Obsessive-Compulsive and Related Disorders) in ICD-11 / Somatic Symptom Disorder or Illness Anxiety Disorder in DSM-5
Post-Traumatic Stress Disorder *plus* Complex Post-Traumatic Stress Disorder in ICD-11 / Post-Traumatic Stress Disorder in DSM-5
Adjustment Disorder
Acute Stress Reaction (in Factors Influencing Health Status or Contact with Health Services) in ICD-11 / Acute Stress Disorder (in Trauma- and Stressor-Related Disorders) in DSM-5
Dissociative Identity Disorder *plus* Partial Dissociative Identity Disorder in ICD-11 / Dissociative Identity Disorder in DSM-5
Bulimia Nervosa
Binge Eating Disorder
Substance Dependence *plus* Harmful Pattern of Use of Substances in ICD-11 / Substance Use Disorder in DSM-5
Oppositional Defiant Disorder with chronic irritability-anger in ICD-11 / Disruptive Mood Dysregulation Disorder in DSM-5
Personality Disorders
Coercive Sexual Sadism Disorder in ICD-11 / Sexual Sadism Disorder (coercive) in DSM-5
Paraphilic Disorder Involving Solitary Behaviour or Consenting Individuals in ICD-11 / Fetishistic Disorder, Transvestic Disorder, Sexual Masochism Disorder, Sexual Sadism Disorder (noncoercive) in DSM-5
Dementia *plus* Amnestic Disorder in ICD-11 / Major Neurocognitive Disorder in DSM-5
Mental or Behavioural Disorders Associated with Pregnancy, Childbirth and the Puerperium, without and with psychotic symptoms in ICD-11 / "with peripartum onset" specifier in DSM-5

For deficits in social communication, the DSM-5 requires all three of the following: a) deficits in social-emotional reciprocity, b) deficits in nonverbal communication, and c) deficits in developing, maintaining and understanding relationships. Consistent with its general approach of focusing on the diagnostic concept rather than on symptom counts, the ICD-11 is less prescriptive, stating that "manifestations may include the following" and providing a list of seven items that include examples which correspond to the three DSM-5 requirements.

For restricted, repetitive and inflexible patterns, the DSM-5 item list is dominated by symptoms that tend to be found in children with both Autism Spectrum Disorder and Disorders of Intellectual Development (e.g., flipping objects, strong attachment or preoccupation with unusual objects, excessive smelling or touching of objects, echolalia). This reflects the emphasis on the association between autism and intellectual disability at the time that diagnostic criteria for autism were initially developed[35]. The ICD-11 examples include items that are more characteristic of individuals without intellectual disability, previously diagnosed as having Asperger's Syndrome but now encompassed within the autism spectrum. Again, the DSM-5 is more prescriptive than the ICD-11, requiring two out of a list of four items, whereas the ICD-11 provides a list of seven items as examples.

Attention Deficit Hyperactivity Disorder

The ICD-11 and DSM-5 diagnostic requirements for Attention Deficit Hyperactivity Disorder (ADHD) are broadly similar. While both diagnostic systems provide separate lists of inattention and hyperactivity-impulsivity symptoms, there are differences in the specifics, again consistent with ICD-11's focus on the overall diagnostic concept.

In the DSM-5, both the inattention and hyperactivity-impulsivity lists contain a total of nine symptoms. At least six out of the nine (or at least five if the person is age 17 or older) on either list is required for the diagnosis. The ICD-11 does not include a precise symptom count requirement, but instead provides two broad groups of symptoms which are intended to reduce the internal redundancy of the items, and requires "several" symptoms to be present in at least one of the symptom groups.

Moreover, while all of the DSM-5 symptoms are included as examples in the ICD-11 symptom groupings, the ICD-11 includes an additional item for hyperactivity-impulsivity that is not included in the DSM-5 list: "a tendency to act in response to immediate stimuli without deliberation or consideration of risks and consequences (e.g., engaging in behaviours with potential for physical injury; impulsive decisions; reckless driving)". This item was added to better correspond to adult manifestations of impulsivity[36].

Table 4 Disorders with minor definitional differences between the two diagnostic systems

Disorders of Intellectual Development in ICD-11 / Intellectual Disability (Intellectual Developmental Disorder) in DSM-5
Developmental Speech Sound Disorder in ICD-11 / Speech Sound Disorder in DSM-5
Autism Spectrum Disorder
Developmental Learning Disorder in ICD-11 / Specific Learning Disorder in DSM-5
Tourette Syndrome in ICD-11 / Tourette's Disorder in DSM-5
Chronic Motor Tic Disorder *plus* Chronic Phonic Tic Disorder in ICD-11 / Persistent Motor or Vocal Tic Disorder in DSM-5
Transient Motor Tics in ICD-11 / Provisional Tic Disorder in DSM-5
Attention Deficit Hyperactivity Disorder*
Stereotyped Movement Disorder in ICD-11 / Stereotypic Movement Disorder in DSM-5
Delusional Disorder
Depressive Episode in ICD-11 / Major Depressive Episode in DSM-5
Recurrent Depressive Disorder in ICD-11 / Major Depressive Disorder, Recurrent, in DSM-5
Cyclothymic Disorder
Generalized Anxiety Disorder
Obsessive-Compulsive Disorder
Body Dysmorphic Disorder
Hoarding Disorder
Reactive Attachment Disorder
Disinhibited Social Engagement Disorder
Bodily Distress Disorder in ICD-11 / Somatic Symptom Disorder in DSM-5
Alcohol Intoxication
Alcohol Withdrawal
Opioid Intoxication
Opioid Withdrawal
Cannabis Intoxication
Cannabis Withdrawal
Sedative Intoxication
Sedative Withdrawal
Stimulant Intoxication
Stimulant Withdrawal
Caffeine Intoxication
Caffeine Withdrawal
Hallucinogen Intoxication in ICD-11 / Other Hallucinogen Intoxication in DSM-5
Nicotine Withdrawal in ICD-11 / Tobacco Withdrawal in DSM-5
Volatile Inhalant Intoxication in ICD-11 / Inhalant Intoxication in DSM-5
Dissociative Drug Intoxication Including Ketamine or PCP in ICD-11 / Phencyclidine Intoxication in DSM-5
Gambling Disorder
Pyromania
Exhibitionistic Disorder
Voyeuristic disorder
Pedophilic Disorder
Frotteuristic Disorder

The asterisk indicates that there are also differences between the two diagnostic systems in terms of degree of specification

Table 5 Disorders with minor differences between the two diagnostic systems due to greater degree of specification in the DSM-5

Catatonia Associated with Another Mental Disorder
Manic Episode
Hypomanic Episode
Premenstrual Dysphoric Disorder
Panic Disorder
Agoraphobia
Specific Phobia
Social Anxiety Disorder
Separation Anxiety Disorder
Conduct-Dissocial Disorder in ICD-11 / Conduct Disorder in DSM-5

There is also a difference in the symptom onset requirement: while both the DSM-5 and ICD-11 require manifestations of ADHD by age 12, the ICD-11 requires evidence of *significant* inattention and/or hyperactivity-impulsivity symptoms prior to age 12, whereas the DSM-5 only requires that "several" symptoms be present prior to age 12.

Schizophrenia and Other Primary Psychotic Disorders

Schizophrenia

The ICD-11 and DSM-5 diagnostic requirements for Schizophrenia differ in several ways.

First, the two diagnostic systems have maintained the historical difference in the minimum duration: as in the ICD-10, the required minimum duration in the ICD-11 definition is "a period of 1 month or more", whereas the DSM-5, like the DSM-IV, requires that "continuous signs of the disturbance persist for at least 6 months". The DSM-5 requirement for an additional 5 months of symptoms can include prodromal or residual symptoms. Although both diagnostic systems require a full month of the defining psychotic symptoms, the DSM-5 diagnostic requirements are more likely to identify patients with a higher tendency to chronicity[37].

The ICD-11's shorter duration requirement, along with the introduction of a first-episode course qualifier (also introduced in the DSM-5), is intended to encourage earlier initiation of appropriate treatment, which has been shown to improve patient outcomes[38]. The DSM-5 category of Schizophreniform Disorder, which differs from Schizophrenia primarily with respect to the duration of symptoms (an episode lasting at least 1 month but less than 6 months), is not included in the ICD-11.

The required pattern of symptoms differs as well. While both the DSM-5 and ICD-11 require at least two types of symptoms lasting at least 1 month, the ICD-11 includes "experiences of influence, passivity or control" as a separate core symptom. These disturbances in the "ego-world boundary"[39] involve patients having experiences such as their thoughts, actions or emotions being imposed by an outside force (passivity experiences), their thoughts being physically removed from their mind (thought withdrawal), or their thoughts being transmitted to others (thought broadcasting).

Such disturbances were included among Schneider's first-rank symptoms[39], which he considered to be characteristic of schizophrenia in the absence of organic conditions. Although first-rank symptoms have been de-emphasized in the ICD-11[40], experiences of influence, passivity or control were judged to be sufficiently important and distinctive to be retained. In the DSM-5, these symptoms are considered to be examples of delusions, while the ICD-11 keeps "experiences" separate from the delusions ("beliefs") which may or not be based on them.

While the DSM-5 restricts negative symptoms of Schizophrenia to diminished emotional expression and avolition, the ICD-11 also includes alogia or paucity of speech, asociality and anhedonia. Furthermore, the DSM-5 requires a deterioration in functioning in one or more major areas, such as work, interpersonal relations or self-care, since the onset of the disturbance. There is no such requirement in the ICD-11, although the text mentions that the diagnosis is "frequently associated" with significant functional impairment. This reflects the WHO's position that functional impairment should not be included in clinical descriptions of mental disorders unless this is necessary to distinguish disorder from normality[28].

Although the DSM-5 and ICD-11 both allow specification of the level of severity for various symptom domains, these domains and their assessment are different in the two systems. The ICD-11 identifies six symptom domains, rated on a 4-point scale (not present, mild, moderate, severe): positive symptoms (which include delusions, hallucinations, experiences of passivity and control, disorganized thinking, and disorganized behaviour), negative symptoms, depressive mood symptoms, manic mood symptoms, psychomotor symptoms, and cognitive symptoms. The DSM-5 identifies three separate domains (hallucinations, delusions, disorganized speech) corresponding to the single ICD-11 positive symptom dimension, in addition to the domains of negative symptoms, impaired cognition, abnormal psychomotor behaviour, depression and mania. These domains are rated on a 5-point scale (not present, equivocal, mild, moderate, severe). In the DSM-5, these ratings are included in an appendix entitled "Emerging Measures and Models", whereas in the ICD-11 they appear in the main body of the CDDG.

Schizoaffective Disorder

There are significant differences between the ICD-11 and DSM-5 in their conceptualization of Schizoaffective Disorder.

In the ICD-11, the diagnostic requirements for schizophrenia have to be met concurrently with those for a moderate or severe depressive episode, a manic episode or a mixed episode, with a duration of at least one month, and an onset of the psychotic and mood symptoms either simultaneously or within a few days of each other. Because this definition focuses on the pattern of

Table 6 Disorders with essentially identical definitions in the two diagnostic systems

Developmental Speech Fluency Disorder in ICD-11 / Childhood Onset Speech Fluency Disorder in DSM-5
Developmental Motor Coordination Disorder in ICD-11 / Developmental Coordination Disorder in DSM-5
Schizotypal Disorder in ICD-11 / Schizotypal Personality Disorder in DSM-5
Single Episode Depressive Disorder in ICD-11 / Major Depressive Disorder, Single Episode in DSM-5
Bipolar Type I Disorder in ICD-11 / Bipolar I Disorder in DSM-5
Bipolar Type II Disorder in ICD-11 / Bipolar II Disorder in DSM-5
Selective Mutism
Trichotillomania
Excoriation Disorder
Dissociative Neurological Symptom Disorder in ICD-11 (in Dissociative Disorders) / Functional Neurological Symptom Disorder in DSM-5 (in Somatic Symptom and Related Disorders)
Dissociative Amnesia
Depersonalization-Derealization Disorder
Anorexia Nervosa
Avoidant Restrictive Food Intake Disorder
Pica
Rumination-Regurgitation Disorder in ICD-11 / Rumination Disorder in DSM-5
Enuresis
Encopresis
Kleptomania
Intermittent Explosive Disorder
Factitious Disorder Imposed on Self (in Factitious Disorders in ICD-11 and in Somatic Symptom and Related Disorders in DSM-5)
Factitious Disorder Imposed on Another (in Factitious Disorders in ICD-11 and in Somatic Symptom and Related Disorders in DSM-5)
Delirium
Mild Neurocognitive Disorder
Secondary Psychotic Syndrome in ICD-11 (in Secondary Mental or Behavioural Syndromes Associated with Disorders or Diseases Classified Elsewhere) / Psychotic Disorder Due to Another Medical Condition in DSM-5 (in Schizophrenia Spectrum and Other Psychotic Disorders)
Secondary Mood Syndrome in ICD-11 (in Secondary Mental or Behavioural Syndromes Associated with Disorders or Diseases Classified Elsewhere) / Bipolar and Related Disorder Due to Another Medical Condition in DSM-5 (in Bipolar and Related Disorders) *plus* Depressive Disorder Due to Another Medical Condition in DSM-5 (in Depressive Disorders)
Secondary Anxiety Syndrome in ICD-11 (in Secondary Mental or Behavioural Syndromes Associated with Disorders or Diseases Classified Elsewhere) / Anxiety Disorder Due to Another Medical Condition in DSM-5 (in Anxiety Disorders)
Secondary Obsessive-Compulsive or Related Syndrome in ICD-11 / Obsessive-Compulsive and Related Disorder Due to Another Medical Condition in DSM-5 (in Obsessive-Compulsive and Related Disorders)
Secondary Personality Change in ICD-11 / Personality Change Due to Another Medical Condition in DSM-5 (in Personality Disorders)
Secondary Catatonia Syndrome in ICD-11 / Catatonic Disorder Due to Another Medical Condition in DSM-5 (in Schizophrenia Spectrum and Other Psychotic Disorders)
Psychological and Behavioural Factors Affecting Disorders or Diseases Classified Elsewhere in ICD-11 / Psychological Factors Affecting Other Medical Conditions in DSM-5 (in Somatic Symptom and Related Disorders)

symptoms during the current episode, an individual's presentation can meet the diagnostic requirements for Schizoaffective Disorder, Schizophrenia or a Mood Disorder during different episodes of his/her illness.

In contrast, as in the DSM-IV, the DSM-5 diagnostic criteria involve a retrospective assessment of the interplay between mood and psychotic symptoms across the entire course of the disturbance. The DSM-5 requires that there be: a) an uninterrupted period of illness during which there is a major depressive or manic episode concurrent with the symptomatic criteria for schizophrenia; b) a period of delusions or hallucinations lasting at least 2 weeks occurring in the absence of a major depressive or manic episode at some point during the lifetime duration of the illness; and c) symptoms that meet criteria for a major depressive or manic episode for the majority of the total duration of the active and residual portions of the illness.

All of this can lead to different diagnoses in the DSM-5 and ICD-11. For example, some cases that would receive a diagnosis of Schizoaffective Disorder in the DSM-5 (e.g., one month of delusions and hallucinations evolving into a month of delusions and hallucinations concurrent with a major depressive episode) would be diagnosed with Schizophrenia according to the ICD-11. On the other hand, some cases that would receive a diagnosis of Major Depressive Episode with Psychotic Features in the DSM-5 (e.g., delusions and hallucinations occurring entirely within the mood episode) would be diagnosed with Schizoaffective Disorder according to the ICD-11.

These approaches to the diagnosis of Schizoaffective Disorder in the ICD-11 and DSM-5 partly reflect different decisions regarding the trade-off between diagnostic stability (an aspect of diagnostic validity)[41] and diagnostic feasibility, which strongly influences reliability. Because the DSM-5 diagnosis depends on a consideration of the lifetime course of the symptoms, it is designed to be relatively stable. But this same lifetime approach can make the achievement of good diagnostic reliability quite challenging. Indeed, reliability problems have long been noted in the DSM diagnosis of Schizoaffective Disorder[42]. In contrast, the ICD-11 approach highlights the changing nature of the clinical presentation of many psychotic disorders over time.

Acute and Transient Psychotic Disorder / Brief Psychotic Disorder

This ICD-11 category of Acute and Transient Psychotic Disorder involves the acute onset of psychotic symptoms within 2 weeks, changing rapidly both in nature and intensity from day to day, and lasting up to three months (although most commonly from a few days to one month).

Unlike the ICD-10, which included several possible presentations, the ICD-11 restricts the diagnosis to the presentation referred to as "polymorphic" in the ICD-10, based on its greater diagnostic stability[43,44], and discourages the use of this category for early presentations of Schizophrenia.

The closest available DSM-5 category, Brief Psychotic Disorder, is based entirely on the duration of psychotic symptoms (less than 1 month) and has no requirement for fluctuating symptoms.

The different approach to Acute and Transient Psychotic Disorders in the ICD-11 is in part related to the international nature of this classification system and the evidence that those conditions are particularly frequent in low- and middle-income countries and among migrant populations[43,45].

Mood disorders

Depressive Episode / Major Depressive Episode

The ICD-11 and DSM-5 definitions of a (major) depressive episode are nearly the same: at least five symptoms persisting nearly every day for at least 2 weeks, of which at least one must be depressed mood or loss of interest or pleasure. The only difference is that the ICD-11 requires five symptoms out of a list of ten, whereas the DSM-5 list includes only nine symptoms. The additional symptom in the ICD-11 is hopelessness about the future, which was included because of empirical evidence that it performs more strongly than about half of the other depressive symptoms in differentiating depressed from non-depressed individuals[46]. In contrast, the DSM-5 includes "feeling hopeless" as one example of a subjective indicator of depressed mood.

The ICD-11 and DSM-5 also differ in their instructions for diagnosing a Depressive Episode during the grieving process. The ICD-11 CDDG direct the clinician to make a diagnosis of Depressive Episode only if the symptoms are not better accounted for by bereavement[47], providing the following guidance: "the presence of a Depressive Episode during a period of bereavement is suggested by persistence of constant depressive symptoms a month or more following the loss (i.e., there are no periods of positive mood or enjoyment of activities), severe depressive symptoms such as extreme beliefs of low self-worth and guilt not related to the lost loved one, presence of psychotic symptoms, suicidal ideation, or psychomotor retardation". Although the DSM-5 does not include a criterion instructing the clinician not to diagnose a depressive episode if the symptoms represent a normal grief reaction, it does provides a note stating the "presence of a Major Depressive Episode in addition to the normal response to a significant loss should… be carefully considered", and then provides a footnote describing some of the differences between normal grief and a Major Depressive Episode.

The ICD-11 approach to this issue has been supported by longitudinal prospective studies[48,49], reporting that the risk of subsequent depressive episodes in individuals with baseline bereavement-related depression was not different from people without a history of depression at baseline, and significantly lower than individuals with baseline non-bereavement-related depression, suggesting that bereavement-related episodes should not be considered equivalent to other depressive episodes.

Mixed Episode / Major Depressive, Manic or Hypomanic Episode with mixed features

The ICD-11 Mood Disorders section provides guidelines for four types of mood episodes: Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode. Mixed Episode is defined as a period lasting at least two weeks characterized by the presence of several prominent manic and several prominent depressive symptoms which either occur simultaneously or alternate very rapidly (from day to day or within the same day). It is specified that, when manic symptoms predominate, common contrapolar symptoms are dysphoric mood, expressed beliefs of worthlessness, hopelessness and suicidal ideation. When depressive symptoms predominate, common contrapolar symptoms are irritability, racing or crowded thoughts, increased talkativeness and increased activity. The mood state is altered throughout the episode (i.e., the mood should be depressed, dysphoric, euphoric

or expansive for at least two weeks).

The DSM-5 includes only three types of mood episodes: Major Depressive, Manic and Hypomanic. Rather than including a Mixed Episode, it provides a "mixed features" specifier that can be applied to all three types of mood episodes. When applied to a manic or hypomanic episode, this specifier indicates that at least three characteristic symptoms of depression have been present for a majority of days of the episode. When applied to a major depressive episode, it indicates that at least three characteristic symptoms of mania (e.g., elevated or expansive mood, increased self-esteem, increased involvement in risky activities) have been present for a majority of days of the depressive episode.

The DSM-5 characterization of major depression with mixed features has been criticized, because it does not include several elements that are regarded as characteristic of mixed depression in both the classic and the recent literature (i.e., irritability and agitation)[50]. Indeed, the implications of a DSM-5 diagnosis of major depression with mixed features in terms of treatment response have been found to be different from those of mixed depression as usually defined in the literature[51]. Furthermore, the DSM-5 does not account for "unstable" mixed episodes, in which depressive and manic symptoms alternate rapidly rather than occurring simultaneously.

Dysthymic Disorder / Persistent Depressive Disorder

The ICD-11 continues to have a separate category for Dysthymic Disorder (persistent depressed mood accompanied by additional depressive symptoms for most of the day, more days than not, without full depressive episodes during the first two years). After the first two years, if the diagnostic requirements for Single Episode Depressive Disorder or Recurrent Depressive Disorder are met, the appropriate diagnosis may be assigned in addition to Dysthymic Disorder. The qualifier "current episode persistent" may be applied to Single Episode Depressive Disorder or Recurrent Depressive Disorder if the current episode has persisted for more than 2 years.

In contrast, the DSM-5 combines dysthymic disorder and chronic major depressive disorder into a single category, Persistent Depressive Disorder, giving priority to chronicity over symptomatic variation and severity. This approach was not adopted in the ICD-11 because the current diagnostic scheme was considered to be more precisely descriptive at any given time, with related treatment implications, and because the evidence that chronic major depressive disorder and dysthymic disorder are the same condition was felt by the Working Group to be insufficient.

Anxiety and Fear-Related Disorders

Generalized Anxiety Disorder

For a diagnosis of Generalized Anxiety Disorder (GAD), both the ICD-11 and DSM-5 require symptoms of anxiety that persist for more days than not. The two descriptions, however, differ in the duration requirement and in the manifestations of anxiety.

Whereas the minimum required duration of GAD symptoms in the DSM-5 is 6 months, the ICD-11 only requires that the symptoms be present "for at least several months", following evidence that individuals with GAD-like presentations lasting less than 6 months are similar to those with episodes of 6 months or more in terms of onset, persistence, impairment, comorbidity, parental GAD, and socio-demographic correlates[52].

Both systems allow the diagnosis to be assigned based on the core feature of anxiety and worry focused on a number of different events, activities or aspects of life, but the ICD-11 also allows general apprehensiveness that is not restricted to any environmental circumstance (so-called "free-floating anxiety") as a basis for the diagnosis. This is supported by evidence that some patients are unable to describe the cognitive content of their worries[53] and that cross-cultural application of the DSM-5 requirement may miss cases[54,55].

The ICD-11 and DSM-5 lists of associated symptoms also differ slightly. They share five out of six symptoms, but the ICD-11 includes "sympathetic autonomic overactivity" rather than "being easily fatigued" in the DSM-5, because of its greater utility in differentiating GAD from a depressive episode[56].

Obsessive-Compulsive and Related Disorders

Hypochondriasis / Somatic Symptom Disorder or Illness Anxiety Disorder

The ICD-11 defines Hypochondriasis as a persistent preoccupation with or fear about the possibility of having a serious medical illness, associated with a catastrophic misinterpretation of bodily symptoms, which can be manifest either in repetitive and excessive health-related behaviours or in maladaptive health-related avoidance[57].

Such cases would be diagnosed in the DSM-5 as either Somatic Symptom Disorder or Illness Anxiety Disorder, depending on whether the person's excessive concerns about medical illness stem from misinterpreting the significance of somatic symptoms currently being experienced (in which case the diagnosis would be Somatic Symptom Disorder) or the health anxiety is occurring in the absence of significant somatic symptoms (in which case the diagnosis would be Illness Anxiety Disorder).

Disorders Specifically Associated with Stress

Post-Traumatic Stress Disorder

The ICD-11 provides two separate diagnostic categories for psychiatric symptoms lasting at least several weeks that develop in the context of exposure to severely traumatic events: Post-Traumatic Stress Disorder (PTSD) and Complex Post-Traumatic Stress Disorder (CPTSD). PTSD is intended to capture the core of

post-traumatic response (re-experiencing the traumatic event in the present, avoidance of traumatic reminders, and heightened sense of current threat). CPTSD is intended to describe more pervasive post-traumatic reactions that, in addition to the core PTSD symptoms, also include the development of persistent symptoms of affect dysregulation, negative self-concept, and difficulties in relationships[58,59].

The DSM-5 offers only the single category of PTSD for post-traumatic symptoms. Three of its constituent symptom clusters ("intrusion symptoms associated with the traumatic event", "avoidance of stimuli associated with the event", and "marked alteration in arousal and reactivity") generally correspond to the three ICD-11 core symptoms. The DSM-5, however, includes an additional symptom cluster ("negative alterations in cognitions and mood") which incorporates two of the three additional required elements of ICD-11 CPTSD (persistent beliefs about oneself as diminished, defeated or worthless; persistent difficulties in sustaining relationships and in feeling close to others).

A comparison of the ICD-11 and DSM-5 diagnostic requirements for PTSD at the item level reveals that, while the disorder is more broadly defined in the ICD-11 in terms of the qualifying traumatic events, it is more narrowly defined in terms of the symptomatic response to those events. The ICD-11 requires for both PTSD and CPTSD that the trauma be "of an extremely threatening or horrific nature" and offers a list of examples that are explicitly not exhaustive. In contrast, the DSM-5 requires that the qualifying traumatic events involve "exposure to actual or threatened death, serious injury, or sexual violence" and specifies four possible modes of exposure: directly experiencing the traumatic event, witnessing it in person as it occurred to others, learning about a violent or accidental traumatic event that has occurred to a close family member or friend, or "experiencing repeated or extreme exposure to aversive details of traumatic events (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse)". The specificity and exclusivity of the DSM-5 requirements are at least partly in response to forensic concerns about the potential misuse of the PTSD diagnosis in personal injury and disability cases. These narrower stressor requirements mean that all qualifying events under the DSM-5 would qualify under the ICD-11, but not vice versa.

From a symptomatic perspective, the ICD-11 core symptoms of re-experiencing the traumatic event in the present and a heightened sense of current threat are more narrowly defined than their DSM counterparts. The ICD-11 includes intrusive memories, flashbacks, nightmares, and re-experiencing the same types of emotions or physical sensations occurring at the time of the trauma as manifestations of re-experiencing the traumatic event. The corresponding DSM-5 symptom cluster is more broadly defined in that it also includes psychological distress or physiological symptoms triggered by reminders of the trauma that are not restricted to emotions or physical sensations experienced at the time of the trauma. The ICD-11 core symptom of perception of heightened threat, restricted to hypervigilance and exaggerated startle response, is much more narrowly defined than the corresponding "marked alteration in arousal and reactivity" cluster in the DSM-5, which also includes irritable behaviour and angry outbursts, reckless or self-destructive behaviour, problems with concentration, and sleep disturbance. So, while the ICD-11 requires that every case of PTSD include hypervigilance or exaggerated startle response, the DSM-5 allows for the diagnosis without either of these classic PTSD symptoms.

Studies comparing the ICD-11 and DSM-5 diagnostic requirements have found somewhat lower PTSD prevalence rates using the ICD-11[60,61], and that the two diagnostic systems do not identify exactly the same groups[25]. Moreover, the inclusion in the DSM-5 of sleep disturbance and problems with concentration, which are also characteristic of many mood and anxiety disorders, as well as items such as persistent negative emotional state, diminished interest or participation in significant activities, and persistent inability to experience positive emotions, may result in inflated rates of co-occurrence with other disorders, especially Depressive Disorders[62].

Adjustment Disorder

Both the ICD-11 and DSM-5 describe Adjustment Disorder as characterized by symptoms developing in response to an identifiable stressor that do not meet the definitional requirements for another mental disorder.

Adjustment Disorder has often been criticized as a poorly defined condition consisting of a sub-threshold symptomatology related to a stressor that is often identified *post-hoc*[63]. In response, the ICD-11 has added a requirement – not included in the DSM-5 – that specific symptoms be present indicating a maladaptive reaction to the stressor: "preoccupation with the stressor or its consequences, including excessive worry, recurrent and distressing thoughts about the stressor, or constant rumination about its implications"[64,65].

Acute Stress Reaction / Acute Stress Disorder

In contrast to its status in both the ICD-10 and DSM-5, Acute Stress Reaction is no longer considered to be a mental disorder in the ICD-11, and is located instead in the chapter on Factors Influencing Health Status or Contact with Health Services.

Acute Stress Reaction describes potentially severe responses to an event or situation of an extremely threatening or horrific nature (the same types of traumas included in the definition of PTSD). By definition, the response to the traumatic event or situation should be judged by the clinician to be "normal given the severity of the stressor". These responses may include transient emotional, somatic, cognitive or behavioural symptoms, such as being in a daze, confusion, sadness, anxiety, anger, social withdrawal, amnesia, depersonalization or stupor. Intervention may be required even though the response is considered to be non-pathological.

In the DSM-5, Acute Stress Disorder is a diagnostic category in the Trauma- and Stressor-Related Disorders grouping, requiring

at least nine symptoms from a list of 14 (most of which appear in the PTSD criteria set), divided into five groups: intrusion symptoms, negative mood, dissociative symptoms, avoidance symptoms, and arousal symptoms. These manifestations typically begin immediately after the trauma, but persistence for at least 3 days and up to 1 month is required to meet the disorder criteria. Acute Stress Disorder may progress to PTSD after 1 month, or may remit within 1 month of trauma exposure.

Dissociative Disorders

Dissociative Identity Disorder

Both the ICD-10 and DSM-IV included a category (Multiple Personality Disorder and Dissociative Identity Disorder, respectively) involving the presence of two or more distinct personality states that recurrently take control of the person's behaviour. However, available evidence indicated that, in a substantial proportion of cases, the multiple personality states did not recurrently take executive control[66]. For this reason, changes were made in both the ICD-11 and DSM-5, but in different ways.

The DSM-5 broadened the Dissociative Identity Disorder category by removing the requirement that two or more personality states recurrently take control of the person's behaviour. The ICD-11, instead, added a new category, Partial Dissociative Identity Disorder, in which one personality state dominates in daily life but is intruded upon by one or more non-dominant personality states.

The other main difference is that Dissociative Identity Disorder in the DSM-5 requires "recurrent gaps in the recall of everyday events, important personal information, and/or traumatic events that are inconsistent with ordinary forgetting", while the ICD-11 does not require dissociative amnesia for the diagnosis of either Dissociative Identity Disorder or Partial Dissociative Identity Disorder. Nevertheless, the ICD-11 guidelines for Dissociative Identity Disorder do note that "substantial episodes of amnesia are typically present at some point during the course of the disorder", while in individuals with Partial Dissociative Identity Disorder dissociative amnesia is absent[67] or "brief and restricted to extreme emotional states or episodes of self-harm".

Feeding and Eating Disorders

Bulimia Nervosa and Binge Eating Disorder

In both the ICD-11 and DSM-5, Bulimia Nervosa and Binge Eating Disorder are characterized by frequent recurrent episodes of binge eating. In Bulimia Nervosa, this is accompanied by repeated inappropriate compensatory behaviours (e.g., self-induced vomiting, fasting, using diuretics, strenuous exercise).

The ICD-11 and DSM-5 differ, however, in their definition of binge eating. While both diagnostic systems require the subjective experience of a loss of control over eating behaviour[68], the DSM-5 also requires an objective component, i.e., that the amount of food eaten in a discrete period of time (e.g., within any 2-hour period) is larger than what most individuals would eat. The ICD-11 simply requires that the individual eat notably more and/or differently than usual.

Consequently, some behaviour that would be considered to be binge eating in the ICD-11 (i.e., episodes in which the amount of food eaten may be within normal limits, but the individual feels unable to stop eating or limit the type or amount of food eaten) would not qualify as binge eating in the DSM-5. Studies to date[69-72] indicate that individuals with subjective binge eating report comparable distress, psychological disturbance, and reduction in quality of life as those whose binge eating is defined objectively.

Disorders Due to Substance Use / Substance Use Disorders

There are several significant differences in the classification of substance use disorders between the ICD-11 and DSM-5.

The ICD-11 includes several substance classes that are not specifically listed in the DSM-5: synthetic cannabinoids (comprised within the DSM-5 cannabis class), cocaine (included within the DSM-5 stimulant class), synthetic cathinones (comprised within the DSM-5 Other or Unknown class), and methylenedioxyphenethylamine (MDMA) (included within the DSM-5 hallucinogen class). These classes were added to the ICD-11 because of their increasingly important global health significance[73], with the goal of facilitating the collection of data regarding their public health impact.

There are also important conceptual differences in the specific disorders that are included. The ICD-11 identifies three disorders on the basis of the pattern of substance use: Episode of Harmful Substance Use (an episode of use that has caused clinically significant damage to a person's physical or mental health or resulted in behaviour leading to harm to others); Harmful Pattern of Substance Use (a pattern of repeated or continuous use that has caused damage to a person's physical or mental health or resulted in behaviour leading to harm to others); and Substance Dependence (characterized by impaired control over substance use, increasing precedence of substance use over other aspects of life, and persistence of use despite harm or negative consequences).

Separate categories for Harmful Substance Use and Substance Dependence are intended to facilitate early recognition and intervention for substance use problems, helping to distinguish between patterns of substance use behaviour that may respond to brief psychological interventions such as motivational interviewing and those needing more substantial treatment that may include detoxification or agonist maintenance treatment[74]. Moreover, the harmful use categories are seen by the WHO as important for capturing the public heath impact of substance use in morbidity and mortality statistics[75].

The DSM-5, in contrast, includes a single Substance Use Disorder category and identifies three levels of severity based on the number of symptom criteria endorsed: mild for two or three,

moderate for four or five, and severe for six or more out of 11 symptom criteria. There are no diagnoses corresponding to either Episode of Harmful Substance Use or Harmful Pattern of Substance Use in ICD-11: none of the DSM-5 criterion items can be met based on the pattern of substance use having caused damage to the person's physical or mental health or health of others.

There is a relatively close correspondence between the 11 DSM-5 criteria for Substance Use Disorder and the three core elements of ICD-11 Substance Dependence[76]. However, many cases of DSM-5 moderate to severe Substance Use Disorder would not meet the diagnostic requirements for ICD-11 Substance Dependence due to several factors. The first is the much lower proportion of items needed in the DSM-5 for a diagnosis of Substance Use Disorder (two out of 11) as compared to ICD-11 (two out of three). Second, the single ICD-11 item "increasing precedence of substance use over other aspects of life" subsumes five DSM-5 items (i.e., time spent using or obtaining substances, failure to fulfill role obligations, continued use despite social or interpersonal problems, important activities given up, and continued use despite physical or psychological problems). Finally, two of the DSM-5 items ("craving" and "recurrent use in situations which are physically hazardous") do not correspond to any of the ICD-11 items.

A study from the World Mental Health Surveys[26], examining the prevalence of disorders due to alcohol and cannabis use, found a high concordance of the ICD-11 with the ICD-10 and DSM-IV (all k values ≥0.94), but the concordance between ICD-11 Substance Dependence and DSM-5 moderate to severe Substance Use Disorder was markedly lower (k≥0.70 for alcohol and k=0.63 for cannabis), suggesting that the DSM-5 is not identifying exactly the same groups. Additional empirical studies are needed to examine differences in the prevalence of other substance classes and the implications of these differences for clinical care.

Disruptive Behaviour or Dissocial Disorders

Oppositional Defiant Disorder with chronic irritability-anger / Disruptive Mood Dysregulation Disorder

The ICD-11 and DSM-5 diagnostic requirements for Oppositional Defiant Disorder (ODD) are essentially the same (i.e., a persistent pattern of markedly defiant, disobedient, provocative or spiteful behaviour that is inconsistent with age and developmental level).

However, the ICD-11 includes two subtypes not present in the DSM-5: ODD with and without chronic irritability-anger. ODD with chronic irritability-anger is characterized by a prevailing angry or irritable mood and severe temper outbursts. Such chronic irritability-anger is predictive of later depression, anxiety and suicidality[31]. In contrast, the DSM-5 classifies such presentations as a separate condition, Disruptive Mood Dysregulation Disorder (DMDD), within the Depressive Disorders grouping.

DMDD was added to the DSM-5 to provide a prominent diagnostic "home" for children who were being misdiagnosed as having bipolar disorder and were therefore receiving inappropriate treatments such as antipsychotics and mood stabilizers[31,77].

The rationale for considering a pattern of chronic irritability-anger as a subtype of ODD in the ICD-11 rather than a distinct disorder relates to: a) substantial evidence supporting the validity and clinical utility of the symptom structure of ODD subtypes based on the presence of a pattern of chronic irritability-anger[31]; and b) what the ICD-11 Working Group considered to be the questionable validity of DMDD[78]. Studies in clinical and community samples have found that 70-100% of children with DMDD have symptoms that meet the diagnostic requirements for ODD[77,79-82], suggesting that the irritability and behavioural symptom dimensions of ODD are not separable into different disorders[31,78].

A recent Internet-based field study using case vignettes found that the ICD-11 diagnostic guidelines led to more accurate identification of severe irritability and better differentiation from boundary presentations. On the other hand, participants using the DSM-5 often failed to use the DMDD diagnosis when it was appropriate and more frequently applied psychopathological diagnoses to developmentally normative irritability[83].

Personality Disorders

In contrast to the DSM-5, which has retained the ten DSM-IV specific personality disorders categories, the ICD-11 approach[84] involves first making a categorical judgement regarding whether or not the general diagnostic requirements for a personality disorder are fulfilled, then determining its severity (mild, moderate or severe), and finally describing the prominent features of the individual that contribute to the personality disturbance using trait domain qualifiers (negative affectivity, detachment, dissociality, disinhibition, and anankastia).

Also available is a "borderline pattern" qualifier, with diagnostic requirements corresponding to those of DSM-5 Borderline Personality Disorder, which was included in response to concerns among clinicians and personality disorder researchers about access to care and continuity with previous research[85]. The ICD-11 also includes a category of Personality Difficulty, listed in the chapter on Factors Influencing Health Status or Contact with Health Services, which refers to pronounced personality characteristics that may affect treatment or access to health services but do not rise to the level of severity deserving a diagnosis of Personality Disorder.

Although there was a proposal during the development of the DSM-5 to adopt a hybrid categorical/dimensional approach to the diagnosis of Personality Disorders, that effort was ultimately unsuccessful[86]. An Alternative DSM-5 Model for Personality Disorders is presented in one of the appendices (Section III) of that diagnostic system.

Paraphilic Disorders

In developing the classification of Paraphilic Disorders, the WHO aimed to distinguish between those conditions that are

relevant to public health and most commonly seen in clinical and forensic settings and those arousal patterns that more commonly reflect private behaviour[21]. Consequently, the ICD-11 distinguishes paraphilic disorders that involve non-consenting individuals or people whose age or status renders them unwilling or unable to consent (e.g., pre-pubertal children, an unsuspecting individual being viewed through a window) from arousal patterns involving solitary behaviour or consenting individuals.

Among those Paraphilic Disorders in which the arousal pattern involves non-consenting individuals, the ICD-11 includes five named categories (Exhibitionistic Disorder, Voyeuristic Disorder, Pedophilic Disorder, Coercive Sexual Sadism Disorder, and Frotteuristic Disorder) and a residual category (Other Paraphilic Disorder Involving Non-Consenting Individuals). For paraphilias not focused on non-consenting individuals, the ICD-11 provides only a single category, Paraphilic Disorder Involving Solitary Behaviour or Consenting Individuals, which should only be diagnosed if the person experiences marked distress about the arousal pattern that is not simply a consequence of rejection or feared rejection by others, or if the nature of the paraphilic behaviour involves significant risk of injury or death either to the individual or to the partner (e.g., asphyxophilia).

The category of Paraphilic Disorder Involving Solitary Behaviour or Consenting Individuals could therefore be used to diagnose arousal patterns involving sexual masochism, consensual sexual sadism, cross-dressing, or fetishism, which correspond to specific diagnoses in the ICD-10, if the requirements related to distress or harm are met. These ICD-10 categories were not carried over to the ICD-11 as named diagnostic entities, because they were seen as contributing unnecessarily to stigmatization of variations in sexual arousal that are not in themselves associated with distress, functional impairment, harm, or violation of the rights of others[87].

In contrast, the DSM-5 continues to have separate categories for Sexual Masochism Disorder, Fetishistic Disorder, and Transvestic Disorder; does not distinguish between consensual and non-consensual sadism; and does not exclude distress related to rejection or feared rejection in the diagnostic requirements for consensual or solitary paraphilias.

The DSM-5 also allows Paraphilic Disorder diagnoses to be assigned based on clinically significant distress or functional impairment in the absence of having acted on the arousal pattern. The ICD-11 makes the same allowance for distress, but does not include functional impairment in the diagnostic requirements for any of the Paraphilic Disorders, because of concerns about the subjectivity and potential misuse of this element to stigmatize and even criminalize atypical sexual behaviours[87].

Neurocognitive Disorders

Dementia and Amnestic Disorder / Major Neurocognitive Disorder

In the ICD-11, Dementia is characterized by a decline from a previous level of cognitive functioning, with impairment in at least two cognitive domains that significantly interferes with independence in the person's performance of activities of daily living. In the DSM-5, Major Neurocognitive Disorder has replaced DSM-IV Dementia, and can be diagnosed based on evidence of significant cognitive decline in only one cognitive domain.

The DSM-5 requirement of only one domain is based on a desire to have the definition of Major Neurocognitive Disorder depend on the severity of functional impairment rather than on a broader range of deficits. As a result, Amnestic Disorder, which is characterized by severe memory impairment that is disproportionate to impairment in other cognitive domains, is not considered a form of Dementia in the ICD-11, but would be considered a form of Major Neurocognitive Disorder in the DSM-5.

The ICD-11 and DSM-5 both include specific types of dementia based on their underlying medical or substance-induced etiology, each type with its own definition. While both the ICD-11 and DSM-5 provide definitions for eleven of the most clinically important types (e.g., due to Alzheimer's disease, due to cerebrovascular disease, due to frontotemporal degeneration), the ICD-11 also includes specific categories for Dementia Due to Exposure to Heavy Metals and Other Toxins, Dementia Due to Multiple Sclerosis, Dementia Due to Normal Pressure Hydrocephalus, Dementia Due to Pellagra, and Dementia Due to Down Syndrome.

In addition, many of the DSM-5 specific dementia categories have separate criteria sets for "Probable" and "Possible", which in most cases have been adapted from the neurological literature[88-91]. Separate categories based on the level of diagnostic certainty are not available in the ICD-11.

Mental or Behavioural Disorders Associated with Pregnancy, Childbirth and the Puerperium / "with peripartum onset" specifier

The ICD-11 includes two categories for Mental or Behavioural Disorders Associated with Pregnancy, Childbirth and the Puerperium, which differ depending on whether their features do or do not include delusions, hallucinations or other psychotic symptoms. In either case, if the symptomatic presentation also meets the diagnostic requirements for another specific ICD-11 mental disorder, that diagnosis is also supposed to be assigned.

The DSM-5 has no such categories, but instead has a "with peripartum onset" specifier (which is not codable) that can be applied to Brief Psychotic Disorder, Bipolar Disorder and Major Depressive Disorder, to indicate that the onset of the disorder was during pregnancy or within 6 weeks of delivery. Thus, the ICD-11 and DSM-5 approaches are functionally equivalent, except that the ICD-11 involves the coding of two diagnoses (e.g., Mental or Behavioural Disorders Associated with Pregnancy, Childbirth and the Puerperium plus a Depressive Disorder) whereas the DSM-5 allows the clinician to communicate this using only one diagnosis (e.g., Major Depressive Disorder, with peripartum onset).

The ICD-11 approach was adopted to reflect the diagnostic practices of obstetricians and other health care providers, whose primary clinical focus tends to be on the woman's pregnancy,

childbirth, delivery and postpartum care, and who tend to make diagnoses such as "postpartum depression" and "postpartum psychosis"[92]. For mental health specialists, the psychiatric presentation is of primary importance, and the fact that its onset is during pregnancy or postpartum is more commonly thought of as a course qualifier.

DISCUSSION

Our analysis indicates that the classification of mental disorders as presented in the ICD-11 is substantially more similar to the DSM-5 than was the ICD-10 to the DSM-IV. We identified 31 disorders with essentially identical diagnostic requirements, and 10 additional disorders that differed only in the greater degree of operational specificity in the DSM-5 as compared to the ICD-11 CDDG. This compares with only one identical disorder in First's analysis of ICD-10 and DSM-IV[13].

There were major differences in slightly less than 20% of the diagnostic entities evaluated, and 26 entities are in one system but not in the other. Minor conceptual differences were present in just over 40% of diagnostic entities. Due to specific steps taken in the development of the ICD-11, these differences are not random or arbitrary, but rather are based on differing priorities and uses of the two classification systems and differing interpretations of the evidence.

With regard to degree of operationalization, it is generally assumed that a strict criteria-based approach leads to a greater reliability, but only one study restricted to childhood disorders has made a direct comparison (of DSM-II and DSM-III), showing only a slight improvement in reliability[93]. The results of ICD-11 field studies in international clinical settings[94] also call this assumption into question.

With regard to major conceptual differences, R. Kendell made an argument 30 years ago[95] that these were almost inevitable given the different constituencies of the two sponsoring organizations, but that these can "provide the research community with a choice between two genuinely different alternatives"[95,p.299]. Indeed, substantial upticks in research activity can already be seen in some areas of ICD-11/DSM-5 divergence, such as PTSD/CPTSD[59-61], Personality Disorders[96-99], and childhood irritability/anger[31,83]. This is one of the most important ways of improving the validity of our concepts over time.

In conclusion, the ICD and DSM classifications of mental disorders are closer today than they have been at any time since ICD-8 and DSM-II. Differences persist based on the differing priorities of the WHO and APA, and the different uses of the two classifications. Divergent ways of describing the same or similar conditions allow for empirical comparison of validity and utility, which can contribute to advances in the field.

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The emergence of cognitive COVID

The scale of the COVID-19 pandemic has impacted health care systems on a global level. As the pandemic moves into its second year, attention is beginning to turn towards the medium- and long-term consequences of the infection. High on the list of priorities is the issue of cognitive impairment, not only as a direct effect of neurotropic viral brain infiltration but also due to indirect factors associated with the pandemic, such as increased social isolation and mental health problems.

While associations between neurotropic respiratory viruses and brain changes have been documented since the 1918 influenza epidemic, the cognitive consequences of these changes have until now received very little attention. The increasing interest in both the spread of coronaviruses to the central nervous system (CNS) and the longer-term clinical presentations of infected individuals has led to a re-evaluation of the importance of cognitive changes.

A meta-analysis[1] of 3,559 adult cases collectively drawn from the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19 epidemics identified memory impairment in one third of cases at hospital admission and in 19% of cases post-illness, with the latter notably also affecting younger adults. Initial studies indicate that cognitive dysfunction may extend beyond the acute stage of COVID-19 infection. A study of 18 patients with mild to moderate COVID-19 disease (not requiring intensive care unit admission) and a mean age of 42 years, examined a median of 85 days after recovery, found that over 75% had episodic memory, attention and concentration difficulties which were not associated with fatigue, depression, hospitalization, treatment, viremia or acute inflammation[2]. These initial data indicate that cognitive changes may occur even after milder infections.

Given the scale of the pandemic and the implications for both working age adults and the older population at risk of dementia, these emerging data highlight the urgent need to better understand the mechanisms resulting in cognitive dysfunction, with a view to introducing interventions and public health strategies to combat these deleterious longer-term effects of the pandemic.

The effect of SARS-CoV-2 on cognition may relate to the vulnerability of various CNS cells to the virus and to its direct infiltration of the CNS. Viral attachment to host cells results from binding of the S1 subunit of the S protein, one of four structural proteins of the SARS-CoV-2 virion, to the angiotensin-converting enzyme 2 (ACE2) receptor on cell surfaces, with subsequent intracellular entry of the viral genome occurring after fusion of viral and host cell membranes. As such, the cellular tropism of SARS-CoV-2 relates to the expression of the ACE2 receptor[3]. Outside the CNS, the receptor is expressed in alveoli, gut, kidney and epidermis, as well as vascular endothelial cells. Within the CNS, it is expressed in neurons, astrocytes, oligodendrocytes and endothelial cells. Regionally, high concentrations of the ACE2 receptor are found in the olfactory bulb, substantia nigra, middle temporal gyrus, and posterior cingulate gyrus[4].

Two direct mechanisms underpin the neurotropism of SARS-CoV-2 and its access to the CNS: a) retrograde axonal transport following invasion of peripheral olfactory neurons, and b) haematogenous breach of the blood-brain barrier following infection of this barrier or choroid plexus endothelial cells. The pathological effect of this direct viral infiltration is augmented by a brisk immune response and inflammation, with the associated cytokine storm further compromising the blood-brain barrier, by vasculopathy arising from disseminated intravascular coagulation, and by hypoxaemia.

The resultant clinical manifestations of this CNS pathology are multiple[5]. They include inflammatory disorders (meningoencephalitis, acute disseminated encephalomyelitis), encephalopathies presenting with behavioural disturbances, seizures, and cerebrovascular disease (both thrombotic and haemorrhagic). The prevalence of CNS manifestations in severe infection is high: of 58 patients with acute respiratory distress syndrome, 69% had agitation and 65% had confusion, with a high proportion of those imaged showing magnetic resonance imaging (MRI) changes in the form of altered perfusion, ischaemic stroke and leptomeningeal enhancement[6].

The relative recency of the pandemic means that there are at present only limited data on the impact of COVID-19 infection on cognitive function beyond the acute illness. However, both direct and indirect effects of the infection indicate a likelihood of longer-term cognitive impairment. SARS-CoV-2 invasion of peripheral olfactory neurons, now recognized as one component of the virally-induced acute anosmia, permits trans-synaptic viral spread to cortical regions receiving primary and secondary input from the olfactory tract, notably the entorhinal cortex and the hippocampus. The involvement of these regions in episodic memory and spatial navigation raises the possibility of COVID-19 infection causing longer-term impairment in these cognitive domains. This will be amplified by indirect consequences of the infection in terms of other pathophysiological effects, notably virally-mediated vascular pathology and inflammatory responses, psychological trauma and need for critical care[7]. Preliminary estimates of the prevalence and timescales of such effects can be gleaned from previous neuropsychological studies of long-term post-ventilation outcomes, with cognitive impairment observed in 78% of patients at one year and with memory problems persisting up to five years in around 50%, independent of psychological problems[8].

Finally, there is the potential risk that COVID-19 infection may cause long-term cognitive decline by accelerating the onset of neurodegenerative dementia. The severity of the infection is greater at higher ages, and the neural pathways along which SARS-CoV-2 may be transported overlap with those implicated at the onset of Parkinson's and Alzheimer's disease, such as the cognitively eloquent regions within the medial temporal lobe. This overlap in regional vulnerability may provide the anatomical basis for an interaction between SARS-CoV-2 and neurode-

generative pathology, mirroring the acceleration of beta-amyloid and tau pathology caused by other neurotropic viruses such as HIV and herpes viruses.

Extensive future work will be needed to map out the mechanisms and prevalence of long-term "cognitive COVID". *In vivo* and *in vitro* lab studies can evaluate the interaction of viral and neurodegenerative proteins and any potential synergistic effect on synaptic and neuronal function, while large scale longitudinal epidemiological studies will be required to identify the demographic, genetic and psychosocial risk factors of COVID-19-related cognitive decline, and to differentiate between direct and indirect effects of the infection. Targeted cognitive testing, focusing on the functions of vulnerable brain regions, will help differentiate cognitive dysfunction directly due to the infection from that associated with depression and other mental health issues.

Lessons learned during the first stage of the pandemic have improved acute clinical outcomes. As the second stage unfolds, it is imperative that attention now focus on the implications of COVID-19 infection for long-term cognitive impairment and dementia risk, to aid prospective detection and intervention with pharmacological and public health strategies.

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Post-traumatic stress disorder in the aftermath of COVID-19 pandemic

Post-traumatic stress disorder (PTSD) is a potentially debilitating mental health disorder which affects an important minority of people exposed to events involving actual or threatened death, serious injury or sexual violence. The COVID-19 pandemic is unfortunately providing multiple opportunities for people to experience traumatic situations which may lead to PTSD.

Imagine the previously fit person who rapidly goes from an active lifestyle to a chemical induced coma, surviving only after weeks on a mechanical ventilator. Or the nurse who volunteers to join a rapidly assembled intensive care team with minimal preparatory training, and faces the stark reality that many of those cared for end up dying alone, with relatives being unable to visit the unit[1]. These situations have a high potential to induce PTSD. Indeed, it has been reported that up to 20% of intensive care unit survivors go on to develop PTSD[2]. On the other hand, there is evidence that repeated exposure to traumatic events in health care workers can lead to the development of PTSD even if the staff member cannot identify which specific traumatic event caused him/her to become unwell[3].

Whilst PTSD must follow trauma exposure, other factors substantially influence the likelihood of developing this condition. Comprehensive meta-analyses of risk factors for PTSD consistently find that the nature of the post-trauma environment is a more important predictor than pre-traumatic factors such as childhood adversity, or demographic factors such as gender or ethnicity. In particular, there is strong evidence that psychological stress experienced during the initial post-exposure period, as well as the availability and quality of post-trauma social support, are highly influential determinants[4]. Whilst we know that social support is highly protective against the development of PTSD, social distancing restrictions are making it more difficult for people to access non-professional support, so that the onset of PTSD after trauma exposure may become more likely.

Another important risk factor for PTSD is moral injury, which is defined as the psychological distress, including feelings of deep shame and guilt, resulting from doing, or not preventing, events that someone believes are "wrong". Many health care workers are likely to experience morally injurious events during this pandemic. Feeling unable to deliver high-quality care, or having to make hard choices about who will and who will not receive a given intervention due to shortage of available equipment, have become somewhat commonplace, especially when the rates of hospitalization are high. Moral injury is also a relevant concept outside of work environments, especially when people are concerned about having infected loved ones who have died. Moral injury is important as it can predispose people to developing PTSD[5] as well as making it less likely that they will seek treatment if they do.

Within organizational settings, a number of approaches have been tried to prevent the onset of PTSD. Pre-employment, or pre-role, psychological health screening aims to identify higher risk individuals, so they can either not be employed in trauma-exposed roles or be provided with extra support to mitigate the risk. However, there is consistent evidence that this approach is ineffective. It may indeed be harmful, by providing employers with false reassurance that screened personnel are resilient to trauma and will not develop PTSD[6]. Whilst health care managers understandably may wish to exclude vulnerable staff from dealing with the most severe COVID-19 patients, in order to protect their mental health, the reality is that the state of the current evidence base on screening is unsatisfactory and this practice cannot be recommended.

Another approach that has been shown to be ineffective, and indeed potentially harmful, is the use of psychological debriefing, or post-trauma counselling, delivered in the days after a traumatic event has occurred. Well-accepted PTSD management guidelines are clear in recommending against the use of such approaches[7]. This evidence is highly relevant during the current pandemic, when mental health professionals want to support their "front-line" physical health colleagues, or assist individuals recovering from serious COVID-19 infection. Whilst both aspirations are laudable, it is important to avoid causing harm.

On the other hand, there is strong evidence that training supervisors to implement supportive and empathetic communication techniques with their team members is highly beneficial to employees' post-trauma mental health and is associated with a reduction in their sickness absence[8]. Good evidence also exists that formal peer support programs can protect the mental health of trauma-exposed employees[9]. Furthermore, it may be useful to ensure that trauma-exposed staff are actively monitored, provided with time away from trauma-prone workplaces, and encouraged to engage in reflective practice protecting them against the onset of moral injury.

For people who do develop PTSD, there are some evidence-based treatments available. Whilst demand for these interventions is likely to be high, given the scale of the pandemic, it remains highly important that evidence-based approaches are utilized. Most evidence exists for trauma-focused cognitive behavioral psychotherapy and eye movement desensitization and reprocessing[6]. Most people will experience substantial improvement from 8 to 12 sessions of cognitive behavioral psychotherapy, although those with more complex presentations of PTSD are likely to require more prolonged treatment. For those who do not accept or respond to psychotherapy, antidepressant medications may help, and they may be especially useful for people who present a comorbid depressive disorder.

As with other mental health conditions, it is important that treatment for PTSD begins early on, before people lose their self-esteem, important relationships or employment, or develop other mental health disorders, including substance misuse. Given the likely increased global incidence of PTSD as a result of the pandemic, the routine use of the effective preventive measures and the dissemination of the evidence-based psychotherapies outlined above should be seen as a priority.

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Prioritizing COVID-19 vaccination for people with severe mental illness

In the global race for a safe and effective COVID-19 vaccination, there are still many challenges that need to be addressed. One of these is being the initial scarcity of doses and the associated ethical considerations as to whom they should be distributed first.

Recently, the National Academies of Sciences, Engineering, and Medicine have proposed an ethical framework for equitable allocation of COVID-19 vaccine in the US[1]. The World Health Organization, as well as several other entities, have produced similar frameworks. In the prioritization of vaccines, these frameworks endorse three universal ethical principles. A first principle concerns minimizing harm and maximizing benefit: an effective vaccine should reduce deaths, disease burden, and societal and economic disruption, and have a minimal side effect profile. The second principle advocates prioritizing populations that may experience disproportionately greater health burdens as a result of the COVID-19 pandemic: some groups are at higher risk of being infected with, dying of or having lasting sequelae of COVID-19, due to their age, profession, medical status or socioeconomic factors. The third principle relates to equal respect for every person, and requires that, in allocation and priority-setting, individuals are considered and treated as having equal dignity and worth. Individuals who, because of vulnerability or structural inequalities, would face barriers to accessing a vaccine, should be offered an equal opportunity to be vaccinated as compared to more privileged groups[2].

People of all ages with comorbid and underlying physical conditions, such as cardiovascular diseases, chronic obstructive pulmonary disease, type 2 diabetes mellitus, chronic kidney disease, obesity, immunodeficiency and cancer, are particularly vulnerable to morbidity and mortality due to COVID-19. The risk of premature death or severe morbidity in these patients is significant enough for the US National Academies of Sciences, Engineering, and Medicine to prioritize these patients in the allocation of vaccines[1].

Even without factoring COVID-19 into the calculation, people with severe mental illness, including schizophrenia, major depressive disorder and bipolar disorder, have a two to three times

higher mortality rate than the general population, resulting in a 10-20 years reduced life expectancy, that appears to be widening. This is mainly attributable to physical diseases. There exists a large body of evidence showing that these people are more likely to develop a wide variety of physical diseases, such as cardiovascular diseases, type 2 diabetes mellitus, and respiratory tract diseases[3]. The risk for obesity, which is an important associated factor for mortality in patients with COVID-19, can be more than four times higher in people with schizophrenia and about one and a half times higher in those with major depressive disorder or bipolar disorder, compared to the general population[3].

Recent studies have shown that people with severe mental illness are at a heightened risk of morbidity and mortality from COVID-19. We therefore argue that they should also be prioritized in vaccine allocation. A case-control study with over 61 million patients found that people who were recently diagnosed with schizophrenia, bipolar disorder, major depressive disorder or attention-deficit/hyperactivity disorder showed very high odds ratios (5.7 to 7.6) of being infected with COVID-19, as compared to patients without mental disorders, even after adjustment for age, gender, ethnicity and the aforementioned medical conditions. These people are also at increased risk for COVID-19 complications, as reflected in higher rates of hospitalization and death[4]. Other recent studies[5,6] have confirmed these data.

To put these findings into perspective with the example of the US: in 2017, there were an estimated 11.2 million adults aged 18 or older in the US with severe mental illness. Taking into account a mortality rate of 8.5% that has been found among COVID-19 patients recently diagnosed with a severe mental illness, this means that about 1 million of patients with severe mental illness in the US would die if all were affected by COVID-19.

Severe mental illness is known to be positively correlated with many environmental variables which are themselves risk factors for COVID-19 infection, such as socioeconomic deprivation, working in unsafe environments, living in overcrowded settings or being homeless, institutionalization and confinement. Furthermore, stigmatization, discrimination, erroneous beliefs and negative attitudes associated with severe mental illness, as well as system factors, act as barriers to the recognition and management of physical diseases in people with severe mental illness[7]. Finally, persons suffering from a severe mental illness have more difficulties in following and applying the confusing and constantly changing rules and obligations that are established in relation to the fight against COVID-19[4,8]. It thus becomes clear why severe mental illness is a major risk factor for COVID infection and negative COVID-19 related outcomes.

In light of this knowledge, and taking into account the second and third ethical principles that should guide vaccine allocation, we consider it paramount that persons with severe mental illness should also be prioritized to guarantee that they receive a COVID-19 vaccine during the first phase of its distribution. It is our responsibility as psychiatrists in this global health crisis to advocate for the needs of our patients with governments and public health policy bodies, as a position paper by the World Psychiatric Association recently stated[9]. In addition, public health bodies should develop and implement targeted programs to ensure that these patients and their health care providers are made aware of these increased risks as well as of the benefits of vaccination.

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A pandemic of social isolation?

On March 11, 2020 the World Health Organization declared COVID-19 infection a global pandemic, prompting closures and other restrictions across the world. A substantial proportion of the world population was suddenly homebound, giving us all a small glimpse into the experiences of the approximately 6% of US older adults who were already homebound. Further closures and restrictions have been implemented worldwide in relation to the second wave of the infection. This raises questions about the effects that social isolation may have on our mental and physical well-being.

Public health concerns about social isolation and loneliness were growing internationally even prior to the pandemic. In 2018, the UK appointed a Loneliness Minister and published a national strategy for tackling loneliness. In the US, the National Academies of Sciences, Engineering, and Medicine released, just two weeks prior to the declaration of the pandemic, an expert consensus report on the relevance of social isolation and loneliness in older adults for the health care system[1]. Nonetheless, social isolation and loneliness have generally been underrecognized and underappreciated relative to the evidence supporting their public health importance[2].

Evidence suggests that a significant portion of the population was already socially isolated, lonely, or both, prior to the pandemic[2]. Social isolation refers to objectively being alone, having few relationships or infrequent social contacts; whereas loneliness

refers to subjectively feeling alone, or the discrepancy between one's desired level of connection and one's actual level. While international standardization of measurement and classification is needed to provide more precise estimates of prevalence and changes over time, substantial evidence from both national and international surveys raise concern. Several surveys suggest that loneliness has increased by 20-30% during the pandemic. Loneliness can occur across age, income levels, living situations and gender; however, rates are highest among those at younger ages, with lower incomes, and with chronic health conditions[1,3]. These risk factors are similar to those identified pre-COVID[3].

In the midst of a global pandemic, the immediate dangers of a deadly novel virus are understandably being prioritized. However, social isolation and loneliness can result in both short- and long-term health effects that cannot be ignored. The lethal effects of social isolation and loneliness may be more immediate, in the case of suicide or domestic violence, or more long-term, in the case of disease-related deaths. International data from over 3.4 million people demonstrate the association of social isolation and loneliness with a significantly increased risk of death from all causes[4]. Conversely, being socially connected is protective and increases odds of survival by 50%[5].

Cumulative evidence over decades of research demonstrates that the magnitude of mortality risk related to social isolation and loneliness is comparable with or exceeds the risk associated with other known public health problems (e.g., obesity, air pollution)[2]. Further, there is compelling evidence that social isolation and loneliness significantly contribute to morbidity, particularly cardiovascular disease and stroke[1]. Furthermore, social isolation and loneliness influence problematic health behaviors, including substance use, poorer sleep and poorer eating habits. Lacking proximity to others, particularly trusted others, may result in a state of alertness both centrally and peripherally. Problematic behaviors and physiological changes may potentially exacerbate or precipitate the onset of acute events among those with pre-existing diseases[6].

Social isolation and loneliness may even influence susceptibility to the COVID-19 infection. They predict worse mental health, and individuals with mental health conditions are more likely to be socially isolated and lonely[1]. This bidirectional association is noteworthy, since an analysis of population-wide electronic health records has found that people with a mental health diagnosis are more likely to be infected and hospitalized and to die from COVID-19[7]. Furthermore, a recent paper summarizing evidence from a 35-year research program found that people experiencing interpersonal stressors such as loneliness had a greater chance of developing an upper respiratory illness when exposed to cold viruses[8].

Steps to limited social contact associated with the global pandemic are becoming more persistent in nature, and both short-term and longer-term public health concerns will emerge if the effects of social isolation and loneliness are not mitigated. We cannot take an either-or position, pitting the dangers of COVID-19 against the dangers of social isolation and loneliness. We must find a way to address both risks to promote public health.

What are actionable steps that can prevent or reduce COVID-19-related isolation and loneliness? A systems approach recognizes that individual, community and societal factors are interdependent and may all contribute to social isolation and loneliness[9], and thus each of these levels need to be considered and targeted. At the individual level, research has shown that high-quality interactions among household members, interacting with neighbors, providing support to others, and expressions of gratitude, all promote social bonds and are negatively correlated with loneliness. At the community and societal level, we have already seen changes in social norms and physical spaces, all aimed at reducing social contact, that may have longer-term public health implications if not mitigated. Community and national leaders should foster norms of support, inclusion and trust, leading to a greater sense of security, an essential component of feeling socially connected to a group.

The relevance of every sector of society not only for COVID-19-related but also for isolation-related public health risks is readily apparent. Thus, we should begin to evaluate existing local and national policies across sectors (health care, transportation, education, housing, employment, nutrition, and environment) aiming to preserve and promote the quality of social contacts. The social needs of the population need to be at the forefront of every pandemic and recovery plan.

It is not clear how long the social and health ramifications of the COVID-19 restrictions will persist. As we create our "new normal" adaptations to the pandemic, they may become more permanent. For example, remote working is becoming the norm and digital tools are increasingly being adopted or required; however, little is known about their equivalence to in-person contact and their influence on social and health outcomes. There is an urgent need for rigorous scientific evaluation of these practices and policies.

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Hierarchical models of psychopathology: empirical support, implications, and remaining issues

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There is an ongoing revolution in psychology and psychiatry that will likely change how we conceptualize, study and treat psychological problems. Many theorists now support viewing psychopathology as consisting of continuous dimensions rather than discrete diagnostic categories. Indeed, recent papers have proposed comprehensive taxonomies of psychopathology dimensions to replace the DSM and ICD taxonomies of categories. The proposed dimensional taxonomies, which portray psychopathology as hierarchically organized correlated dimensions, are now well supported at phenotypic levels. Multiple studies show that both a general factor of psychopathology at the top of the hierarchy and specific factors at lower levels predict different functional outcomes. Our analyses of data on a large representative sample of child and adolescent twins suggested the causal hypothesis that phenotypic correlations among dimensions of psychopathology are the result of many familial influences being pleiotropic. That is, most genetic variants and shared environmental factors are hypothesized to non-specifically influence risk for multiple rather than individual dimensions of psychopathology. In contrast, person-specific experiences tend to be related to individual dimensions. This hierarchical causal hypothesis has been supported by both large-scale family and molecular genetic studies. Current research focuses on three issues. First, the field has not settled on a preferred statistical model for studying the hierarchy of causes and phenotypes. Second, in spite of encouraging progress, the neurobiological correlates of the hierarchy of dimensions of psychopathology are only partially described. Third, although there are potentially important clinical implications of the hierarchical model, insufficient research has been conducted to date to recommend evidence-based clinical practices.

Key words: Psychopathology, dimensions, hierarchical approach, general factor of psychopathology, internalizing, externalizing, bifactor model, second-order model

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Although the dominant view in psychiatry and psychology conceptualizes psychopathology as consisting of discrete diagnostic categories of mental disorders, some scholars have argued since at least the 1960s that psychopathology is better conceptualized as consisting of continuous dimensions of maladaptive behaviors, emotions and cognitions[1-4]. More recently, a cross-disciplinary movement has forcefully argued for abandoning categorical diagnoses and replacing them with an entirely dimensional taxonomy of psychopathology[5-8].

This international movement is fueled by three key issues. First, there are inherent advantages to dimensional measures of psychopathology that make them both more reliable and more valid[9-11]. Second, an important tenet of the movement is that all dimensions of psychopathology are positively correlated to varying degrees, and that the patterns of correlations are as important as the dimensions themselves[12-14]. Third, there is no empirical justification for not including all symptoms of both previously distinguished clinical and personality disorders in the same dimensional taxonomy[6,15].

The proposed hierarchical taxonomies of phenotypic dimensions of psychopathology have garnered considerable empirical support, but our understanding of these dimensions at this time requires extrapolation from limited evidence. In particular, we are hampered by the current absence of a comprehensive dimensional measure of psychopathology that includes all symptoms. This makes efforts to develop such a measure a top priority; we cannot comprehensively define the dimensions of psychopathology until we can study all of the symptoms that define the universe of psychopathology at the same time and in the same way.

DIFFERENCES AMONG STATISTICAL MODELS OF THE HIERARCHY OF PSYCHOPATHOLOGY DIMENSIONS

Several theorists have argued that the patterns of correlations among the first-order dimensions of psychopathology (e.g., generalized anxiety, depression) can be organized into a hierarchy[6,14,16]. In meaningfully different ways, these theorists have posited that the hierarchy consists of a broad general factor of psychopathology that reflects positive correlations among all symptoms – also referred to as the p factor – and two or more specific factors of psychopathology (e.g., internalizing, externalizing)[6,14,16-19].

There are similarities among the several proposed hierarchical taxonomies, but an important unresolved issue concerns the statistical models used by different theorists. Some authors have used a simple series of exploratory principal component or factor analyses in which increasing numbers of factors are specified in each analysis. That is, one factor is extracted in the first analysis (i.e., the general factor), two factors in the second analysis (e.g., internalizing and externalizing factors), and so on until the largest number of specific factors that the data will justify have been extracted. These successive factor analyses describe a hierarchy from more general to more specific dimensions[20], but they do not constitute or imply a specific and comprehensive statistical model of the hierarchy.

Other theorists have used second-order models to describe the hierarchy of di-

mensions of psychopathology[21]. In these models, every symptom (or first-order dimension of symptoms) loads on one of several correlated lower-order factors and these lower-order factors load, in turn, on a second-order general factor (Figure 1). This operationalizes the hierarchy in a single integrated model, but the general factor and the lower-order factors are not statistically independent, making their unique correlates impossible to parse.

The bifactor model[22-24] defines the hierarchy of general and specific dimensions of psychopathology proposed by Lahey et al[14,16,17] and Caspi et al[18,19]. In a bifactor model (Figure 1), each symptom (or first-order dimension of symptoms) loads both on the general factor and on one (and only one) of some specific factors. Thus, the general factor is defined by residual correlations among all items when accounting for the correlations among items that load on each specific factor. Conversely, the specific factors are defined solely by residual correlations among symptoms within each domain when accounting for the correlations that define the general factor[22,23].

On the surface, bifactor and second-order factor models are similar in defining general and specific factors of psychopathology, but they actually differ in important ways[23]. Tests of associations of factor scores with external variables – such as clinical outcomes, risk factors and neurobiological variations – of the two models are necessarily different in form and meaning.

In bifactor models, all of the general and specific factors are orthogonal, meaning that they are not correlated with one another. Thus, using a bifactor model, one can regress an independently defined and measured external variable on all of the general and specific factors simultaneously to determine if each of these factors accounts for unique variance in that variable.

In contrast, the factors in second-order models are not statistically independent. Although one can regress an external variable on the general factor, the lower-order factors cannot be included in the same regression model, because the general factor is defined by their loadings. Conversely, one can regress an external variable on lower-order factors, but the general factor cannot be included because it is not independent of them. That is, the lower-order and general factors are perfectly collinear in second-order models. This means that determining the unique correlates of the lower-level factors when controlling for the general factor is impossible. This limits the use of second-order models in attempting to discover the unique causes and mechanisms of each general and specific factor. Even if the general factor were included in predictive models with only one specific factor at a time, thereby avoiding the perfect collinearity, the results would be uninterpretable, because the lower-order factors are part of the very definition of the general factor.

In contrast to the above issues with the second-order models, the bifactor model is optimal for testing unique effects simultaneously, because all of the general and specific factors are orthogonal.

There are both similarities and differences among the factors defined in bifactor and second-order models. The general factors defined in bifactor and second-order models are actually very highly correlated and, for some purposes, can be used interchangeably[6,25]. In contrast, the specific factors defined in these two statistical models are quite different and only moderately correlated[25]. For instance, in one study of adults testing the bifactor model, first-order dimensions capturing all types of phobias had lower loadings on the general factor than the first-order dimensions of generalized anxiety and depression[26]. This means that the specific internalizing factor in a bifactor model reflects fears more, and generalized anxiety and depression less, than the internalizing factor in a second-order model.

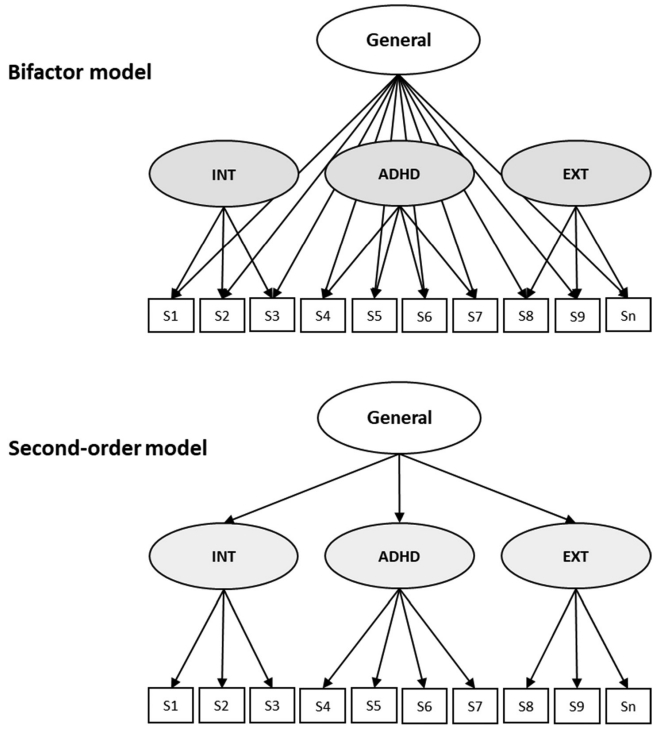

Figure 1 Illustrations of the different structure of bifactor and second-order models for defining general and specific factors of psychopathology. INT – internalizing, ADHD – attention-deficit/hyperactivity disorder, EXT – externalizing, S – symptom (or first-order dimension of symptoms)

CONCERNS ABOUT BIFACTOR MODELS

The discriminant validity of general and specific factors of psychopathology using bifactor models has been supported in several studies with large samples. These studies have shown that, over and above the prediction from specific factors such as externalizing and internalizing, the general factor of psychopathology predicts independently measured adverse functional outcomes, such as psychoac-

tive drug prescriptions, incarceration, poor academic progress, suicidal behavior, and self-harm[27-31].

Nonetheless, the use of bifactor models in hierarchical approaches to psychopathology has been controversial. Some of the controversy stems from the fact that fit indices sometimes favor bifactor models over second-order models when they conceptually should not[32]. This is a valid concern, but not a telling issue. One should not choose among well-fitting but substantively different statistical models only on the basis of the model fit in any case. Rather, one should choose among well-fitting models on the basis of their validity and utility[32].

A second concern raised about bifactor models focuses on the replicability of the specific factors in those models. The H index uses cross-sectional data to estimate how replicable a latent factor may be. One study raised a concern about bifactor models by reporting adequate H for the general and externalizing factors, but unacceptable H values for the internalizing factor[33]. However, other studies using stronger samples and measures have reported acceptable H values for both the general and all specific factors in bifactor models[21,25,34].

Moreover, rather than trying to estimate the replicability of the general and specific factors of psychopathology from a single analysis of cross-sectional data, it is far more informative to conduct longitudinal studies in which these factors are independently estimated in the same persons. When this has been done, both general and specific factors of psychopathology defined in bifactor models have proven to be replicable in the same persons over multiple years[34-39]. Thus, although estimates of the replicability of specific factors as indexed by H in single assessments warrant attention, there is strong evidence from longitudinal studies that all factors of psychopathology are replicable over time.

CAUSAL VS. PHENOTYPIC HIERARCHICAL MODELS

It is important to note that the hierarchical taxonomies of psychopathology that have been proposed to date all necessarily include a descriptive model of dimensional phenotypes. The most extensive hierarchical phenotypic model has been offered by the group operating under the name of Hierarchical Taxonomy of Psychopathology (HiTOP)[6,15]. The HiTOP has advanced a comprehensive taxonomy based on the existing empirical literature on phenotypic structure and advocated for the utility of applying such a model to psychopathology in both research and clinical practice.

We have offered a complementary approach that addresses both the hierarchy of phenotypes and the causes that create the hierarchy of phenotypes[14]. In one of our studies, we collected data on psychopathology dimensions from a large and representative sample of child and adolescent twins[17]. Based on differences in correlations among these phenotypic dimensions in monozygotic and dizygotic twin pairs, genetic and environmental correlations among the phenotypic dimensions were estimated and then each analyzed in bifactor models. The results suggested the causal hypothesis that phenotypic correlations among all dimensions of psychopathology captured by the general factor are largely the result of the same familial factors. That is, many genetic variants and environmental factors shared by family members appear to non-specifically influence risk for manifesting psychopathology of some sort, but not specific dimensions of psychopathology. On the contrary, other genetic and environmental influences, particularly person-specific experiences, play the largest role in determining the specific dimensions of psychopathology that will be exhibited[17].

Thus, we hypothesized a hierarchy of causal influences, from the most non-specific to the most specific, that gives rise to the hierarchy of phenotypes[14]. This hypothesized hierarchy of genetic and environmental influences has been confirmed in a large sample of siblings in Sweden[40]. Moreover, molecular genetic research has supported the hypothesis that the hierarchy of correlated phenotypes results partly from highly pleiotropic genetic variants that non-specifically increase the risk for many or all forms of psychopathology[41-43].

Members of the HiTOP group have recently proposed that their hierarchical, dimensional and data-driven classification system provides a more effective approach to identifying genes that underlie mental disorders, and to studying psychiatric etiology, than current diagnostic categories. Specifically, genes are expected to operate at different levels of the HiTOP hierarchy, with some highly pleiotropic genes influencing higher-order psychopathology (e.g., the general factor), whereas other genes confer more specific risk for individual spectra (e.g., internalizing), sub-factors (e.g., fear disorders), or narrow symptoms (e.g., mood instability)[44].

We strongly agree that this is the hypothesis that we should be testing. Indeed, this hypothesis has already received considerable empirical support. We would only add that family level environmental influences may also be highly non-specific, while person-specific experiences more likely play a role in determining which specific symptoms a person exhibits at each point in time. We note in this context that the bifactor model is optimized to test such general versus specific hypotheses, whereas second-order models are not.

NATURE OF GENERAL AND SPECIFIC FACTORS DEFINED IN BIFACTOR MODELS

A great deal has been learned in a short amount of time about the nature of the hypothesized general and specific factors of psychopathology from the bifactor model. Here we focus on several issues, including the stability of the hierarchy of factors of psychopathology over time, the correlated psychobiological processes, and the neurobiological mechanisms.

Stability over time

To what extent do persons' scores on the general and specific factors of psychopathology change or remain the same? Across 1-2 years in childhood and adolescence, several studies have found that each general and specific factor of psychopathology significantly predicted itself primarily or exclusively in the next assessment, revealing moderate to strong stabil-

ity over time[34-36,39].

In a study of a representative sample of 43,000 adults, the general and all specific factors of psychopathology predicted only themselves over 3 years, with the exception of a specific distress factor defined by major depression, dysthymia, and generalized anxiety disorder[37]. In contrast, a study of 499 persons assessed in childhood or adolescence and then evaluated again 12 years later in adulthood found that general factor scores were significantly stable over time, but specific internalizing and externalizing factors were not stable over this long interval[38].

More needs to be learned, but it appears that all factors of psychopathology defined in bifactor models are stable over time during childhood and adolescence, but some of the specific factors may be less stable during adulthood or from adolescence into adulthood.

Correlated psychobiological processes

What is the nature of the general factor in psychological and biological terms? Because the general factor is simply a statistical construct, it is very important for us to understand the processes that it reflects to gain the greatest theoretical leverage on psychopathology. A growing amount of replicated data already reveals something of the psychobiological nature of the general factor defined in bifactor models.

Negative emotionality

It is well known that individual differences in negative emotionality (neuroticism) are robustly and positively associated with every form of psychopathology[45]. Thus, it is not surprising that multiple studies have found negative emotionality to be associated with the general factor defined in bifactor models[34,46,47].

In nearly all of these studies, the measure of negative emotionality was also significantly associated with specific internalizing psychopathology. In one study, it was also associated with externalizing psychopathology[47]. Thus, the individual differences in the experience of negative emotions captured by measures of negative emotionality appear to be at the heart of the general factor, but are also related to more specific dimensions of psychopathology.

Cognitive abilities, including executive functions

A number of studies have also consistently reported significant associations of the general factor of psychopathology with both intelligence[19] and global and specific measures of the executive functions[18,25,48-50]. The term executive functions refers to a related set of highly heritable cognitive processes that are believed to regulate attention and foster adaptive goal-directed behavior[51]. Much remains to be learned, but it is possible that deficits in executive functions are one of the psychobiological processes that underlie the general factor of psychopathology[52].

It is important to note that both twin and molecular genetic studies suggest that the general factor of psychopathology is moderately heritable[53,54]. Furthermore, two twin studies have determined that both measures of negative emotionality[47] and of executive functions[55] share their genetic influences with the general factor of psychopathology in children and adolescents. These findings strengthen the view that high negative emotionality and deficits in executive functions are at least part of what constitutes the non-specific tendency to develop psychopathology that is captured by the general factor.

Impulsive responsivity to positive and negative emotions

Johnson et al[56] have argued that impulsive responding to both positive and negative emotions is a key factor underlying all dimensions of psychopathology through the general factor[57]. Thus, they posit that it is the cognitive control of emotion that is important, and argue that deficits in controlling both negative emotions and exuberant positive emotions are involved in psychopathology.

We recently used data from the large Adolescent Brain Cognitive Development (ABCD) Study to examine associations between the general factor of psychopathology in children and self-report measures of dispositions, including the positive urgency and negative urgency scales of a short form of the UPPS impulsivity measure[58]. Consistent with the above hypothesis, these scales, which tap impulsive responding to positive and negative emotions, were both positively associated with the general factor of psychopathology defined in a bifactor model[25].

Disordered thinking

Caspi and Moffitt[19] have added another hypothesis regarding the underlying psychobiological nature of the general factor of psychopathology. They suggest that the general factor is partly the result of disordered thought processes common to essentially all dimensions of psychopathology.

They defined disordered thought as "thought processes [that] are illogical, unfiltered, tangential, and reality-distorted and -distorting"[19]. This refers broadly to the altered cognitions revealed in difficulty making decisions, misattributions, body image disturbances, irrational fears, dissociative states, depersonalization and derealization, beliefs that there will be terrible consequences if a logically unrelated action is not performed, and delusions and hallucinations.

This new hypothesis is cogent, plausible and intriguing. One difficulty is that reliable and valid measures of the full breadth of disordered cognition referred to by Caspi and Moffitt do not exist at this time. This means that only piecemeal tests of their hypothesis are currently possible.

Neurobiological mechanisms

We have only begun to map the biological correlates of the general and specific factors of psychopathology defined in bifactor models. This research is vitally important to understand the mechanisms that link causes and symptoms and, fortu-

nately, is continuing at a rapid pace[59].

A recent review of this research literature stated that the general factor "has been associated with a number of neurobiological measures in youths, including reduced gray matter volume[60,61], reduced activity in executive regions[62], elevated resting-state cerebral blood flow[63], reduced fractional anisotropy[64], and delay in connectome distinctiveness"[65,66].

Replications of some findings have already been published, including associations between the general factor of psychopathology and atypical white matter development[67-69], atypicalities in the cerebellum and its connections[70-72], and lack of typical segregation between the default mode and executive networks during rest[73]. Thus, we may not be far from an understanding of at least some of the neurobiological mechanisms related to the general factor of psychopathology.

CLINICAL IMPLICATIONS

There are several ways in which hierarchical dimensional models of psychopathology are important in clinical settings. The most immediate implication of these models is a change in how we conceptualize psychopathology. There is a continuous relationship between dimensions of symptoms and adverse outcomes. This relationship between gradually more symptoms and greater impairment begins well below diagnostic thresholds, which argues against limiting care to only those who meet binary diagnostic thresholds[74-78]. Similarly, the extensive changes in symptoms over time – heterotypic continuity – refutes the view of mental disorders as enduring discrete conditions[79].

Furthermore, the robust correlations among dimensions of psychopathology tell us that meeting diagnostic criteria for a categorical diagnosis does not imply that a person has a distinct mental disorder. The ubiquitous correlations among symptoms and dimensions mean that people do not fit neatly into diagnostic categories. People exhibit widely varying patchworks of symptoms from multiple dimensions, even if they meet criteria for a single diagnosis.

In considering the implications of the hierarchical taxonomy of psychopathology for clinical practice, it is essential to understand that the general factor of psychopathology is not being proposed as a new "kind" of psychopathology. It is certainly not being proposed as the basis for a new diagnosis. Nonetheless, bifactor models that include a general factor do give us an opportunity to view dimensions of psychopathology through a new lens.

In simple terms, the general factor reflects a "weighted average" of some aspects of all symptoms exhibited by each person at that point in time. Symptoms that are more correlated with all other symptoms – controlling for correlations among symptoms captured by more specific second-order factors, such as internalizing or externalizing – contribute more to the general factor score. Conversely, specific factor scores, such as internalizing, reflect only the residual correlations among just a subset of symptoms after controlling for the widespread correlations among all symptoms.

The general factor score may prove to have particular value in improving prognosis in clinical practice and in targeted prevention programs. Although much remains to be learned, it appears that youth with higher general factor scores experience greater serious functional impairment over time, independent of the specific symptoms they exhibit. As noted above, this includes greater risk for incarceration, suicidal behavior, and non-suicidal self-harm[27-31].

The difficulty is that there currently is no comprehensive standard measure of the general and specific factors of psychopathology that is ready for clinical use to improve prognosis. One group has used a large set of psychopathology items administered to a large sample of children and adolescents to develop a computer-administered measure of general and specific factors of psychopathology that may eventually be useful in clinical settings[80]. The psychometric properties of this measure are encouraging, but it has not been replicated and validated enough to be ready for clinical application.

These replications and tests would need to be conducted in large samples representing a variety of geographic locations, cultures and languages before they can be widely usable. Such measures may not be available in the near future, which means that no evidence-based practices can be recommended even for improving prognosis. On a commonsense basis, it seems reasonable for clinicians to suspect that persons with simply more symptoms from across multiple domains are at higher risk for serious adverse outcomes. However, we do not have enough evidence at this point to be confident in that practice.

The hierarchical model is likely to play an important role in treatment research. At least one clinical research study used the hierarchical taxonomy of psychopathology to measure changes associated with randomly assigned interventions to better understand the general and specific effects of treatment[81]. Other researchers are developing and testing new treatment methods that are designed to remediate the processes, e.g. negative emotionality, that all dimensions of psychopathology appear to share[82,83]. Tests of these new treatments may not only lead to better treatments with more widespread benefits, but will help us understand what underlies the general and specific factors of psychopathology.

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Hierarchical dimensional models of psychopathology: yes, but…

I strongly concur with Lahey et al's advocacy of hierarchical dimensional models for psychopathology[1]. How could I do otherwise? I have been developing and advocating such models for over half a century[2,3]. But God (or the devil, if you prefer) is in the details. Consequently, I address here some details of Lahey et al's paper that must be considered in order to advance our knowledge of psychopathology and ways of modeling it.

First, although its title does not include the word "dimensional", the paper focuses mainly on hierarchies of dimensions based on factor analyses of associations between items that are rated in samples of individuals. The contents of the dimensions – i.e., the particular sets of items that are found to have substantial loadings on particular factors – are shaped by the nature of the items themselves (e.g., descriptive vs. inferential); the scales for rating the items (e.g., present/absent vs. 0-1-2); the content of the items (e.g., diagnostic criteria vs. colloquial descriptions); the periods spanned by the ratings (e.g., days vs. weeks, months or years); people who rate the sample of individuals (e.g., self vs. collaterals or clinicians); the age of assessed individuals (e.g., preschool vs. school age, adult or elderly); methods for computing associations between item ratings (e.g., Pearson r vs. tetrachoric); methods of factor analysis (e.g., principal factor vs. principal component); sample size (e.g., N=100 vs. 1,000); criteria for retaining factors (e.g., Kaiser's criterion vs. scree plot); criteria for retaining items on each factor (e.g., loadings that are statistically significant vs. ≥.30); methods for applying factors to the scoring of individuals (e.g., factor scores vs. unit weighting of items), and so forth.

The diverse results obtainable with factor-analytic methods argue against expecting a single model to validly represent all psychopathology for all ages, genders, cultural groups, sources of data, and degrees of severity. Instead, statistical tools such as factor analysis organize large quantities of data into models whose value depends on judgments and criteria external to the statistical tools. Consequently, rather than seeking a single model for all psychopathology, we need to compare the value of different models for different purposes. As our methods and knowledge advance, we may find that different models are valid and useful for different purposes.

Second, Lahey et al focus on the relative merits of second-order versus bifactor models for representing psychopathology hierarchically. Second-order factor analysis derives higher-order, broad-spectrum factors by analyzing associations between scores obtained in samples of individuals on first-order, narrow-spectrum factors, often called syndromes. As an example, Lahey et al repeatedly cite second-order factors designated as internalizing and externalizing, which are found so often that the constructs they represent have been used in over 75,000 published studies[2,4]. Second-order factor analysis takes first-order factors (syndromes) at face value and then analyzes associations among scores obtained in large samples of individuals on the syndromes to derive groupings of syndromes. Second-order internalizing factors often include first-order syndromes comprising problems such as depression, anxiety, social withdrawal, and somatic complaints without apparent medical cause. Second-order externalizing factors, by contrast, often include first-order syndromes comprising problems such as aggressive and rule-breaking behavior.

Bifactor analysis partitions the variance in ratings of each problem item into variance unique to the problem itself and variance in the problem's ratings that is shared by a general psychopathology (p) factor. Because second-order factor analysis retains first-order syndromes as constructs operationally defined as the aggregated scores of their constituent problems, it maps more closely onto clinical practice than bifactor analysis, which focuses on components of variance in the ratings of each problem. Neither bifactor analysis nor second-order factor analysis is necessarily optimal for all applications, and each has many methodological variations.

The essential point is that we can usefully view psychopathology in terms of hierarchies that start at the "bottom" (the most molecular level) with specific problems. Associations among the problems are then analyzed to yield narrow-spectrum syndromes roughly analogous to DSM and ICD diagnoses. Associations among the syndromes are analyzed to yield broad-spectrum groupings such as those designated as internalizing and externalizing.

Third, the p factor can be conceptualized as the apex of hierarchies that range from specific problems at the bottom, through narrow-spectrum syndromes, broad-spectrum groupings such as internalizing and externalizing, and culminate in a dimension comprising all the problems. General psychopathology dimensions can be obtained with both second-order and bifactor methods. Measures based on diverse problems – such as p – are likely to be especially good prognosticators, just as aggregations of diverse measures of ability are better indices of general intelligence (g) and better prognosticators than are narrow-spectrum measures of ability.

There are multiple biological and environmental reasons for this, but neither p nor g have single gold-standard operational definitions. Lahey et al argue for the superiority of p factors derived from bifactor analyses that weight individual problems on the basis of residual variance (i.e., the variance remaining after lower-order variance is extracted). However, loadings of problems on the first principal factor can also be used to weight items on p. Item weights are affected by the factor-analytic method, the procedures for assessing problems, the samples from which the data are obtained, and so forth. Moreover, because the precise value of each problem's weight may fail to replicate in new samples, unit weighting of problems is often more robust.

Fourth, Lahey et al argue for a "dimensional measure of psychopathology that includes all symptoms". Unfortunately, this is unrealistic, because it implies that the same measure of "all symptoms" would suffice for people of all ages, genders, cultures, and degrees of impairment. Regarding age, for example, the relevant "symptoms" and

methods for assessing them differ greatly between such ages as 1, 9, 18, 50 and 80 years. It is also unrealistic to expect that "all symptoms" can be identified before research yields operational definitions of disorders in people of each age, assessed by multiple methods, such as self-reports, collateral reports, clinicians' observations, tests, and biomedical procedures. And the term "symptom" assumes that all phenotypic problems are clinical manifestations of underlying diseases, which is a problematic assumption.

Finally, at the end of the paper, Lahey et al allude to the need for "replications in a variety of cultures and languages". Nearly all of their references are based on Anglophone samples. Rather than being added as an afterthought, multicultural studies of the structure, prevalence, and other aspects of psychopathology should be fundamental components of ongoing research on hierarchical models[5,6].

To inspire confidence, hierarchical models need to be continually tested via methods such as confirmatory factor analysis of data from samples differing from those on which the models were based, rather than accepting the results of exploratory analyses at face value.

Despite the growing popularity of hierarchical dimensional models, their value may be undercut if researchers fail to deal scientifically with the many details to be mastered in properly constructing, testing, and applying such models.

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The utility of hierarchical models of psychopathology in genetics and biomarker research

In their incisive paper, Lahey et al[1] discuss empirically-derived, hierarchical taxonomies of psychopathology that in recent years have gained prominence in psychiatric research. This is a timely opportunity to reflect on some of the implications and future directions for leveraging redefined psychiatric constructs in research efforts.

The authors highlight genetics as a leading edge in the paradigm shift in psychiatric nosology. Indeed, behavioral (family and twin) and molecular genetic studies provide some of the strongest evidence to date that biological vulnerability transcends diagnostic boundaries between disorders, as well as boundaries between psychopathology and normality[2].

First, there is ample evidence that genetic liability to mental illness is continuously distributed, on a dimension from heathy traits in the general population (e.g., personality trait neuroticism) to corresponding clinical diagnoses (e.g., major depressive disorder)[3].

Second, the genetic architecture of psychopathology appears to consist of sets of genetic influences operating at different levels of specificity, across a multi-tiered hierarchy. For example, models using genetic loci identified in genome-wide association studies (GWAS) found that a significant proportion of genomic influences is common to numerous psychiatric disorders (e.g., schizophrenia, depression, attention-deficit/hyperactivity disorder)[4,5]. The remaining risk, which is considerable in size, is disorder-specific, indicating that genetic factors unique to narrow constructs also play a role in the etiology of psychopathology. In sum, the genetic architecture of psychopathology is dimensional and hierarchical. Its correspondence to one classification system – the Hierarchical Taxonomy of Psychopathology (HiTOP) – has been detailed previously[2].

The hierarchical structure of genetic risk has major implications for future research, in that it provides empirically-validated targets for genetic inquiry. In particular, it promises to advance GWAS, which continue to be a leading approach to discovering genetic variations associated with psychiatric conditions. Specifically, GWAS calibrated to reliable, empirical constructs at different levels of specificity – e.g., general factor or internalizing spectrum – could identify more genetic risk loci than traditional case-control studies. For example, more genetic variants were found when a higher-order, dimensional "fear" factor was used as a GWAS target, compared to a case-control anxiety disorder status[6]. However, additional empirical studies are needed to interrogate this hypothesis comprehensively.

Consequently, the hierarchical approach to GWAS might help explicate which genetic effects are transdiagnostic vs. specific. Knowing the specificity of identified genetic loci is crucial for follow-up characterization of downstream biological processes, as well as for translation of GWAS results into research tools and clinical instruments.

One such instrument is polygenic risk score, which captures part of an individual's genetic susceptibility to a disease. An increasing number of research studies demonstrate associations between polygenic risk scores and psychiatric conditions, although the clinical utility of these scores has not yet been established. The quality of psychiatric assessment in the GWAS is a major determinant of the power and precision of the resulting polygenic risk score. Currently, genetic risk scores developed for one disorder (e.g., schizophrenia) have been found to predict many other conditions and outcomes (e.g., post-traumatic stress disorder, substance use, cognitive performance), with little specificity, and thus limited potential for research and clinical utility[7]. Future GWAS on hierarchical and dimensional constructs could help create more

robust polygenic risk scores.

This approach can be extended to longitudinal lifespan research which aims to investigate how genetic factors shape the course of psychopathology over time. Lahey et al[1] describe key evidence that higher-order dimensions, in particular the general factor, are highly stable across development. However, age differences and developmental trajectories of the hierarchically-organized genetic influences have been investigated in only a handful of prospective longitudinal twin studies. Overall, evidence suggests that general, transdiagnostic genetic influences contribute to the continuity and co-occurrence of psychopathology over time[8]. In other words, the developmental stability of the general factor of psychopathology appears to be driven predominantly by transdiagnostic genetic vulnerability.

One implication of this finding is that a polygenic risk score created explicitly to capture genetic risk to the general factor might in the future help predict individual's vulnerability to a broad range of co-occurring and chronic psychiatric illnesses, or help identify a subgroup of individuals at the highest genetic risk for recurrent, cross-disorder psychiatric illness course. Such individuals at a very high genetic risk to enduring general psychopathology could be identified early and prioritized for prevention programs. Genetic influence (transdiagnostic, stable, or otherwise) does not preclude the possibility of effective prevention and treatment.

Beyond the interface with psychiatric genetics, Lahey et al[1] highlight how hierarchical models have driven novel discoveries in neurobiology, such as by delineating patterns of gray matter volume alterations associated with the general factor. The same principles could be applied to other psychiatric biomarker research. To date, this literature largely consists of disparate studies of single diagnostic categories, obscuring transdiagnostic processes. When cross-disorder research has been attempted, however, commonalities are observed. For example, there is a very high correlation between transcriptome profiles for bipolar disorder and schizophrenia, with both disorders also showing significant, albeit smaller, transcriptome profile overlap with depression[9]. This pattern of overlap suggests that gene expression in the brain could be mapped onto the general and specific factors of psychopathology.

Similarly, many epigenetic, inflammatory, hormonal and metabolic biomarkers are implicated across studies of different psychiatric disorders. The hierarchical approach provides a more powerful and systematic way for these fields to probe which biological correlates are general vs. disorder-specific, allowing for the derivation of biomarker signatures at different levels of specificity. Importantly, significant genetic and environmental influences at the lower levels of the hierarchy suggest that symptom-specific downstream biomarkers can be identified alongside transdiagnostic biomarkers. Consequently, screening and interventions could be developed to target biological processes that all dimensions of psychopathology appear to have in common, or target processes unique to one or a subset of dimensions.

To achieve these research goals, studies need to assess a wide range of psychopathology across the full spectrum of severity, ranging from personality traits to severe clinical problems. While a comprehensive dimensional measure of psychopathology is currently under construction by researchers affiliated with the HiTOP model, existing instruments can be combined to assess general and lower-order dimensions[2]. Many of these measures have been validated in short versions and can be administered remotely for feasibility.

Overall, as Lahey et al[1] point out, the hierarchical conceptualization of psychopathology will benefit clinical practice. This improvement will in part come from this model's unique utility for advancing basic and translational psychiatric research.

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On hierarchically-informed measures of psychopathology

Lahey et al[1] provide an overview of superordinate structural models of psychopathology, focusing on the role of a general psychopathology factor within them. The authors review differences between hierarchical and higher-order accounts, structural findings from family and longitudinal designs, theories about the nature of the structures, and remaining questions and tasks facing research and clinical communities.

They argue that these communities are "hampered by the current absence of a comprehensive dimensional measure of psychopathology that includes all symptoms", and suggest that "we cannot comprehensively define the dimensions of psychopathology until we can study all of the symptoms that define the universe of psychopathology at the same time and in the same way".

Although there are certainly pressing needs for psychopathology measures, is it true that there is an absence of comprehensive dimensional measures of psychopathology? What would it mean to "include all symptoms"? Is an optimal measure one in which different symptoms of psychopathology are quantified in the same way? What would an ideal measure look like?

A truly comprehensive measure of psychopathology might be unattainable, given that measurement needs evolve with fields and will always change. However, reason-

able proxies for this ideal arguably do exist – the Achenbach System of Empirically Based Assessment (ASEBA)[2] is an important example. On the other hand, one can point to a myriad of domain-specific measures, such as measures of mood, somatic symptoms, or thought disorder, which have been carefully constructed to represent the phenomena they purport to measure, although they may be circumscribed in depth or breadth, or otherwise limited in some way. These measures are not comprehensive individually but, jointly assembled, they usually cover their respective terrain well. Many studies of superordinate psychopathology structure are reasonably based on these types of measures, consolidated into wholes.

As research on superordinate structure progresses, it is important to ask what, exactly, the field needs in a comprehensive measure. A hierarchical model such as a bifactor model typically differs from alternatives in that its general factor either has direct expression in indicators (i.e., there are "pure" indicators of the general factor) or its expression is not otherwise mediated through specific factors (i.e., relationships between indicators of different specific factors cannot be explained in terms of general factor relationships)[3].

The former case suggests that pure indicators of the general factor could be developed, possibly in the process of testing hypothetical underlying mechanisms of that factor, such as those enumerated by Lahey et al (i.e., variables such as negative emotion, cognitive ability, impulsive response to emotions, disordered thinking, or various neurobiological factors). The latter case, perhaps encountered through an eventual failure to identify pure indicators, might suggest more systemic factors at play, and an emergent, rather than correspondent, general factor where very detailed processes acting across specific factors dynamically relate[4].

A comprehensive measure is arguably inseparable from an underlying set of hypotheses or assumptions, implicit or explicit, about the nature of its constituent factors and how they manifest in indicators. The development or consolidation of such a measure, by extension, would probably have greatest utility if those assumptions are systematically evaluated as part of the design.

It remains to be seen how much the specific origins of a measure affect structural-causal modeling of indicators, even though the need for a single origin seems to be an implicit assumption of many current superordinate measurement efforts. For example, if two research groups were to independently develop two measures of the same psychopathology variable, how much would conclusions about the structure of that variable differ depending on which measure was used?

Independently developed measures of psychopathology are commonly used together in structural studies, and few questions have been raised about method effects outside of major variables such as type of respondent or time of assessment. What are the limits? How much do unspecified method effects associated with origin, such as unarticulated patterns of item construction, affect results? Is there anything significant about sharing a common origin beyond the associated hypotheses underlying their construction? Does focusing on a comprehensive measure inhibit competitive evaluation of measurement and structural theories?

It is also important to consider whether, in a comprehensive measure, "all of the symptoms that define the universe of psychopathology" would ideally be assessed "at the same time and in the same way". It is possible that different types of psychopathology might be best assessed in different ways, either due to the nature of the psychopathology, or due to issues pertaining to insight, unreliable recall, reliable or unreliable situational variability, or other variables. Disorders with cognitive ability deficits might be assessed differently than mood disorders, for example; delusions or narcissistic psychopathology might be optimally assessed by different informants than would be used to assess distress; it might be that a general factor impels a different measurement approach than specific factors.

At some level, it is unclear if an exhaustive set of symptoms could be defined. One must consider the possibility that idiographic assessment components would be necessary to achieve comprehensiveness. In that case, one might essentially have different measures for each individual, an extreme case of symptoms not being assessed at the same time or in the same way.

One interesting problem raised by the hierarchical or bifactor model is how to conceptualize severity of psychopathology symptoms, especially in a clinical context. One classic conception of severity is in terms of risk conferred by a symptom for some significant sequelae or outcomes, such as death, serious injury, hospitalization, or significant loss. Another common, more recent conceptualization of severity is found in item response theory, in which severity is framed in terms of level of psychopathology required to endorse a symptom.

Typically, in unidimensional item response theory models, endorsement of more symptoms points to greater levels of an underlying psychopathology dimension and therefore severity. However, in hierarchical models, endorsement of more symptoms might reflect something etiologically distinct. That is, as an individual endorses more and more diverse symptoms, the most appropriate inference might not be that the individual is elevated on many specific factors, but rather that he/she is elevated on a general factor, with distinct etiology, reflecting a different set of pathologies. This shifts perspective on the meaning of diverse symptom endorsement somewhat, away from severity *per se* or multifactoriality.

Development and use of hierarchical comprehensive measures should ideally address these types of issues in how they are scored, and how responses to the measures are interpreted.

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Psychometrics, interpretation and clinical implications of hierarchical models of psychopathology

As described eloquently by Lahey et al[1], recent research on hierarchical models of psychopathology, which include a general factor of psychopathology at the top and several specific factors at lower levels, is changing psychiatry and clinical psychology.

We believe that a general psychopathology factor could provide clinicians with a reliable measure of patients' overall distress and impairment, and that the specific factors might better highlight ways in which patients differ from one another. Nevertheless, as Lahey et al mention, the three issues of psychometrics, interpretation and clinical implications are still unsettled, and the discussion should be continued.

Regarding psychometrics, Lahey et al note that the field has not yet settled on a particular statistical model to measure the hierarchy of psychopathology. We agree that it might be unwise to select a measurement model based on statistical comparisons, given that second-order and bifactor solutions both tend to fit reasonably well. Our view is that the two statistical models are differently preferential depending on the research question, and that both have their respective advantages and disadvantages.

An advantage of second-order models is that the lower-order factors tend to be relatively easy to interpret, because they are identified before isolating the general factor. In contrast, since bifactor models identify the general factor at the same time as the lower-order factors, the latter can sometimes be difficult to interpret, because they do not necessarily conform to preconceived construct notions.

An advantage of bifactor models is that they allow for estimating associations between all the factors and covariates simultaneously. In contrast, as Lahey et al point out, second-order models with covariates lack one degree of freedom, and can therefore not be estimated. A statistical solution to this problem is to impose one constraint on the associations (e.g., assigning one lower-order factor as a perfect indicator of the general factor, such that it has zero residual variance, and thereby not estimate its association with the covariate), but the estimated association parameters are likely to differ depending on where the constraint is imposed. A different way to circumvent this problem is to use a second-order factor rotation matrix within an exploratory structural equation modeling framework[2]. This approach is advantageous because it allows for estimating associations between all the factors in second-order models and covariates simultaneously.

Regarding interpretation, Lahey et al note that it remains somewhat unclear what the general and specific factors measure. Interpretation problems become apparent when associating general factor models with covariates that are partly non-specific. For example, whereas past research has indicated that the general factor is correlated with negative emotionality[3], it is unclear whether this association is attributable to the unique part of negative emotionality, or what it shares with all other emotion traits. To address this question, it might be advantageous to identify general and specific factors also of such covariates. After isolating a general factor from negative emotionality in a sample of children, it was shown that the negative emotionality fear subscale correlated more strongly with internalizing than general psychopathology. Furthermore, the fear subscale switched sign from correlating positively to negatively with externalizing psychopathology[4].

On a related note, although all forms of mental health problems tend to be positively associated, a consequence of bifactor models can be that the residual factors sometimes become negatively associated. For example, in two of the initial bifactor studies of psychopathology, the observed and genetic correlations between internalizing and externalizing problems switched sign from positive to negative after adjusting for general psychopathology[3,5]. However, it is unclear whether this inverse association reflects behavioral tendencies or a psychometric artifact, because isolating a general factor is akin to subtracting the mean correlation from a correlation matrix, after which some residual correlations are bound to be above zero and some below zero[6].

Emerging findings indicate that this inverse association might reflect behavioral tendencies. For instance, the criteria for psychopathy include a higher degree of antisocial traits but also a lower degree of negative emotionality. This inverse association seems to replicate when based on biological measures. A meta-analysis of male offenders demonstrated that there is a negative association between clinician-rated callousness and bodily reactivity to threatening stimuli (e.g., startle blink reflex)[7]. Furthermore, in a study of over one million Swedish male military conscripts, higher resting heart rate (adjusted for physical fitness as measured by a bike test, height, weight, and parental education) at age 18 predicted an increased risk of anxiety disorders decades later. Conversely, lower resting heart rate predicted an increased risk of later criminal convictions[8]. Because resting heart rate is considered an indicator of the fear circuitry system, one speculation is that the fearful versus fearless continuum might represent one factor that partly contributes to the inverse association between the internalizing and externalizing dimensions in bifactor models.

Regarding clinical implications, Lahey et al note that there is not yet adequate data on whether the general factor of psychopathology could assist mental health practitioners. It might therefore be beneficial to look at other domains where a general factor has been used. A general factor has been used for over a century in the intelligence domain to diagnose learning disability and predict academic performance. Because the general factors of intelligence and psychopathology appear to have relatively similar magnitude and predictive validity[2], general psychopathology might be as useful in the psychiatric domain as general intelligence has been in the education domain. One speculation is that general psychopathology could provide clinicians with a reliable measure of overall distress and impairment[9], which could, for example, help

predict prognosis or how much treatment a patient might need.

A general factor has also been used in the self-reported personality pathology domain. Tellegen et al[10] developed a Minnesota Multiphasic Personality Inventory scale to measure non-specific variance associated with unpleasant mood states, which they labeled demoralization. They observed that "this general factor appears to inflate correlations between attributes that are considered relatively independent"[10]. Therefore, they aimed to "remove from each clinical scale items primarily marking demoralization" in order to improve the ability to differentiate among patients[10].

We share their sentiment about the importance of discriminant validity, and speculate that one potential clinical advantage of measuring a general factor is that the remaining scales might better highlight differences between patients. This, in turn, might help guide treatment modality. For example, without isolating a general factor, individuals with a broad symptom load often display elevated scores on a wide range of psychiatric scales. However, after isolating a general factor, such individuals might only display elevated scores on a smaller subset of scales, which might represent a suitable target for initial treatment.

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The p factor is the sum of its parts, for now

The general factor of psychopathology, or p factor, has received increasing attention over the last half decade, but questions remain about how to best conceptualize it[1,2].

Here, we use data from a large-scale survey (National Epidemiologic Survey on Alcohol and Related Conditions, NESARC), conducted in a nationally representative US sample, to demonstrate that, statistically, p is nearly identical to the sum of diagnoses it is estimated upon. The same holds for specific factors such as internalizing and externalizing, and our results are robust to various estimation methods. We discuss implications of this finding for the nature of these factors, and raise the question whether the sole reliance on reflective latent variable models used in the p factor literature is justified, given that nearly identical scores can be obtained by a much simpler statistical procedure that has fewer parameters and imposes fewer assumptions on the data.

Questions about the interpretation of p are important, because this factor carries at least two meanings. Statistically, p refers to a latent variable estimated on a covariance matrix of psychopathology symptoms or diagnoses in a given dataset. The field has utilized one specific class of models, the reflective latent variable model, in several flavors, such as the bifactor and second-order factor models, that decompose variance somewhat differently[3]. No matter the specific model, general factors such as p necessarily emerge when data feature a positive manifold[4]. Statistically speaking, p is just a different way of stating that observed items are positively related.

The p factor's second meaning is conceptual: what p represents. Conceptualizations of p vary widely, including severity/dysfunction and a general liability for psychopathology through non-specific genetic and environmental influences, disordered thought processes, and/or trait-like attributes (e.g., negative emotionality)[1,2]. It is an open question how these conceptualizations of p fit the data and methods used in the field. If p represents liability, for example, it is unclear why models are estimated on data on symptoms and diagnoses rather than data on risk factors and etiology, such as early adversity, mentalization/reflective functioning, and attachment insecurity[5,6].

To shed light on the relation between the statistical and the conceptual p factor, we estimated two types of general factor models: the bifactor model (M1) and the higher-order factor model (M2). We repeated analyses for these general factor models' specific factors (distress, fear and externalizing), as well as the correlated 3-factor (M3: distress, fear, externalizing) and correlated 2-factor (M4: internalizing, externalizing) models. The rationale for estimating numerous models was to investigate the degree to which latent variables are generally more than the sum of their indicators and to rule out that results are due to one particular parameterization.

We utilized two waves of the NESARC dataset (W1: N=43,093, W2 follow-up: N=34,653; see https://osf.io/yrpw8 for details), which has commonly been used in the p factor literature[7]. Our main findings are as follows. First, in both waves, we identified high correlations between sum scores of all diagnoses and p, approaching unity for both M1 (range: 0.87-0.99) and M2 (range: 0.87-1.00). Second, domain-specific factors and their respective sum scores (e.g., externalizing factor with sum of externalizing diagnoses) were also highly related across all models: 0.82-0.94 for M1, 0.87-0.96 for M2, 0.78-1.00 for M3, and 0.82-0.96 for M4. Third, correlations between W1 and W2 latent variables were strikingly similar to those between W1 and W2 sum scores (e.g., M1 p factor vs. total sum score: 0.40 vs. 0.44). These findings hold regardless of whether the relations between latent factors and sum scores were estimated using factor scores or a single structural equation model.

In sum, we show that the p factor as well as domain-specific factors are identical or

nearly identical with the sum of diagnoses that go into these respective factors, and that results hold in both general factor and correlated factor models. We see three main implications of our findings.

First, we compare two types of models: a simple sum of indicators vs. a class of highly sophisticated structural equation models that estimate a large number of parameters and impose considerable assumptions on the data, such as hierarchies in which factors are organized, or relations among factors that are constrained to zero[3]. Both models produce nearly identical scores for participants. If replicated in other studies, this finding suggests that the use of reflective latent variable models should be considered more carefully: what are the specific benefits of this modeling framework for the p factor literature, and do they outweigh the potential costs, such as over-parameterization and stringent assumptions imposed on the data[3,4]? Such deliberations will benefit from explicit goals to determine whether specific statistical models are adequate in the context of a given research question. In general, scientific progress is often hampered by overreliance on any particular type of model[8], and thinking more clearly about conceptualizations of p may offer opportunities to diversify methodology.

Second, we provide evidence that p is simply a re-expression of the sum of diagnoses that individuals experience. This is not surprising: about 70 years ago, Cattell[9] described scores on the general factor as "essentially the sum of the scores", and Lahey et al[1] acknowledge the p factor is a "weighted average" of items. Our results imply that p represents severity or comorbidity, not liability, much in the same way as the sum of flu symptoms provides a rough index for severity, not liability. Whether competing accounts of p offer better explanations, such as the idea that it represents liability, requires that models be estimated on variables that actually denote liability, rather than variables denoting severity and comorbidity.

Third, if p is a mere index of the data, this suggests that the meaning of p will only be invariant across studies inasmuch as the data that go into our models are invariant across studies.

Overall, data can be brought to bear on theories when statistical models impose assumptions on the data that are in line with the theories. The p factor literature has been largely atheoretical and primarily concerned with *description* of data – a crucial first step to establish phenomena that can then be explained. But let us not lose sight of the fact that p is an effect that needs to be explained (i.e., *explanandum*), not something that does the explaining (i.e., *explanans*). It necessarily emerges from a positive manifold, and tells us nothing about the mechanisms that generated the data[4,6]. Further, if the goal is the description of data, it is unclear why the reflective latent variable model that is solely relied upon in the literature should be the only model suited for this goal.

Thinking more clearly about theories of p[1,2], and spelling out these theories precisely, will help adjudicate between different conceptual accounts of p. Criticizing and modifying theories requires that we know exactly where they start and end. Clearer theories will then facilitate choosing appropriate statistical models that can in turn guide theory reform.

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Why hierarchical dimensional approaches to classification will fail to transform diagnosis in psychiatry

At the outset, I would like to stipulate that the current DSM and ICD approaches towards diagnostic classification are not perfect. Others have elaborated on the limitations of these categorical approaches towards diagnosis[1]; so I do not repeat them here. I also stipulate that there are some advantages to a dimensional conceptualization of psychopathology over a categorical one. Nonetheless, I am fairly confident that an empirically derived dimensional classification will not replace the DSM-5/ICD-11 anytime soon, if ever.

Eight potential barriers to the integration into clinical practice of one such model, the Hierarchical Taxonomy of Psychopathology (HiTOP), have been identified[2]. Among them, are the length of clinical evaluations, billing for clinical encounters, and incorporating the model into training. The implicit message is that clinicians will require some convincing. That is, clinicians are likely to resist such a seismic change unless a compelling case is made to support the adoption of a new approach towards assessment and diagnosis. While the supporters of dimensional approaches have identified some obstacles to be overcome to transform the categorical system to a dimensional one[2], there are some further important obstacles that they have not addressed, which make such a transformation highly unlikely.

Recognizing that such a change will be a challenge, Lahey et al[3] note that it will be essential to demonstrate that a hierarchical dimensional diagnostic approach improves patient outcomes. If patient outcomes are not demonstrably better, it will be difficult to convince the clinical community that it is worth the effort to learn a new diagnostic language.

Clinician surveys demonstrating acceptance of a dimensional approach are not sufficient to justify a change. It will also not be enough to demonstrate that patients who are evaluated using a dimensional model improve with treatment. No doubt many patients will get better. Such a research design is analogous to an open-label medication trial. In an open-label treatment study, some patients get better, but that does not mean that the medication is effective.

To warrant an overhaul of the approach towards the assessment and diagnosis of patients needing mental health treatment, it will be necessary to conduct a randomized controlled treatment trial. Patients will be randomized to be evaluated under the categorical or dimensional approaches, treated per usual clinical practice, and then outcome assessed. I would predict that such a study will find equivalent outcomes in the two groups.

I would not expect a difference in outcome because a relatively large group of patients will respond to the non-specific aspects of treatment, no matter how they are assessed and diagnosed. In psychiatric practice, where the vast majority of patients are prescribed medication, the placebo effect accounts for much of the response to pharmacological intervention[4]. In placebo-controlled studies of major depressive disorder, bipolar disorder, schizophrenia, obsessive-compulsive disorder and anxiety disorders, it can be conservatively estimated that there is a 30% placebo response rate[4-8]. Thus, a sizable number of patients would be expected to have a positive treatment response regardless of the classification approach.

Another relatively large group of patients, albeit smaller than the placebo response group, will not respond to treatment no matter how they are assessed and diagnosed. Perhaps 20% of patients fall into this treatment resistant group.

One may quibble about the exact percentage of placebo responders and treatment resistant patients that would make up the sample in such a study. And the size of these groups will be affected, in part, by the diagnostic composition of the sample. Nonetheless, I would estimate that the response trajectory of approximately 50% of patients we treat in clinical practice is largely pre-ordained, and the classification system will be irrelevant with regards to whether or not these patients get better.

For the remaining 50% of the patients in the sample, the question is: in how many will a different approach towards classification result in improved outcome? Given the broad-based efficacy of some medications and psychotherapeutic techniques, I suspect that the positive impact of a new classification would be modest and apply to no more than half of these patients. Thus, I would estimate that diagnostic precision has the potential to improve outcome in, at most, 25% of a sample of patients. To be sure, this is not an insignificant number of patients. However, it makes it difficult to demonstrate that a new classification approach is superior to the already established one.

Let's consider the attempt to demonstrate improved outcome based on one classification approach over another from a different perspective. How many patients will have a better outcome because they are treated differently than had they been diagnosed according to the current classification system? I would expect that the treatment of most patients would be the same regardless of the diagnostic approach. For example, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors will be prescribed whether patients were diagnosed with major depressive disorder or generalized anxiety disorder, or have elevated scores on an internalizing dimension with high scores on depression or fear subfactors. Because treatment will be different in only a minority of cases, it will be difficult to demonstrate that the new and improved diagnostic approach results in a better outcome.

Aside from the difficulty in convincing the mental health clinical community of the benefits of a hierarchical dimensional approach, a significant practical problem with the possible paradigm shift in psychiatric classification is the adoption of such an approach by providers who are not mental health specialists. A substantial proportion of mental health care is delivered outside of the specialty care sector. Convincing mental health professionals to change will be a big enough lift. Convincing non-mental health professionals such as primary care providers to learn a dramatically different way to conceptualize and evaluate psychopathology seems highly unlikely. It is not tenable for different segments of the health care community to use different diagnostic approaches.

Finally, one cannot ignore the potential political forces that would oppose a change because of possible lost revenue. Might the American Psychiatric Association resist a change because of the possible loss of income accrued from the publication of the DSMs and the DSM library? Might the pharmaceutical industry oppose a change that could compromise their efforts to develop and sell new pharmaceuticals while regulatory agencies determine how to evaluate products for patients assessed under the new conceptualization of psychopathology?

In conclusion, an empirically supported system of classifying psychopathology is, of course, highly desirable. But let's not throw out the proverbial baby with the bathwater. While there may be problems with the current diagnostic systems, there is also a robust empirical literature providing evidence of validity. Despite their limitations, before I put forth the time and effort to learn and use HiTOP, or a HiTOP-like system, I will need to see data demonstrating that this will improve the care I provide to my patients. Specifically, I would need to see studies showing that more of my patients are likely to get better.

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The important gain is that we are lumpers *and* splitters now; it is the splitting that needs our hard work

Anyone who has done a fair bit of factor analyzing broad measures of psychopathology knows about the general factor that dominates the covariance among the symptoms. He/she also knows that, when the measure includes sufficient depression and anxiety symptoms on the one hand, and aggression and conduct problem symptoms on the other, two broad factors of internalizing and externalizing psychopathology can robustly be identified, which are typically correlated at about .50, again indicative of the general factor.

Spending years on factor analyzing broad measures of psychopathology, I learned that: a) with the tentacles of the general factor so dominantly present in the covariance structure, deriving a meaningful fine-grained factor solution that replicates in the next sample, even when using the same or only a slightly different instrument, is hard; and b) while internalizing and externalizing symptoms are always well represented in broad measures of psychopathology, so that the corresponding factors easily emerge, symptoms of other problem domains (such as psychosis, autism spectrum or attention-deficit/hyperactivity) are generally less well represented, so that the corresponding factors are less robustly identified. I concluded[1,2], therefore, that factor analysis and its dimensional approach to psychopathology is a useful tool for psychometric analysis and scale development, but will never "carve nature at its joints"[3].

Current work on the general factor of psychopathology suggests that I was partly mistaken, overlooking the obvious – i.e., this dominant general factor that is always present in broad measures of psychopathology *is* the nature of psychopathology. Its validity follows, for example, from its fit with heterotypic continuity across the lifespan[4], partly overlapping genetic architectures[5], or cross-diagnostic executive functioning problems[6]. Yet, the realization that the general factor captures meaningful variance provides only temporary relief. Clearly, this factor does not suffice to understand psychopathology. While the DSM with its >200 diagnostic categories may be overly zealous on specificity, the question of which specific dimensions we can validly differentiate in psychopathology remains.

In psychiatry, we tend to find generic associations with external variables (i.e., etiological, environmental, therapeutic, prognostic)[7]. In the past, this raised the question: are our concepts in psychiatry so confounded that we do not find specificity?[8] Now, we can follow this up by "yes": our concepts are confounded by the general factor. Much of the generic relations we tend to find may be tied to the general factor, and whichever specific associations we are hoping to uncover are always "spoiled" by the dominant general factor which seeps right through our findings.

The paper by Lahey et al[7] makes a strong case that we are in a better position to improve our understanding of specific associations with external variables in psychopathology if we delineate the specific factors by splitting the variance of the general and the specific factors using the bifactor model. In my view, this delineation should be pursued: only with the general factor variance removed can we have a clear window into the remaining covariance patterns among the symptoms in our measures. Only with specific measures unconfounded by the general factor can we have a clear window into specific etiological or prognostic associations.

Lahey et al should be lauded for their pioneering and persistent work in the past 10 years focused simultaneously on the general and the specific factors, following from their re-introduction of the bifactor model. Their work has, for example, suggested that the shared familial factors were associated with the general factor, while person specific influences were more likely associated with specific symptom domains[7]. While, so far, we have seen modest knowledge gains for the specific factors, relative to the "lower hanging fruits"[4-6] easily caught by the comprehensive and currently better measured general factor, the approach advocated by Lahey et al should be widely followed by many more research groups to get to the heart of specificity in psychopathology.

It is important to note in this context the frequent misunderstanding of the meaning of the specific factors in the hierarchical vs. the bifactor models. There is a critical difference: lower-order factors in the hierarchical model represent the dimensionality of psychopathology *within* the general factor, while the specific factors in the bifactor model represent this dimensionality *beyond* the general factor.

Empirical comparisons of the two types of specific factors to determine "the winner", therefore, make no sense. Of course, the factor loadings of the specific factors in the bifactor model are lower, with larger standard errors, less stability over time, and so forth. This is only reflecting what we knew from our factor analytic efforts all along: free from the dominant general factor, a chaotic covariance structure of high instability often remains. This situation of poor measurement of the specific factors is a major obstacle in finding etiological or prognostic specificity.

The work ahead is therefore clear: for progress in understanding specific associations (in as much as these exist), strong measures of the specific factors are needed, which, separate from the general factor covariance, still demonstrate high internal construct validity. The critical problem we are facing is that our existing measures of broad psychopathology have insufficient dimensionality[1,2], which is solvable but needs our work.

Measures that were not originally developed with a clear blueprint for specific content domains of psychopathology will not have optimal dimensionality[9], and therefore will show low and unstable factor loadings, which becomes immediately apparent in the bifactor model. When we construct our measures using the bifactor model, we are in a better position to create, evaluate and refine this dimensionality, since we are not "fooled" by the covariance from the general factor, that overestimates the internal construct validity of our specific

measures.

The number and type of domains of psychopathology can never be clarified on the symptomatic level alone. A continuing back-and-forth validation between internal (i.e., factor structure) and external (i.e., genetic, neurobiological, cognitive, environmental, therapeutic, prognostic, and so forth) construct validity would remain. To illustrate, it has often been said that "our DNA has not read the DSM", and this obviously holds for any conceptualization of psychopathology at the symptom level.

High-quality multidimensional measurement will not be achieved by subjecting "all existing symptoms of psychopathology" to factor analysis. Rather, the dimensionality of our measures should be created using a top-down approach, pragmatically choosing clusters of items representing relevant conceptual domains of psychopathology. By subjecting these item clusters to the bifactor model, it will be possible to achieve a dimensional measurement that both lumps (into the general factor) and splits (into specific dimensions). Only then can we fully evaluate the specific associations of psychopathology.

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Taxonomy of psychopathology: a work in progress and a call for interdisciplinary research

Taxonomy is an essential element in the process of understanding and organizing concepts that form part of any scientific discipline. This exercise of classification has its origins in the mid 1700s with Carl Linnaeus' biological taxonomy, that provided the original rank-based classification of organisms, including plants, minerals and animals. For mental health disciplines, including psychiatry and psychology, this process of classification has been made especially challenging because of issues related to both the conceptualization and the measurement of psychopathology. Some other scientific disciplines work with clearly defined sets of criteria to identify and categorize the phenomena they study. Mental health problems bring complex issues related to symptom presentation and comorbidity that have yet to be agreed on.

The usefulness and applicability of psychiatric nosology stand on at least two pillars. The first is that a taxonomy must reflect clinical reality: patients with mental health problems often present heterogeneous symptoms and comorbid disorders. The second is that a taxonomy must soundly summarize clinical information, based on appropriate statistical models, but without losing fine-grained details that are relevant for research and treatment.

Significant concerns have been raised as to whether the current categorical classification systems of psychopathology meet either of these requirements. There is indeed extensive recognition that comorbid presentation of psychiatric disorders is the norm rather than the exception[1], and that symptoms vary across illnesses instead of being limited to individual diagnoses. A dimensional approach may be best suited to reflect this reality.

A productive debate about the appropriateness of a categorical diagnostic system is still ongoing, and concerted scientific efforts have resulted in proposals for sophisticated models as alternative approaches to psychiatric nosology, including the Hierarchical Taxonomy of Psychopathology (HiTOP)[2], the transdiagnostic approach[3] and the Research Domain Criteria (RDoC)[4]. While a consensus has not been reached yet, there is an undeniable recognition of the pressing need to find more suitable models and methods for classifying psychopathology. Mental health research depends on it but, most importantly, clinical services rely on a suitable nosology to provide appropriate treatments to those who need it.

Lahey et al[5] provide an overview of the hierarchical approach to psychopathology. This approach – which is strongly embedded in psychometric methods – proposes models in which a higher-order, or general, factor (otherwise known as the p factor) captures correlated symptoms, and lower-order, or secondary, factors encapsulate specific symptoms[6,7].

There are valuable strengths in this approach, as it provides a concise summary of symptoms across mental health problems and retains a dimensional approach to psychopathology. However, three points deserve further considerations.

First, there is a risk that the bifactor model remains limited to a statistical representation of psychopathology. Findings reviewed by Lahey et al indicate that the p factor is genetically influenced and more stable than the secondary factors. However, this may be an artefact of statistical organization of data with, for example, secondary factors being more prone to include stochastic (i.e., randomly determined) measurement errors that are not influenced by genetic factors and are less inherently stable. These secondary factors may also, in effect, hold key information for treatment and precision medicine.

Second, the development of mental health problems is a dynamic process that changes throughout the life course and depends on social context. While there are findings supporting the validity of the p factor in samples of young children[8], it is

not clear how the hierarchical approach to psychopathology takes developmental processes and transient problems into account and whether the bifactor model applies to all ages, ethnicities and socio-economic strata.

Third, it is yet not clear to what extent the bifactor model has practical value for clinics and mental health services. A categorical approach has the merit of identifying critical points at which an individual supposedly needs treatment. Without information about impairment, it is hazardous to establish clinical needs based on a continuous representation of psychopathology.

For the growing community of mental health researchers, psychiatric nosology is one of the biggest challenges of our times. It has generated passionate debates about the value, the relevance and the usefulness of current approaches, which are part of a useful process that can lead to a new meaningful and practical classification system. Recent attempts to unify the field into adopting new ways of thinking about psychopathology are unavoidably being developed via a process of trial and error. And, while no proposed models fit the bill just yet, there is great value in this process. This is a work in progress. One recent study, for example, reported that high scores on the p factor derived from mental health information collected across four decades in a well-characterized birth cohort were correlated with neurocognitive difficulties throughout the life span[1]. Future work from this cohort is expected to further validate this taxonomy.

The bifactor model can be at the intersection where statistical approaches meet clinical knowledge. Interdisciplinary research will be key to addressing remaining concerns with the development of a new nosology of mental health problems. Collaborations across researchers and mental health professionals will hopefully produce a unified dimensional approach and conceptualization of psychopathology that both summarizes information and retains specificity. This needs to be developed with statisticians and psychometricians and to embed philosophical, social and ethical dimensions of psychopathology. Epidemiology, genetics and neuroscience will add value to further tests of validity.

Despite profound changes, the Linnaean taxonomy remains important and relevant to biologists today, two centuries after it was first put forward[9]. We should aim to carry over some worthy aspects from the current classification systems into a new nosology of psychopathology. One such aspect is the relevance to treatment and clinical services. Linnaeus did not have the difficult task of considering how to treat animals, vegetables or minerals when he developed his taxonomy. But we do. A nosology that stands the test of time will have to be both relevant and useful for the development of new treatments and prevention programs to reduce the burden of psychopathology on individuals and society.

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The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis

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The idea that a longer duration of untreated psychosis (DUP) leads to poorer outcomes has contributed to extensive changes in mental health services worldwide and has attracted considerable research interest over the past 30 years. However, the strength of the evidence underlying this notion is unclear. To address this issue, we conducted an umbrella review of available meta-analyses and performed a random-effects meta-analysis of primary studies. MEDLINE, Web of Science, PsycINFO and EMBASE were searched from inception to September 3, 2020 to identify relevant meta-analyses of studies including patients with schizophrenia spectrum disorders, first-episode psychosis, or affective and non-affective psychosis. Thirteen meta-analyses were included, corresponding to 129 individual studies with a total sample size of 25,657 patients. We detected potential violations of statistical assumptions in some of these meta-analyses. We therefore conducted a new random-effects meta-analysis of primary studies. The association between DUP and each outcome was graded according to a standardized classification into convincing, highly suggestive, suggestive, weak, or non-significant. At first presentation, there was suggestive evidence for a relationship between longer DUP and more severe negative symptoms (beta=–0.07, $p=3.6\times10^{-5}$) and higher chance of previous self-harm (odds ratio, OR=1.89, $p=1.1\times10^{-5}$). At follow-up, there was highly suggestive evidence for a relationship between longer DUP and more severe positive symptoms (beta=–0.16, $p=4.5\times10^{-8}$), more severe negative symptoms (beta=–0.11, $p=3.5\times10^{-10}$) and lower chance of remission (OR=2.16, $p=3.0\times10^{-10}$), and suggestive evidence for a relationship between longer DUP and poorer overall functioning (beta=–0.11, $p=2.2\times10^{-6}$) and more severe global psychopathology (beta=–0.16, $p=4.7\times10^{-6}$). Results were unchanged when analysis was restricted to prospective studies. These effect sizes are clinically meaningful, with a DUP of four weeks predicting >20% more severe symptoms at follow-up relative to a DUP of one week. We conclude that DUP is an important prognostic factor at first presentation and predicts clinically relevant outcomes over the course of illness. We discuss conceptual issues in DUP research and methodological limitations of current evidence, and provide recommendations for future research.

Key words: Duration of untreated psychosis, outcomes, negative symptoms, positive symptoms, schizophrenia, remission, functioning, global psychopathology, recommendations for research

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Psychotic disorders such as schizophrenia are often marked by persistent symptoms, reduced quality of life, and long-term disability[1]. There have been few advances in drug treatment in the past 30 years, with a concomitant growth of interest in modifiable factors which may determine outcomes[2]. The 1986 Northwick Park study highlighted that some patients with psychosis experienced considerable delays before starting treatment, and that this delay was associated with poorer outcomes once treatment was initiated[3]. This was subsequently conceptualized as the duration of untreated psychosis (DUP), which is generally considered to be the period from onset of psychotic symptoms to the initiation of treatment[4].

It was later proposed that psychosis has a persistent neurotoxic effect which cannot be fully reversed even once treatment is initiated[5]. The critical window hypothesis extended this concept to suggest that deterioration in psychotic disorders is non-linear, with the peak deleterious effects of psychosis on long-term outcomes occurring within the first two years, so that this period should be the focus for intervention[6]. These ideas have been highly influential, with the development of early intervention services explicitly aimed at reducing the DUP[7-9]. To assess how interest in the concept of DUP has developed, we conducted a search of PubMed on July 31, 2020 using the term "duration of untreated psychosis". The results are presented in Figure 1, which shows increasing research interest, particularly in the last ten years.

Many mental health services devote significant resources to early intervention in psychosis based, at least partly, on the premise that reducing DUP improves outcomes[10-15]. This notion has been investigated in over a hundred studies examining a number of different outcomes, summarized in several meta-analyses[16-23]. However, due to the inclusion of overlapping samples in different meta-analyses, and differences in inclusion criteria, definition of outcomes, reporting standards and analysis techniques, it is difficult to generate a clear hierarchy of evidence. Furthermore, analyses at first presentation (during the first psychotic episode, soon after the onset of the disease, or at first contact with specialist services) have all included mixed samples of antipsychotic naïve and treated participants[16-18,22]. Thus, no previous analyses have delineated the effects of DUP on outcomes in antipsychotic naïve subjects.

In view of this, we conducted an umbrella review of previous available meta-analyses and performed a new random-effects meta-analysis of primary studies, in order to generate a hierarchical classification of evidence to inform the planning and targeting of interventions to reduce DUP. We aimed to address two related questions: a) what is the relationship between DUP and clinical measures at first presentation?; b) what is the relationship between DUP and outcomes following treatment for psychosis?

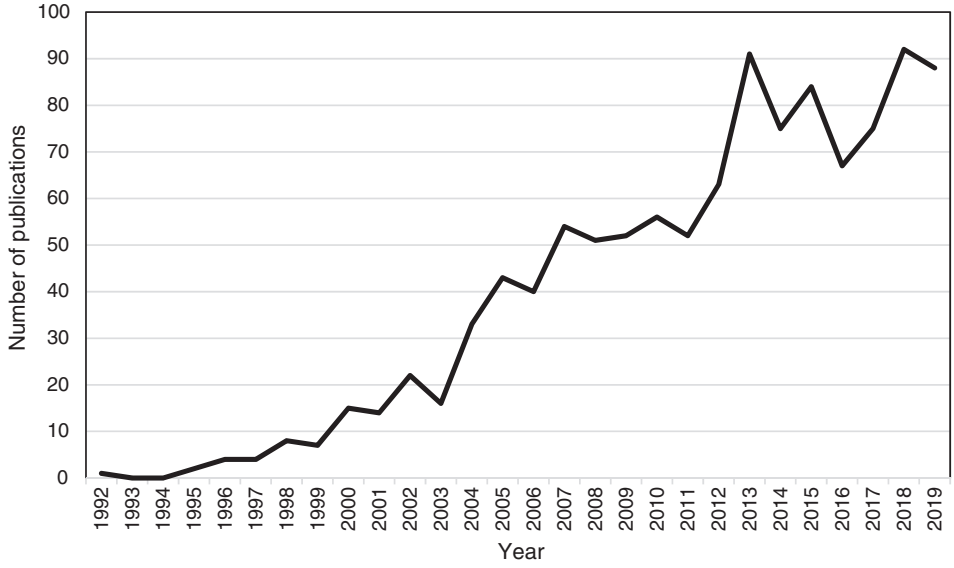

Figure 1 Number of publications per year in PubMed for "duration of untreated psychosis"

METHODS

The umbrella review was performed in line with the relevant guidelines, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations, and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[24-26]. The protocol was registered with PROSPERO on June 30, 2020 (no. CRD42020193673) and accepted on August 30, 2020.

Study selection

A search of MEDLINE, Web of Science, PsycINFO and EMBASE was carried out from inception to September 3, 2020, with no date or language restrictions, to identify meta-analyses of studies on the relationship between DUP and outcomes.

We included meta-analyses of studies on patients with schizophrenia spectrum disorders, first-episode psychosis, or affective and non-affective psychosis, which provided data sufficient to allow the calculation of an effect size for the relationship between DUP and outcomes comparable with other studies.

We excluded meta-analyses which: a) focused specifically on affective disorders without psychosis, substance induced psychosis, or psychosis secondary to an organic condition; b) calculated the relationship between DUP and outcomes without using subject level data (e.g., by meta-regression of study level statistics), because this provides a measure of the relationship between DUP and outcomes across studies that is not necessarily comparable with the effect within studies, due to aggregation bias[27-29]. We excluded primary studies which: a) used affective and negative symptoms in the definition of DUP; b) only reported relationships with duration of untreated illness (DUI); c) were follow-up studies from the pre-antipsychotic era, or studies examining the natural course of psychotic disorders where no subjects were treated; d) were based on carer or patient rated symptom outcomes; e) had more than 10% of participants with substance induced or organic psychosis. Exclusion criteria for primary studies were added after registration of the study protocol, as studies with such designs were not comparable with other included studies, and it was not anticipated that these designs would be encountered.

Only meta-analyses available in English were included, as no systematic bias has been found in meta-analyses including only English language studies, and the majority of countries with specialist early intervention services where DUP research is expected to originate from are either English speaking or have samples which have been extensively described in English[30]. If a primary study was not in English, but was included in a meta-analysis published in English, we included it if sufficient data for analysis and assessment against inclusion criteria could be obtained from the paper and the meta-analysis.

The process from screening to inclusion was conducted independently by two of the authors (MO and LT), with disagreements resolved by discussion. The search strategy used the key words ("systematic review" OR "meta-analysis") AND ("DUP" OR "duration of untreated psychosis" OR "untreated psychosis" OR "duration of untreated illness"). The reference lists of all included papers were also screened to identify further meta-analyses for inclusion. Two authors (MO and TW) individually checked all included meta-analyses and primary studies independently, to assess for overlapping samples, determine selection of outcomes, and ensure that the primary studies met inclusion criteria, resolving disagreements by discussion.

We selected primary studies from identified meta-analyses for two syntheses. To address our first question, we examined

the relationship between DUP and clinical variables at first presentation. To address our second question, we examined the relationship between DUP and outcomes at follow-up following initiation of treatment. Samples could appear in both of these separate analyses if relevant data for each question were available. Cross-sectional studies were considered as part of the first presentation analysis if they took place during the first psychotic episode. Follow-up samples were those assessed after the first psychotic episode or after study baseline in longitudinal studies, regardless of duration of follow-up. Where the information reported was insufficient, corresponding authors were contacted and invited to provide further details.

We identified overlapping samples as recommended in the Cochrane Handbook[31]. When there was substantial overlap, we preferred samples identified from meta-analyses based on individual patient data, if these were available. Otherwise, only the largest dataset was retained for analysis. If the overlap was less than 5%, both samples were included. For follow-up studies, if data for the same sample were available at multiple follow-up points, we preferred the larger sample to maximize sample size, unless the sample sizes were within 15% of each other, in which case we preferred the longer follow-up sample.

Data extraction

From each meta-analysis, we extracted data related to quality of studies, and assessed this quality using the AMSTAR 2 checklist modified for observational studies by Hildebrand et al[32].

All data were re-extracted from each primary study onto piloted forms. One author (MO) performed the primary data extraction, and this was independently checked by at least one other author. Disagreements were resolved by discussion.

From each primary study, we extracted the following data: design, years and location, sample size, patient characteristics, outcomes considered and measures, method of measuring DUP, mean/SD/median of DUP, mean/SD of each outcome (for continuous outcomes), statistics used for analysis (including whether transformations or dichotomization were performed), and effect size. If duration of psychosis was not reported, we calculated it as age at study entry minus age at onset of psychosis.

Where results were presented for pooled outcomes and subgroups, we preferred pooled outcomes to maximize sample size. If results were presented across several different measures on the same outcome (e.g., a study using more than one scale for neurocognition, quality of life or symptoms), effect sizes were averaged across all reported assessment measures, to avoid bias associated with selective preference for significant results.

We preferred unadjusted to adjusted relationships if both were available, as, although adjusted relationships address the issue of confounding, there was no consistency among studies in the variables used for adjustment. If only adjusted relationships were available, we extracted these and planned a sensitivity analysis to exclude such studies. Where data were only available in graphical format, we used WebPlot digitizer to extract them[33].

We included all outcomes considered in the original meta-analyses. As there is no consensus on how to measure some outcomes in psychosis (e.g., remission, quality of life, overall functioning, cognition), we analyzed outcomes as defined in the original meta-analyses, and did not combine similar variables if they were analyzed separately by the original reviews, with the following pre-specified exceptions: a) if the relationship between DUP and outcome was pooled across first presentation and follow-up studies, we separated them to perform two separate analyses; b) if separating the outcomes or including subgroups would allow pooling across different meta-analyses which considered the outcomes separately, we separated outcomes or included the subgroups to maximize overall sample size and ensure consistency in outcome definitions; c) if positive and/or negative symptoms subscale ratings were available, we included these separately, as the relationship between DUP and these outcomes is of clinical interest.

Statistical analysis

We planned to analyze relationships using the effect size measure most commonly reported in the original meta-analysis. However, it became necessary to deviate from the pre-specified protocol, as previous syntheses had combined outcome measures and effect sizes which are not comparable for meta-analysis.

DUP is usually right skewed, as the majority of individuals are treated relatively quickly, but a long tail of people experience a prolonged DUP. For example, in a meta-analysis[34] including 1,391 patients, DUP was not normally distributed, with a mean value (61.7 weeks) exceeding the value of the third quartile (56 weeks), due to the long tail which extended up to 1,200 weeks (23 years). DUP therefore violates the major assumption of the Pearson's product moment correlation, which is that the data are sampled from an underlying bivariate normal distribution[35]. Some of the primary studies of DUP use Pearson's correlation for analyses despite the violation of that assumption, whilst the others use different statistical approaches, either transforming DUP (often with a log or log10 transformation), dichotomizing it into long and short categories, or using non-parametric statistics such as the Spearman's rank correlation coefficient.

The skewed distribution of DUP and these manipulations of the data have important implications for meta-analysis[36], which have not been considered by the majority of previous analyses. Meta-analysis of Pearson's correlations is likely to result in reduced power, and lead to poor performance for point and interval estimates[36,37]. Spearman's and Pearson's correlations should not be combined in the same meta-analysis[38-40]. Effect sizes based on log transformed data should not be combined with untransformed effect sizes in the same meta-analysis[31]. Dichotomization may lead to loss of power and obscure the true relationship between DUP and continuous outcomes, particularly for those with a very long DUP[41]. Moreover, there is no consensus on the threshold separating short vs. long DUP, and cut-off points ranging from four weeks to five years were used in primary studies included in this review[42,43].

The point biserial correlation explores the relationship between a continuous and a dichotomous variable[44]. This correlation may be encountered when studies dichotomize DUP into long/short, or if DUP remains continuous and the outcome is either naturally dichotomous (completed suicide) or artificially dichotomous (high/low symptom scores). When utilizing commonly recommended formulae for converting among effect sizes, it is the point biserial correlation and not the Pearson's correlation which is obtained when converting from means/SDs, t values or Cohen's d into the r family of effect sizes[45]. On the other hand, the phi coefficient represents the correlation between two dichotomous outcomes[44], generated when DUP has been dichotomized and the outcome is either artificially or naturally dichotomous. When utilizing common formulae for converting chi squared statistics into correlations, it is the phi correlation which is obtained[46]. The point biserial correlation and phi correlation coefficients obtained by converting from artificially dichotomized data are not comparable with Pearson's product moment correlations, and should not be combined in the same meta-analyses[44]. Another index, the biserial correlation coefficient, estimates the underlying continuous relationship between a continuous variable and an artificially dichotomized one, and can be synthesized with the Pearson's product moment correlation for the purposes of meta-analysis[44]. The point biserial correlation calculated from artificially dichotomized data is always less than 80% of the biserial correlation[47].

To address all these issues, we analyzed continuous outcomes by using the formulae proposed by Souverein et al[48] to convert Pearson's correlations, Spearman's rank correlations, log transformed correlations, and regression beta values into a single comparable effect size measure, the regression coefficient between log DUP and the log outcome (LogBetaXY). We also calculated the sampling variance of LogBetaXY as recommended by Souverein et al[48]. This approach required the mean and SD of both DUP and the outcome to be reported. If means and SDs were reported separately by subgroup, we calculated the pooled mean/SD using standard formulae[31]. If ranges, medians or interquartile ranges were reported instead of means/SDs, we used Souverein et al's formulae to estimate the log mean and log SD[48]. If no data regarding the mean or SD were reported, we imputed these data, referring to other publications describing the same sample, or, if not available, using results from similar studies. If no comparable data were available for imputation, we excluded these studies.

The above approach assumes that the natural logarithm of DUP and the natural logarithm of the outcome have a bivariate normal distribution, which allows the relationship between DUP and the outcome in the natural scale to be linear, monotonic convex or monotonic concave[48]. Support for this distributional assumption comes from a meta-analysis[18] demonstrating a monotonic concave relationship between DUP and negative symptoms, and a primary study[49] documenting a similar relationship between DUP and Positive and Negative Syndrome Scale (PANSS) total and subscale scores. Due to the double log transformation, the effect size measure (beta) represents the difference in the log e-transformed predicted value of the outcome for each one-unit difference in the log e-transformed value in DUP[50]. Therefore, an overall beta of 0.1 means that, for every doubling in DUP, the predicted difference in the outcome is 2^{beta} ($2^{0.1}$=1.07 or 7%)[51].

When DUP or the outcome were artificially dichotomized, we employed Jacobs and Viechtbauer's formulae[44] to obtain the biserial correlation coefficient. This coefficient was then used to calculate an estimate of LogBetaXY using the above-mentioned formulae. Its sampling variance was estimated by rearranging the formulae for the sampling variance of LogBetaXY with the Soper's approximate method for the sampling variance of the biserial correlation coefficient described by Jacobs and Viechtbauer[44]. The sampling variance obtained from a biserial correlation is larger than one obtained from a product moment correlation, reflecting the underlying uncertainty associated with the conversion[44].

All calculations were performed in Microsoft Excel, Version 16. All continuous data are expressed such that a negative value indicates a relationship between DUP and poorer outcome (for example, more severe symptoms, poorer functional status, smaller reduction in symptoms).

For categorical outcomes, we synthesized effect size measures using the odds ratio (OR). If the point biserial correlation was reported, we calculated the OR using standard formulae[45]. Where 2x2 tables were reported or could be constructed, we calculated the OR and its sampling variance using standard formulae[52]. When means/SDs of DUP were reported at the level of the dichotomous outcome, we calculated the Cohen's d effect size and then converted it to the (log) OR and its standard deviation using standard formulae[45]. For the few studies that reported hazard ratios, we estimated the OR using previously proposed formulae[53]. All categorical data are presented such that an OR above 1 indicates a relationship between DUP and poorer outcome.

Final value and change in correlations were not combined in the same analysis, including syntheses of treatment response with remission. Effect size measures for truly binary outcomes, artificially dichotomized outcomes and continuous outcomes were not combined in the same meta-analysis. Log transformed and untransformed effect sizes were not combined in the same meta-analysis. Studies where a comparable effect measure and outcome measure could not be calculated were excluded. We only performed meta-analysis when there were more than three studies.

Random-effects meta-analysis

Data were analyzed with the metafor package in R to calculate the random-effects p value, effect size, confidence interval, heterogeneity (I^2) and prediction interval for each outcome[54]. Random-effects models were used as we anticipated considerable heterogeneity in DUP definitions and values, outcome definitions and sample characteristics. Where there were two subsamples from the same study reporting effect sizes, the subsamples

were first combined using fixed effects meta-analysis[31]. If significant relationships were reported only for one subsample or outcome, with no comment on results in the other subsample(s), the other subsample(s) was assumed to have an effect size of 0 to be conservative.

We performed Egger's test for small study effects[55]. A p value <0.10 combined with a more conservative effect in the largest study than in the random-effects meta-analysis was judged to provide evidence for small study effects, as in previous umbrella reviews[56]. When Egger's test was significant, we used the Duval and Tweedie's trim-and-fill procedure to estimate true effects controlling for any detected bias[57].

Excess significance bias was calculated using Ioannadis and Trikalinos' test[58]. With the metaviz package in R, we estimated the power of each study using a non-central p distribution[59]. The sum of all power estimates provides the expected number of significant datasets. The actual observed number of statistically significant datasets is then compared to the expected number using a χ^2-based test. Significance was assessed at two-sided p<0.10 with observed > expected, as in previous umbrella reviews[56].

For significant results, we also conducted "file-drawer" analysis, where we calculated the number of fail-safe studies that would have to be added to the observed set of results to reduce the p value associated with the weighted average random-effects effect size to 0.05[60].

We applied the following criteria to assess the level of evidence for the association between DUP and outcomes, as in previous umbrella reviews[56]: a) convincing (class I): meta-analysis based on sample size >1,000, results show significance with $p<10^{-6}$, I^2<50%, 95% prediction interval excluding the null, no small study effects, and no excess significance bias; b) highly suggestive (class II): N>1,000, $p<10^{-6}$, largest study with a statistically significant effect, and class I criteria not met; c) suggestive (class III): N>1,000, $p<10^{-3}$, and class I-II criteria not met; d) weak (class IV): p<0.05 and class I-III criteria not met; e) non-significant: p>0.05.

Outliers, heterogeneity assessment, meta-regression, sensitivity and subgroup analyses

We used the above software to run analyses with and without outliers, defined as studies whose effect size confidence interval did not overlap with the confidence interval of the pooled effect size[61]. We calculated I^2 and Cochrane's Q to test for heterogeneity of study effects.

Meta-regression required a minimum of ten complete data points for continuous variables, and four studies per subgroup for categorical variables, to ensure adequate power[29]. The p values for meta-regression were corrected using the Benjamini-Hochberg procedure, with a false discovery rate (FDR) of 5%[62].

For the purposes of meta-regression, DUP startpoint, DUP endpoint and previous antipsychotic exposure were assigned into categories to see if these moderated effects. Samples were categorized into antipsychotic naïve (all participants antipsychotic naïve at study entry), minimal antipsychotic treatment (all participants had received less than 1-month antipsychotic treatment, or more than 75% participants were antipsychotic naïve and the others had less than 3-month antipsychotic exposure at study entry), and appreciable antipsychotic treatment (greater than 1-month antipsychotic treatment at study entry, or first presentation measures recorded at or after end of first hospitalization)[63]. If the duration of previous treatment was unclear, samples were categorized in the appreciable antipsychotic treatment group if the majority of participants had been exposed to antipsychotics, and in the minimal group if the majority were antipsychotic naïve. Studies in which previous antipsychotic exposure was unclear were excluded from this analysis.

DUP onset definitions and DUP endpoints varied among studies. We adapted the criteria used by Oliver et al[64] to define DUP onset as either the onset of the first ever recalled psychotic symptom, or the point at which psychotic symptoms met a clearly defined threshold (either above a cut-off on the PANSS, a description of "clear" or "overt" psychotic symptoms, or continuous psychotic symptoms over a given time period). We did not distinguish between different symptom, severity or duration thresholds used. DUP endpoints were categorized as initiation of antipsychotic treatment, first hospitalization, first contact with health services or study entry, and endpoints requiring either a response to treatment or a specified duration of treatment (such as 4-week antipsychotic treatment).

Meta-regression was undertaken after the removal of outlying studies, as defined above. This analysis aimed to test if there was a relationship between year of publication, scale used to assess outcome measure, duration of follow-up and dropout percentage (for follow-up studies), percent of subjects diagnosed with schizophrenia (or, separately, percent diagnosed with schizophrenia spectrum disorders if insufficient studies reported the percent with schizophrenia), mean age, mean duration of psychosis, gender composition, mean DUP, DUP startpoint, DUP endpoint, and statistics used to calculate effect size.

Where sample sizes permitted, we performed subgroup analyses on subjects who were antipsychotic naïve at study entry (in first presentation analyses) and on studies excluding patients with affective psychosis. We performed planned sensitivity analyses removing studies that provided adjusted relationships, those where data were imputed from other samples, and those including any participants with drug induced or organic psychosis. For follow-up studies, subgroup analysis was conducted on prospective studies only for variables rated class I to III.

RESULTS

Included studies

The systematic search identified 149 unique meta-analyses (Figure 2). Two additional items were identified through being referenced in the included papers. Of these, thirteen meta-analyses met inclusion criteria. A full list of excluded studies with reasons for exclusion is provided in the supplementary information.

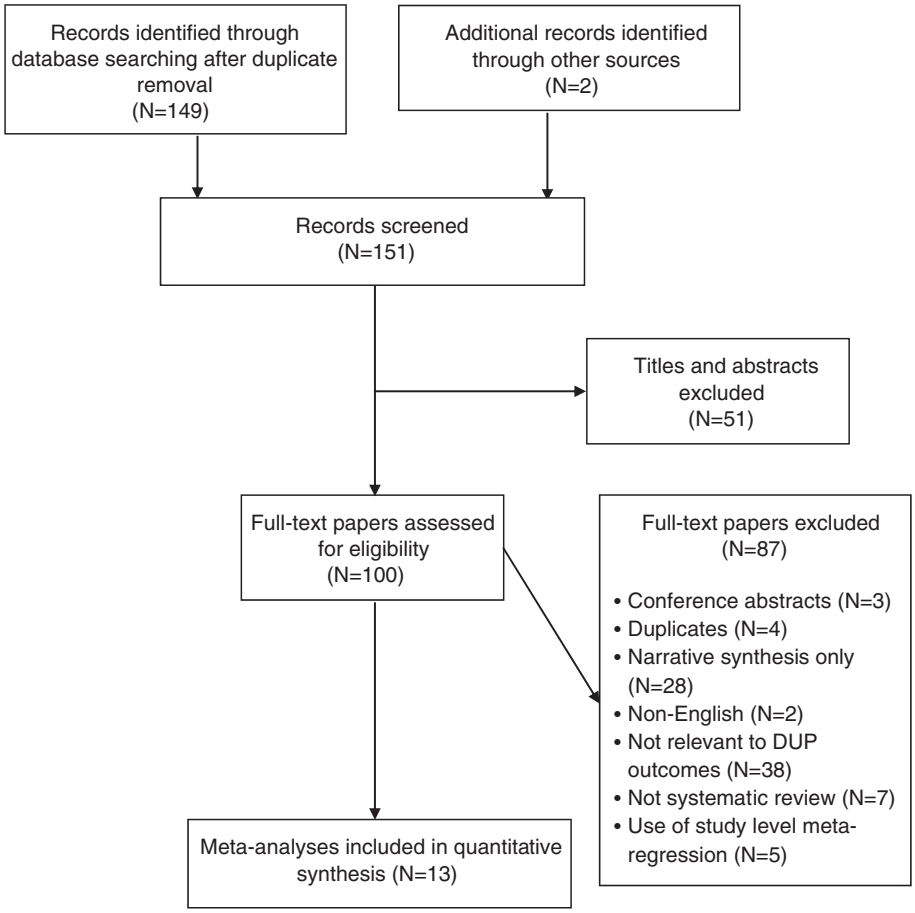

Figure 2 PRISMA flow chart. DUP – duration of untreated psychosis

Table 1 summarizes the meta-analyses included, with their flaws and other methodological considerations. From these meta-analyses, we identified 129 reports of non-overlapping primary studies for inclusion, with a total sample size of 25,657 patients. Some studies appeared in multiple meta-analyses; they were coded as being identified from the most recent meta-analysis. The list of the primary studies included is provided in the supplementary information.

Definitions of outcomes

As pre-specified, we avoided redefining outcomes as much as possible. However, there were discrepancies between meta-analyses on definitions of some outcomes, and some meta-analyses combined effect measures and outcomes which were not comparable. We defined overall, social and vocational functioning as in Santesteban-Echarri et al[20], relapse as in Alvarez-Jimenez et al[67], global psychopathology as in Perkins et al[17], and remission as in Marshall et al[16]. We conducted subgroup analysis of studies which defined remission as in Penttila et al[19], using the operationalized Andreasen et al's consensus criteria[70]. We combined violence and serious violence into one category since, after excluding one study on serious violence which measured DUI, there were only two remaining studies assessing serious violence, and both were subgroup analyses in studies also assessing violence.

Hospitalization was the only outcome not defined as in any previous meta-analyses. Some studies which were included in "hospital treatments" in Penttila et al[19] were re-categorized as assessing relapse for consistency with Alvarez-Jimenez et al[67], and the remaining studies measured either duration of hospitalization or number of hospitalizations. We considered these two outcomes separately as they measured different underlying constructs.

Relationship between DUP and clinical variables at first presentation

The relationship between DUP and clinical variables at first presentation is summarized in Table 2, and in Figure 3 for continuous variables and Figure 4 for categorical variables. At first presentation, there was suggestive (class III) evidence for a rela-

tionship between longer DUP and more severe negative symptoms and greater risk of previous self-harm, and weak (class IV) evidence for a relationship between longer DUP and poorer quality of life. There was no significant relationship between DUP and positive symptoms, global cognition, overall functioning, global psychopathology, risk of violence, and cannabis, alcohol or substance misuse at first presentation.

There was evidence of significant publication bias and small study effects for negative symptoms (Egger's test p=0.045). There was no evidence of significant publication bias, excess significance bias or small study effects for the other significant variables (Egger's test p=0.24 for deliberate self-harm, p=0.49 for quality of life). Using the trim-and-fill method, no studies were imputed on the right-hand side for negative symptoms. "File-drawer" analysis suggested that the significant results for deliberate self-harm and negative symptoms would require 30 and 559 missing studies, respectively, with an effect size of 0 to negate their statistical significance. The overall random-effects result for the quality of life analysis was marginally significant and, accordingly, only one study would be required to negate its significance.

There was no statistically significant evidence of heterogeneity in analyses of cannabis misuse, alcohol and substance misuse, global cognition, deliberate self-harm, or overall functional status. We encountered substantial heterogeneity in our analyses of negative symptoms, quality of life, violence, global psychopathology and positive symptoms (all p values <0.0001) (see Table 2).

Removal of outliers led to variable reductions in heterogeneity, causing absolute reductions in I^2 between 17 and 30% for negative symptoms, quality of life and positive symptoms, with a 3% reduction seen in global psychopathology. No statistically significant result changed from significant to non-significant after removal of outliers. On the contrary, all classes of evidence remained the same with the exception of quality of life, which increased from class IV to class III due to a decrease in the random-effects p value.

Meta-regression was conducted to explore the residual heterogeneity in the relationship between DUP and negative symptoms, quality of life, and positive symptoms. For negative symptoms, year of publication and DUP endpoint definition were significant predictors after Benjamini-Hochberg correction, with a FDR corrected p value of 0.039 and 0.001, respectively. Studies which were published more recently reported a smaller relationship between DUP and negative symptoms (intercept=–12.5845, beta=0.0064, residual I^2=59%). Studies which used hospitalization as the endpoint for DUP reported a larger effect size for the relationship between DUP and negative symptoms (beta=–0.11) compared to those which used adequate treatment (beta=–0.02) or initiation of treatment (beta=–0.05). There was no significant residual heterogeneity in the negative symptom analysis (I^2=27%, p>0.05) after inclusion of DUP endpoint in the random-effects model.

Using meta-regression, we did not find any moderator variables to explain the remaining heterogeneity following removal of outliers in quality of life (I^2=77%, p=0.0001) or positive symptoms (I^2=59%, p=0.02). These analyses were limited, as we were only able to examine the effect of three moderator variables for positive symptoms and one for quality of life, due to sample size limitations. Although there was also substantial unexplained heterogeneity in the violence analysis (I^2=85%), there were no outliers and too few data points for meta-regression for this variable and for global psychopathology (I^2=81% after removal of outliers).

For the majority of analyses, sensitivity analysis which excluded samples recruiting participants with affective psychosis had no discernible impact on the heterogeneity. The exceptions were alcohol and substance misuse, where I^2 dropped from 32% to 0%, and deliberate self-harm, where I^2 increased from 0% to 56%. Removing studies that included patients with affective psychosis also did not affect the class of evidence for most analyses. However, in the negative symptom analysis, removing the eight samples which included participants with affective psychosis reduced the class of evidence from III to IV, due to an increase in the random-effects p value from $3.6x10^{-5}$ to 0.003. For deliberate self-harm and quality of life, removing these samples reduced the class of evidence from III and IV respectively to non-significant, because the random-effects p value became >0.05.

There was also no discernible impact on the heterogeneity when we removed the small number of samples which included participants with drug induced psychosis (up to 10%) from the negative symptoms, quality of life, deliberate self-harm, global cognition, violence and substance misuse analyses, apart from finding that the relationship between DUP and quality of life decreased from class IV to non-significant, because the random-effects p value became 0.10. Inclusion of adjusted effect sizes and imputations of the mean/SDs of DUP and/or the outcome from other samples had no effects on classes of evidence and minimal effect on heterogeneity for all analyses.

We conducted subgroup analyses of antipsychotic naïve subjects where data were available. We found that there was an absolute reduction in I^2 of 23% for the relationship between DUP and negative symptoms after removal of patients who had received any previous antipsychotic treatment, and results remained statistically significant.

Relationship between DUP and outcomes at follow-up

The relationship between DUP and outcomes at follow-up is summarized in Table 3, and in Figure 5 for continuous outcomes and Figure 6 for categorical outcomes.

We found highly suggestive (class II) evidence for a relationship between longer DUP and more severe negative symptoms, more severe positive symptoms and lower chance of remission at follow-up. We found suggestive (class III) evidence for a relationship between longer DUP and more severe global psychopathology and poorer overall functional outcome at follow-up. There was weak (class IV) evidence for a relationship between longer DUP and poorer social and vocational functioning, poorer quality of life, and smaller reduction in total symptoms at follow-up.

Table 1 Description of included meta-analyses

	Variables assessed at first presentation and follow-up	AMSTAR 2	Other methodological comments
Marshall et al[16]	First presentation None Follow-up (prospective, 2 months - 1 year) Remission	Total: 4/14 6/7 critical flaws relating to: • Lack of pre-registration • No reporting of excluded studies and reasons for exclusion • Lack of satisfactory technique for assessing risk of bias in included studies • Statistical techniques – Lack of adjustment for heterogeneity • No assessment of publication bias • No discussion of impact of risk of bias on results	Includes one sample of "naturalistic" never-treated patients from pre-AP era in a follow-up comparison with long-term AP-treated patients. Combines change in and final value positive symptom scores. Includes one study with affective and negative symptoms in definition of DUP. Combines Pearson's correlation coefficients with Spearman's rank correlations, and with Pearson's correlation between log transformed DUP and outcome in natural scale. However, conducts sensitivity analyses excluding the untransformed Pearson's correlations.
Perkins et al[17]	First presentation Global psychopathology, positive symptoms, negative symptoms, overall functional status Follow-up (prospective, 1 month - 15 years) Global psychopathology, positive symptoms, negative symptoms, overall functional outcome, remission	Total: 2/14 7/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not search at least 2 databases, did not justify search restrictions, did not search trial/study registries) • No reporting of excluded studies and reasons for exclusion • No assessment of risk of bias in included studies • Statistical techniques – Lack of justification for unadjusted effects and no adjustment for heterogeneity • No assessment of publication bias • No discussion of impact of risk of bias on results	Includes one study with affective and negative symptoms in definition of DUP. Includes one sample which assessed DUI, not DUP. Combines change in and final value positive symptom scores. Combines Pearson's correlation coefficients with Spearman's rank correlations, and with Pearson's correlation between log transformed DUP and outcome in natural scale.
Farooq et al[65]	First presentation Positive symptoms Follow-up (prospective, 1 month - 2 years) Reduction in total symptoms, overall functional outcome	Total: 4/14 7/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not search trial/study registries) • No reporting of excluded studies and reasons for exclusion • No assessment of risk of bias in included studies • Statistical techniques – Lack of investigation of heterogeneity • No assessment of publication bias • No discussion of impact of risk of bias on results	Includes one sample of "naturalistic" never-treated patients in a follow-up comparison with long-term AP-treated patients. Combines outcome measure of remission in these patients with scale-assessed overall function in other samples. One significant data extraction error: uses SE of beta value as correlation coefficient. Combines adjusted and unadjusted effect size measures with no sensitivity analysis. Combines Pearson's correlation coefficient with phi coefficient, point biserial coefficient, and Spearman's rank correlation.
Large & Nielssen[66]	First presentation Violence/serious violence Follow-up None	Total: 5/14 6/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not justify search restrictions, did not search trial/study registries) • No reporting of excluded studies and reasons for exclusion • No assessment of risk of bias in included studies • Statistical techniques – Lack of investigation of heterogeneity and unclear if authors used adjusted or unadjusted effects with lack of justification for choice • No discussion of impact of risk of bias on results	Combines log transformed and untransformed effect sizes. Unit of analysis error whereby the same sample is included twice in the same meta-analysis for different outcomes, causing it to be given disproportionate weight. Assessment time frames for violence vary, encompassing lifetime violence, violence only during DUP, violence preceding/precipitating first admission and violence during defined time periods prior to assessment. Includes one sample which assessed DUI, not DUP.

Table 1 Description of included meta-analyses (*continued*)

	Variables assessed at first presentation and follow-up	AMSTAR 2	Other methodological comments
Alvarez-Jimenez et al[67]	First presentation None Follow-up (prospective, 1-7.5 years) Relapse	Total: 7/14 4/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not provide search strategy) • No reporting of excluded studies and reasons for exclusion • No discussion of impact of risk of bias on results	Varying definitions of relapse: readmission to hospital due to psychosis, symptom defined and combinations of the two.
Boonstra et al[18]	First presentation Negative symptoms Follow-up (prospective, 1-8 years) Negative symptoms	Total: 4/14 6/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not justify publication restrictions, did not search trial/study registries and reference lists of included studies, did not conduct search within 24 months of completion of review) • No reporting of excluded studies and reasons for exclusion • No assessment of risk of bias in included studies • Statistical techniques – Lack of adjustment for heterogeneity • No discussion of impact of risk of bias on results	Obtains individual patient data for each study in order to compute comparable summary effect sizes for all (Spearman's rank correlation).
Burns[68]	First presentation Alcohol and substance misuse, cannabis use Follow-up None	Total: 3/14 6/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not justify search restrictions, did not search trial/study registries) • No reporting of excluded studies and reasons for exclusion • Statistical techniques – Lack of adjustment for heterogeneity • No assessment of risk of bias in included studies • No discussion of impact of risk of bias on results	Includes three overlapping samples on the same outcome. Assessment time frames for substance misuse vary, encompassing either lifetime misuse, a diagnosable substance misuse disorder at the time of assessment, or misuse during a previous defined time period. ~60% of studies assess alcohol and substance misuse, ~40% assess substance misuse alone. Combines adjusted and unadjusted effect sizes with no sensitivity analysis.
Challis et al[69]	First presentation Deliberate self-harm Follow-up (prospective and retrospective, 1.5-4 years) Deliberate self-harm	Total: 8/14 5/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not justify search restrictions, did not search trial/study registries) • Lack of satisfactory technique for assessing risk of bias in included studies • Statistical techniques – Unclear if authors used adjusted or unadjusted effects, lack of justification for choice • Lack of satisfactory technique for assessing risk of bias	Combines log transformed and untransformed effect sizes. Combines adjusted and unadjusted effect sizes with no sensitivity analysis. Assessment time frames for DSH vary, encompassing either lifetime self-harm, self-harm during DUP, DSH during a previous defined time period, and unspecified.

Table 1 Description of included meta-analyses (*continued*)

	Variables assessed at first presentation and follow-up	AMSTAR 2	Other methodological comments
Penttila et al[19]	First presentation None Follow-up (prospective, cross-sectional and retrospective, 2-28 years) Global psychopathology, positive symptoms, negative symptoms, number of hospitalizations, time hospitalized, relapse, overall functional outcome, quality of life, remission, social functioning, vocational functioning	Total: 6.5/14 5/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not search trial/study registries and reference list of included studies) • Did not report full list of excluded studies and reasons for exclusion • Did not use a satisfactory method for assessing risk of bias in included studies • Statistical techniques – Lack of adjustment for heterogeneity	Minor data extraction errors. One outcome (vocational functioning) included in social functioning meta-analysis in error. Includes one study with carer-rated symptoms. Includes one study with negative symptoms and social decline in DUP definition. Combines relationship between DUP and level of final value negative symptoms with point biserial correlation between DUP and persistent negative symptoms. Combines relationship between DUP and change in symptom scores with relationship between DUP and final value symptom scores. GAF appears as a measure of social functioning and global outcome in different studies. Combines Pearson's correlation coefficients with phi correlation, point biserial correlation, Spearman's correlations, Pearson's correlation between log transformed DUP (log 10 and/or natural log) and outcome in natural scale, and Pearson's correlation between log transformed DUP and the log transformed outcome. All outcome categories other than quality of life include studies measuring different underlying constructs.
Santesteban-Echarri et al[20]	First presentation None Follow-up (prospective, 1-5 years) Overall functional outcome, quality of life, social functioning	Total: 7/14 4/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not justify language restrictions) • Lack of satisfactory technique for assessing risk of bias • Did not satisfactorily discuss impact of risk of bias on results	Three sets of overlapping samples included in same meta-analysis (7 studies in total). Combines Pearson's correlation coefficients with phi correlation, point biserial correlation, Pearson's correlation between log transformed DUP (log 10 and/or natural log) and the outcome in its natural scale, and Pearson's correlation between log transformed DUP and log transformed outcome.
Allott et al[21]	First presentation Global cognition Follow-up None	Total: 7/14 5/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not justify language restrictions, did not search reference lists of all included studies, did not search trial registries) • Did not report a full list of excluded studies and reasons for exclusion • Statistical techniques – Does not state whether used adjusted or unadjusted effect sizes and does not justify this choice • Did not discuss impact of risk of bias on results	Combines unmedicated and AP-treated patients in same meta-analysis. Combines adjusted and unadjusted effect sizes with no sensitivity analysis. Minor data extraction errors. Combines Pearson's correlation coefficients with point biserial correlation, Spearman's correlations, and Pearson's correlation between log transformed DUP (log 10 and/or natural log) and outcome in natural scale.

Table 1 Description of included meta-analyses (*continued*)

	Variables assessed at first presentation and follow-up	AMSTAR 2	Other methodological comments
Bora et al[22]	First presentation Global cognition Follow-up (prospective, 3 months-3 years) Global cognition	Total: 6.5/14 5/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not justify search restrictions, did not search trial/study registries) • Did not report a full list of excluded studies with reasons for exclusion • Statistical techniques – Does not state whether used adjusted or unadjusted effect sizes and does not justify this choice, does not fully investigate heterogeneity • Did not discuss impact of risk of bias on results	Combines unmedicated and AP-treated patients in same meta-analysis. Combines adjusted and unadjusted effect sizes with no sensitivity analysis. Combines Pearson's correlation coefficients with point biserial correlation, Spearman's correlations, and Pearson's correlation between log transformed DUP (log 10 and/or natural log) and outcome in natural scale.
Watson et al[23]	First presentation Quality of life Follow-up (prospective, 6 months-12 years) Quality of life	Total: 4/14 6/7 critical flaws relating to: • Lack of pre-registration • Systematic search (did not search at least two databases, justify publication restrictions, search trial/study registries, search reference lists of included studies) • Did not report a full list of excluded studies and reasons for exclusion • Statistical techniques – Lack of justification for unadjusted effects and no adjustment for heterogeneity • No assessment of risk of bias in included studies • No discussion of impact of risk of bias on results	Combines first-presentation, never-medicated patients with long-term follow-up (8 and 12 years) in same meta-analysis. No presentation of effect sizes or sampling variance for meta-analysis. Unclear which measure was chosen when results for different time points and subscales were available. Combines Pearson's correlation with Spearman's correlation coefficient, and Pearson's correlation between log transformed DUP (log 10 and/or natural log) and outcome in natural scale.

DUP – duration of untreated psychosis, AP – antipsychotic, DSH – deliberate self-harm, DUI – duration of untreated illness, GAF – Global Assessment of Functioning, SE – standard error

Table 2 Evidence for associations between duration of untreated psychosis (DUP) and clinical variables at first presentation

Outcome	Studies	Total sample size (N)	Random-effects p value	Random-effects measure (95% CI)	I^2 (p value)	95% prediction interval	Small study effects/excess significance bias	Largest study significant	Class of evidence	Predicted difference in continuous outcome for every doubling in DUP
Negative symptoms	23	4,165	$3.60x10^{-5}$	beta=–0.07 (–0.10 to –0.04)	87.1% (<0.0001)	–0.21; 0.08	No/Yes (fail-safe N: 559)	No	III	5% worse
Deliberate self-harm	8	1,752	$1.07x10^{-5}$	OR=1.89 (1.42-2.52)	0% (0.15)	1.42; 2.52	No/No (fail-safe N: 30)	Yes	III	NA
Quality of life	9	1,726	0.044	beta=–0.14 (–0.29 to –0.004)	99.2% (<0.0001)	–0.58; 0.29	No/No (fail-safe N: 1)	Yes	IV	11% worse
Global cognition	14	1,970	0.17	beta=–0.01 (–0.02 to 0.004)	1.0% (0.85)	–0.02; 0.005	No/No	Yes	NS	NA
Violence and serious violence	4	1,008	0.23	OR=1.66 (0.70-3.94)	89% (<0.0001)	0.26; 10.48	No/No	No	NS	NA
Alcohol and substance misuse	7	2,281	0.29	OR=0.88 (0.7-1.1)	31.9% (0.25)	0.59; 1.32	No/No	No	NS	NA
Global psychopathology	8	796	0.33	beta=–0.02 (–0.05 to 0.02)	83.5% (<0.0001)	–0.11; 0.07	No/Yes	Yes	NS	NA
Positive symptoms	12	1,084	0.55	beta=0.01 (–0.03 to 0.05)	88.9% (<0.0001)	–0.12; 0.15	No/No	No	NS	NA
Overall functional status	4	333	0.60	beta=–0.04 (–0.21 to 0.12)	0% (0.84)	–0.21; 0.12	No/No	No	NS	NA
Cannabis misuse	7	1,508	0.90	OR=0.99 (0.82-1.19)	0% (0.58)	0.82; 1.19	No/No	No	NS	NA

OR – odds ratio, NS – not significant, NA – not applicable

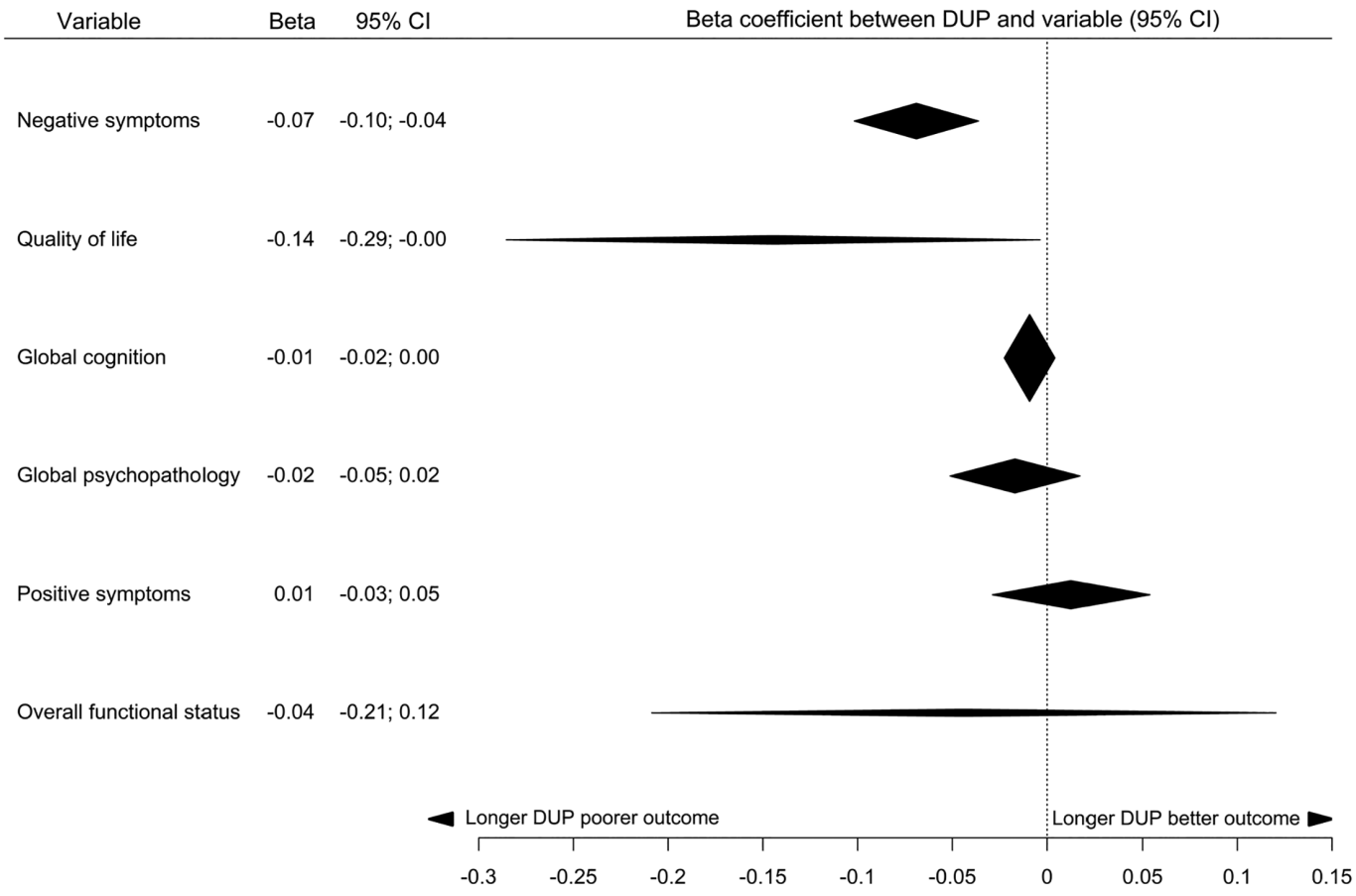

Figure 3 Summary of effect sizes for relationships between duration of untreated psychosis (DUP) and continuous clinical variables at first presentation

In follow-up studies, there was no significant relationship between DUP and risk of relapse, risk of deliberate self-harm, global cognition, time hospitalized, and number of hospitalizations.

Egger's test was statistically significant with evidence of small study effects for the analyses of positive symptoms (p=0.025), remission (p<0.001) and number of hospitalizations (p<0.001). Using the trim-and-fill method, no studies were imputed on the right-hand side for positive symptoms or number of hospitalizations. Seven studies were imputed on the left-hand side in the remission analysis; the class of evidence remained unchanged. "File-drawer" analysis showed that more than 1,650 null studies would be needed to nullify the results of the negative symptom analysis, whereas the marginally significant results for vocational functioning, reduction in total symptoms and quality of life would require only one null study.

There was no statistical evidence of heterogeneity in analyses of social functioning, vocational functioning or deliberate self-harm at follow-up. There was mild heterogeneity present in global cognition (p=0.01). We encountered moderate to substantial heterogeneity in negative symptoms, positive symptoms, remission, overall functional outcome, global psychopathology, reduction in total symptoms, quality of life, relapse, and number of hospitalizations (all p<0.0001).

Removal of outliers led to large (21-64%) absolute reductions in I^2 for negative symptoms, relapse, quality of life, overall functional outcome and remission. There were smaller reductions (5-12%) in heterogeneity for positive symptoms and global psychopathology. The majority of results were minimally affected by removal of outliers – no results went from significant to non-significant, although remission decreased from class II to class III, due to removal of the largest significant study, despite a large decrease in the random-effects p value (3×10^{-9} to 2×10^{-19}). Global psychopathology, overall functional outcome, and quality of life increased class of evidence (from III to II, III to II, and IV to III, respectively) following outlier removal, due to decreases in the random-effects p values.

Where sample sizes allowed, meta-regression was conducted for outcomes with moderate to substantial heterogeneity remaining after outlier removal. There were insufficient data available for exploration of the residual heterogeneity in quality of life, relapse, reduction in total symptoms, global cognition and the hospitalization outcomes. For positive symptoms, no potential moderators survived FDR correction. For negative symptoms, dropout percent (corrected p=0.035) survived FDR correction. Studies where fewer subjects were lost to follow-up (intercept=–0.1364, beta=0.2247, residual I^2=44%) reported

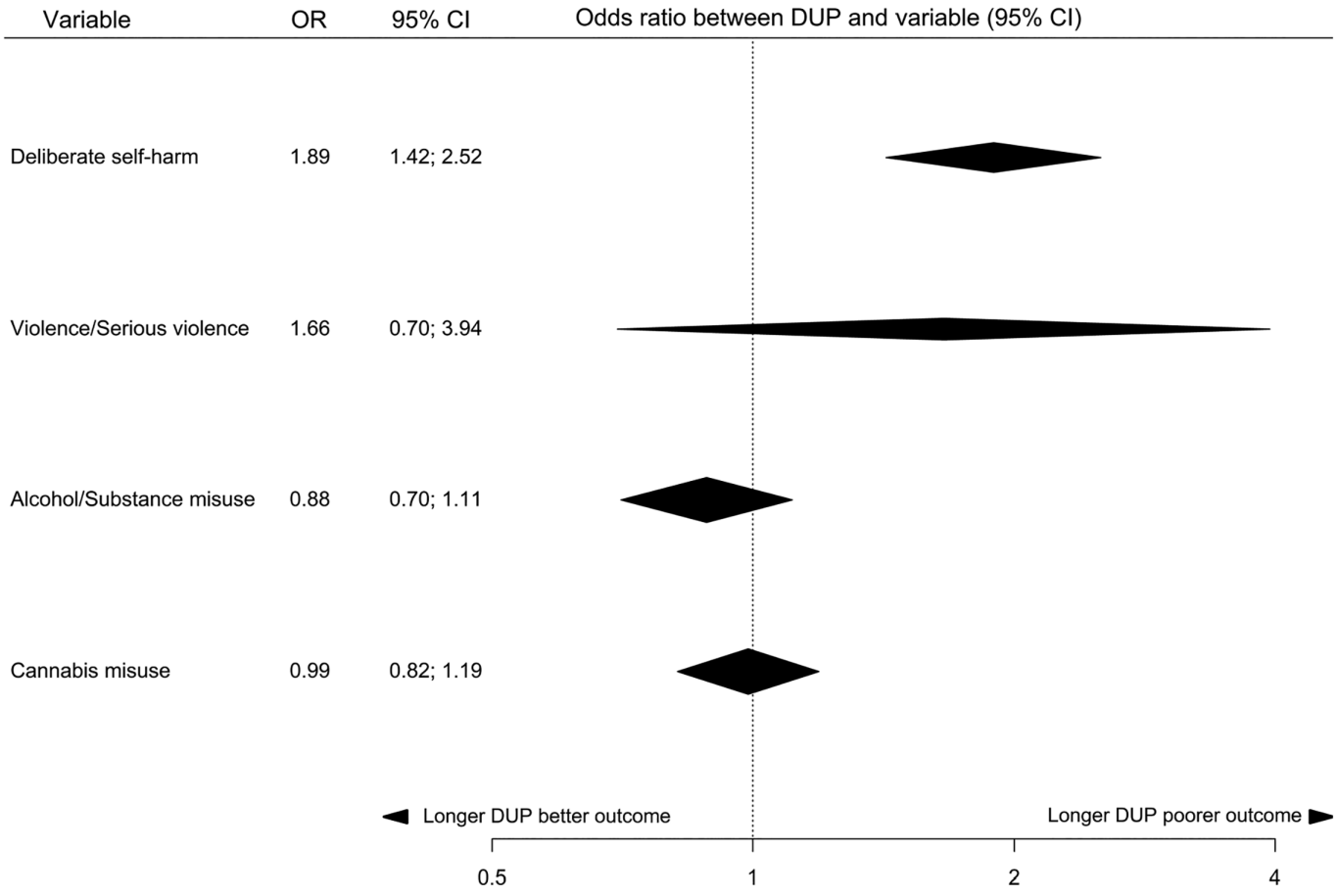

Figure 4 Summary of effect sizes for relationships between duration of untreated psychosis (DUP) and categorical clinical variables at first presentation

larger relationships between DUP and negative symptoms. For global psychopathology, percent of subjects with schizophrenia (corrected p=0.0003) and dropout percent (corrected p=0.044) survived Benjamini-Hochberg correction. Studies with higher proportions of subjects with schizophrenia (intercept=–0.0260, beta=–0.1530, residual I^2=36%) and studies where fewer subjects were lost to follow-up (intercept=–0.1819, beta=0.2658, residual I^2=42%) reported larger relationships between DUP and global psychopathology.

For overall functional outcome, the definition of the endpoint of DUP moderated the effects seen. Studies which used the initiation of antipsychotic treatment as the endpoint for DUP reported larger effects than those using adequate antipsychotic treatment (corrected p=0.022; beta=–0.06 for studies using adequate treatment, beta=–0.11 for studies using the initiation of treatment). There was no statistically significant heterogeneity following inclusion of DUP endpoint definition in the model (I^2=0%, p=0.44).

For the majority of outcomes, sensitivity analysis which excluded samples recruiting participants with affective psychosis had no discernible impact on the heterogeneity. The exceptions were quality of life and remission, where I^2 fell by 51% and 59%, respectively. For positive symptoms, removing these samples reduced the class of evidence from II to III, through an increase in the random-effects p value from $5x10^{-8}$ to $4x10^{-5}$. There was no effect on the class of evidence for any other analysis. There was one sample which included people with drug induced psychosis in each of the social functioning, remission and overall functioning analyses. Removal of this sample had no discernible impact on results. Restricting analysis of studies examining remission to those using Andreasen et al's operationalized criteria[70] reduced the class of evidence from II to IV, due to an increase in the random-effects p value.

Imputations of the mean/SDs of DUP and/or the outcome from other samples had no effect on the class of evidence and a negligible effect on heterogeneity in most analyses. However, for global psychopathology, removing studies where data were imputed reduced I^2 by 20% and the class of evidence from III to IV, due to a reduction in the sample size below the class III threshold of 1,000, although the p value was more significant. Overall, findings were similar when removing studies which calculated adjusted effect sizes, and most analyses remained in the same class of evidence. The exception was remission, where heterogeneity fell to 0% and the class of evidence decreased from II to III,

Table 3 Evidence for associations between duration of untreated psychosis (DUP) and outcomes at follow-up

Outcome	Studies	Mean/median follow-up (years)	N	Random-effects p value	Random-effects measure (95% CI)	I^2 (p value)	95% prediction interval	Small study effects/excess significance bias	Largest study significant	Class of evidence	Predicted difference in continuous outcome for every doubling in DUP
Negative symptoms	27	5.9/2	3,633	$3.46x10^{-10}$	beta=–0.11 (–0.15 to –0.08)	86.7% (<0.0001)	–0.27; 0.05	No/No (fail-safe N: 1,667)	Yes	II	8% worse
Remission	22	6.1/2.1	3,570	$2.98x10^{-10}$	OR=2.16 (1.7-2.75)	63.7% (<0.0001)	1.003; 4.67	Yes/Yes (fail-safe N: 46)	Yes	II	NA
Positive symptoms	21	6.8/3	2,934	$4.52x10^{-8}$	beta=–0.16 (–0.22 to –0.11)	94.4% (<0.0001)	–0.42; 0.10	Yes/No (fail-safe N: 47)	Yes	II	12% worse
Global psychopathology	14	9.1/10.6	1,412	$4.72x10^{-6}$	beta=–0.16 (–0.22 to –0.09)	96.0% (<0.0001)	–0.41; 0.09	No/No (fail-safe N: 3)	Yes	III	12% worse
Overall functional outcome	27	6.9/3	3,104	$2.16x10^{-6}$	beta=–0.11 (–0.16 to –0.07)	96.3% (<0.0001)	–0.35; 0.12	No/No (fail-safe N: 13)	Yes	III	8% worse
Social functioning	4	5.5/4.5	286	$1.38x10^{-11}$	beta=–0.06 (–0.08 to –0.04)	0% (0.64)	–0.08; –0.04	No/No (fail-safe N: 41)	Yes	IV	4% worse
Vocational functioning	3	9/10	371	0.0005	beta=–0.04 (–0.06 to –0.02)	0% (0.61)	–0.06; –0.02	No/Yes (fail-safe N: 1)	Yes	IV	3% worse
Reduction in total symptoms	4	0.6/0.16	350	0.031	beta=–0.14 (–0.26 to –0.01)	94.5% (<0.0001)	–0.41; 0.14	No/No (fail-safe N: 1)	Yes	IV	10% worse
Quality of life	8	3.7/1.5	1,162	0.042	beta=–0.09 (–0.17 to –0.003)	96.9% (<0.0001)	–0.33; 0.16	No/No (fail-safe N: 1)	Yes	IV	6% worse
Relapse	9	4/2	1,264	0.09	OR=1.67 (0.93-3.02)	100% (<0.0001)	0.29; 9.71	No/No	Yes	NS	NA
Global cognition	5	1.9/2	590	0.11	beta=–0.04 (–0.09 to 0.01)	44.9% (0.01)	–0.13; 0.05	No/No	No	NS	NA
Time hospitalized	3	6.7/6	233	0.42	beta=–0.09 (–0.31 to 0.13)	60.3% (0.08)	–0.45; 0.27	No/No	No	NS	NA
Number of hospitalizations	3	13.1/11.1	355	0.56	beta=–0.24 (–1 to 0.57)	98.7% (<0.0001)	–1; 1	Yes/No	Yes	NS	NA
Deliberate self-harm	4	2.4/2.1	1,611	0.91	OR=1.02 (0.74-1.40)	0% (0.79)	0.74; 1.40	No/No	No	NS	NA

OR – odds ratio, NS – not significant, NA – not applicable

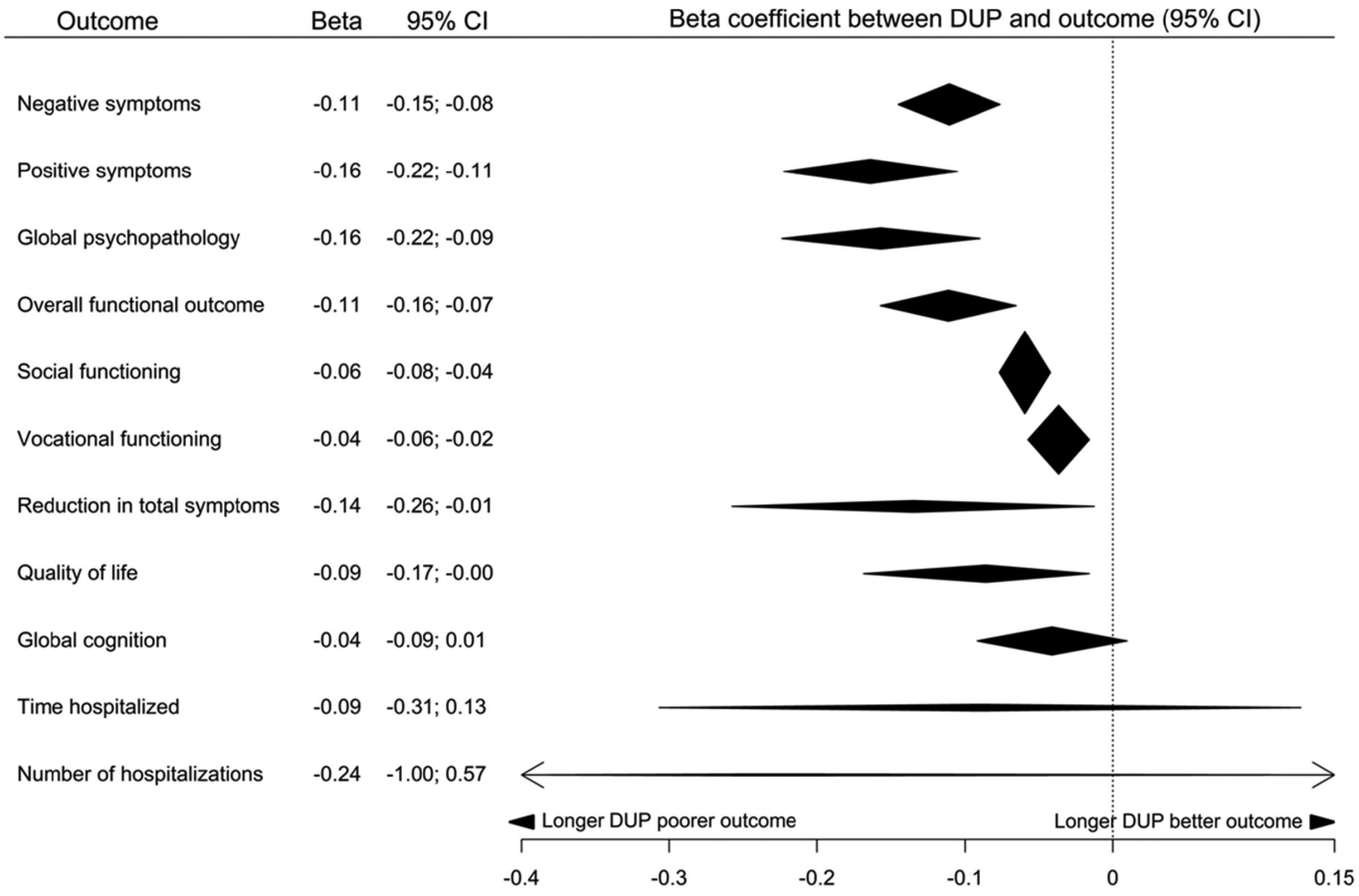

Figure 5 Summary of effect sizes for relationships between duration of untreated psychosis (DUP) and continuous outcomes at follow-up

despite a more significant overall p value, due to exclusion of the largest study.

For outcomes rated class I to III, 85-95% of studies were prospective. Restricting analyses to these prospective studies led to no changes in the classes of evidence and did not significantly alter heterogeneity.

DISCUSSION

Findings and comparison with previous studies

We found highly suggestive evidence for a relationship between longer DUP and more severe positive symptoms, more severe negative symptoms and lower chance of remission at follow-up, and suggestive evidence for a relationship between longer DUP and more severe global psychopathology and poorer overall functioning at follow-up. More than 85% of studies were prospective, and these findings were all replicated in subgroup analyses restricted to prospective studies, indicating that they are unlikely to be affected by reporting bias.

There was also suggestive evidence for a relationship between longer DUP and more severe negative symptoms and higher chance of previous self-harm at first presentation. The relationship between DUP and negative symptoms at first presentation was also evident in a subgroup analysis of antipsychotic naïve patients.

There was weak evidence for a relationship between longer DUP and poorer quality of life at first presentation and at follow-up, and also weak evidence for a relationship between longer DUP and lower chance of remission using operationalized Andreasen et al's criteria, smaller reduction in total symptoms, poorer social functioning and poorer vocational functioning at follow-up.

There was no relationship between DUP and global cognition, violence, global psychopathology, overall functioning or positive symptoms at first presentation, and between DUP and global cognition, relapse, hospitalization or deliberate self-harm at follow-up.

Our findings extend previous reviews of DUP by considering all the evidence from meta-analyses together and generating a clear hierarchy of evidence. In addition, we present the first meta-analysis of the relationship between DUP and outcomes in antipsychotic naïve patients.

Table 3 shows that each doubling in DUP predicts 8-12% more severe symptoms, and 3-8% poorer functional outcomes. Thus,

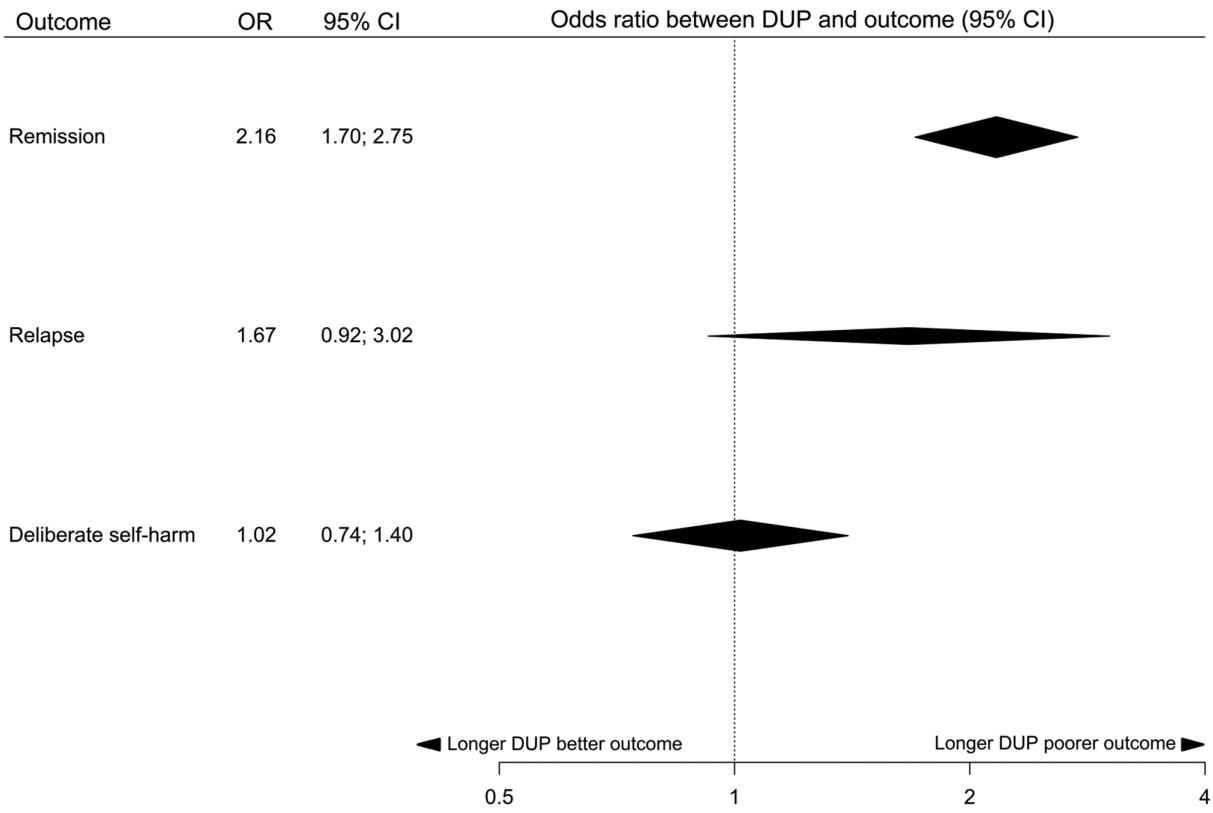

Figure 6 Summary of effect sizes for relationships between duration of untreated psychosis (DUP) and categorical outcomes at follow-up

an increase in DUP from 1 week to 4 weeks is associated with >20% more severe symptoms if the relationship is linear, which it approximates for short DUP[18,49]. This is a clinically meaningful increase. Many services have been designed worldwide with the aim of reducing DUP, and our review supports this approach by indicating that DUP is an important prognostic factor.

It is noteworthy that the largest effect size at follow-up was found between DUP and severity of positive symptoms. This suggests that the mechanism underlying positive symptoms could be central to the relationship between DUP and outcomes. Striatal dopaminergic dysfunction is thought to underlie the development of psychosis[71,72], and it has been hypothesized that psychosis feeds back on the regulation of dopamine neurons to cause further dysregulation[73,74]. Thus, a longer DUP could lead to continuing progression of dopaminergic dysfunction that makes the system less responsive to D2 antagonism when antipsychotic treatment is started[75]. However, this model does not explain more severe negative symptoms at first presentation, and we found no link between DUP and severity of positive symptoms at first presentation, which would be expected if there was a feedback loop. In addition, it remains to be determined if untreated psychosis is associated with other neurobiological changes, such as lower synaptic markers[76,77].

There are a few points of divergence from previous meta-analyses. We found a weak relationship between DUP and vocational functioning at follow-up, unlike Penttila et al[19] and Santesteban-Echarri et al[20]. Penttila et al[19] considered a broad category of vocational functioning, which included assessments of that functioning by rating scales, real-life outcome measures (such as weeks employed or on disability pension) and binary assessments of good or poor vocational outcome based on clinician impression. Given that these assessments result in effect size measures which should not be combined in a meta-analysis, and target different underlying constructs, it is unsurprising that their results differ from our analysis. Accordingly, we encountered no significant heterogeneity in our analysis, whereas there was moderate heterogeneity in Penttila et al[19]. We defined vocational functioning as in Santesteban-Echarri et al[20]; the discrepancy with our findings is likely to be due to the inclusion, in their analysis, of a study[78] that we excluded because the sample overlapped with that of another larger included study.

Our finding of a relationship between longer DUP and more severe negative symptoms at first treatment contact is in contrast to Marshall et al[16] and Farooq et al[65], but in keeping with two larger meta-analyses[17,18]. Similarly, our finding of no relationship between DUP and first presentation positive symptoms is in contrast to the findings of Farooq et al[65], but in line with other larger meta-analyses which did not restrict inclusion criteria to low and middle income countries[16-18].

We found no relationship between DUP and risk of previous violence at first treatment contact, in contrast to the analysis by Large and Nielssen[66]. This could be explained by a unit of

analysis error in that paper, where two different outcomes which derive from the same participants (risk of violence and risk of serious violence) are combined in random-effects meta-analysis as if they were independent measures.

Strengths and limitations

Our study has several strengths, such as providing a comprehensive analysis of the relationship between DUP and clinical outcomes, and generating a clear hierarchy of evidence. We performed data extraction not just from the meta-analyses, as is common in umbrella reviews, but from the primary studies themselves, to deal with the problems of non-normally distributed data, variable reporting of different test statistics, and pooling of transformed and untransformed effect sizes, that were not addressed in many of the previous meta-analyses.

Unlike previous analyses, we used comparable outcome categories and effect sizes. Whilst the formulae used required some data imputation, which may lead to error or bias in the estimation of the effect sizes, we consider this approach preferable to exclusion of relevant studies. Sensitivity analyses indicated that our findings were robust to these data imputations, as no results went from significant to non-significant after exclusion of studies where data were imputed, and there were no significant changes in heterogeneity. Moreover, we examined the effects of DUP in antipsychotic naïve patients, and have shown for the first time that varying definitions of the endpoint in DUP moderates some of the effects observed.

We encountered considerable heterogeneity in our analyses. However, we used a random-effects model which is robust to heterogeneity[29]. The most comparable previous meta-analysis[19] also encountered moderate to substantial heterogeneity. The heterogeneity we encountered was greater, which is unsurprising as we included more studies, included studies regardless of duration of follow-up, preferred pooled results rather than schizophrenia spectrum only results if both were available, and placed no restriction on the percentage of patients with schizophrenia in our inclusion criteria.

All statistically significant results remained significant after removal of outliers. Other than remission, where the class of evidence was reduced from II to III (although with a still highly significant p value of 2×10^{-19}), all classes of evidence for significant findings remained either unchanged or were increased after removal of outliers.

Whilst our further analyses identified a number of potential contributors to heterogeneity, there remained substantial heterogeneity in first presentation quality of life, and in follow-up positive symptoms and reduction in total symptoms, which we were unable to account for. This residual heterogeneity may reflect differences in study designs, settings, outcomes and inclusion criteria.

We identified important methodological issues with previous meta-analyses. Twelve of them had critical flaws in their systematic search strategy, none were pre-registered, and only 50% performed both study selection and data extraction independently in duplicate. We attempted to mitigate these flaws as much as possible in our own meta-analysis, by pre-registering, conducting all data extraction and study selection in duplicate, and extracting all data from primary studies to ensure the fidelity of data extraction. However, as with any other meta-analysis and umbrella review, we were limited to some extent by the methodological flaws of the primary studies and meta-analyses we included.

We were reliant on the included meta-analyses to identify primary studies, and it is therefore possible that some studies were missed. However, our "file-drawer" analyses indicated that 559-1,667 null studies would be needed to negate the significant relationships we observed at both time points between DUP and negative symptoms, indicating that these findings are robust, although we also found that some other results could be sensitive to future null studies. We observed that adjusted effect sizes moderate the impact of some variables, highlighting the need to account for this aspect in future meta-analyses on DUP.

To be conservative, we categorized a sample including any treated patients as a medicated sample, as very few studies reported results separately by medication status. However, this may mean that any effect of antipsychotic treatment was diluted by the inclusion of untreated patients in some analyses. Our finding that previous antipsychotic treatment explains heterogeneity in the relationship between DUP and symptoms highlights the importance of conducting future studies at first presentation in antipsychotic naïve patients exclusively, or reporting results separately for medicated and naïve patients.

Conceptual issues in assessing DUP

We found evidence that the relationship between DUP, negative symptoms and functioning is influenced by the definition of DUP. A number of studies defined DUP as the time from the onset of psychosis to first hospitalization. Whilst this has the advantage that hospital admission is a straightforward variable, it has the disadvantage of being dependent on health service organization. However, DUP defined this way showed the strongest relationship with negative symptoms.

Another issue relating to the definition of DUP is what constitutes treatment. In some studies, it is the first dose of antipsychotic medication. However, this could be criticized, as single dose is not considered adequate treatment[79]. Some studies required 28 days of antipsychotic treatment or treatment response as the endpoint for DUP rather than initiation of treatment. Studies which used the initiation of antipsychotic treatment as the endpoint of DUP showed a stronger relationship with functional outcome than studies using adequate treatment.

These issues could be addressed through the development of operationalized criteria for DUP, as has been achieved with both remission[70] and treatment resistance[80] in psychosis.

DUP has always been assessed retrospectively in the available studies. This raises the possibility of recall bias, as patients who

are severely psychotic may have poorer long-term recall, or may attach increased significance to the transition in their mental state compared to those who are less impaired or have partially recovered. Recall bias may also be more likely as DUP becomes longer, although serial assessments of DUP during the course of clinical recovery would be needed to illuminate this aspect. Finally, recall bias may be more or less likely with different methods of ascertaining DUP, or depending on the startpoint of DUP used.

Earlier detection of psychosis may alter outcomes because the observation window is shifted (lead-time bias). Long-DUP patients may experience most of their decline in psychosocial function prior to first admission, whereas short-DUP patients may experience it after that admission[81]. It would be useful to systematically assess this potential bias in future studies.

A related issue is confounded presentation. Severe, disruptive symptoms hasten presentation and therefore shorten DUP, which could confound the relationship between DUP and variables at first presentation[49]. This may partly explain the weaker relationships in our analyses between DUP and measures at first presentation compared to follow-up measures, and could be a particular issue for our finding on deliberate self-harm. However, as longer DUP was associated with higher risk of deliberate self-harm, this confounder does not explain our finding and, if anything, would reduce the association. Nonetheless, the studies included were not well designed to address this question. Future analyses should control for severity of symptoms at first presentation to account for this potential confounder.

The studies included were all observational, which limits inferences on causation. It is possible that an unmeasured third variable explains the relationship between DUP and positive symptoms, negative symptoms, remission and functioning. Examples of potential confounding variables include premorbid adjustment and diagnosis. A meta-analysis of almost 1,400 participants found that DUP is almost four times longer in subjects with schizophrenia compared to those with affective psychosis[34]. Most studies did not report results separately for patients with affective and non-affective psychosis, but we found that diagnosis was an important moderator, with larger effect sizes for global psychopathology seen in studies with higher percentages of subjects with schizophrenia.

Moreover, it is important to consider the possibility of reverse causality. For example, our finding that a longer DUP is associated with more severe negative symptoms at first presentation could be the result of negative symptoms predating the onset of psychosis, which lead to delayed first contact with health services and persist through follow-up as they show little treatment response[77].

A further issue to take into account is that many of the outcome measures show a degree of interrelation. For example, some functional measures include assessments of symptoms, and remission is partly defined by the level of symptoms. A longitudinal modelling study showed that the effect of DUP on functional outcome measures was partly mediated by symptoms[49]. It would be useful to determine if symptom improvement mediates the relationship between DUP and other outcomes.

Adjusted effect sizes were generally smaller in the studies included in our review, which raises the possibility of selective reporting and publication of uncorrected relationships. We detected some evidence of this, with statistically significant evidence of publication bias in around 15% of our analyses. Nevertheless, no results changed from significant to non-significant and no classes of evidence changed after use of the trim-and-fill method.

It is crucial that research on DUP be designed and analyzed with confounding and reverse causality in mind. Prospective studies in people at clinical high risk, where measures can be obtained prior to the onset of the first psychotic episode, may be one approach to address these issues, albeit there will still be challenges even with such designs. For example, patients who do not engage with services, who are expected to have the longest DUP, may be unlikely to participate in these studies. Extra efforts will be required to recruit such patients and ensure representative samples.

CONCLUSIONS

The concept of DUP has contributed to a paradigm shift in psychosis services, resulting in the establishment of extensive networks of early intervention teams in many countries[11]. Our analyses show significant relationships between longer DUP and a number of important outcomes. The evidence is very suggestive for the relationships between DUP and positive symptoms, negative symptoms and chance of remission, and the effect sizes indicate that the relationships are clinically meaningful. However, more evidence is needed, particularly at first presentation and for some functional outcomes.

Future work should also investigate the mechanisms which may underlie the relationship between DUP and outcomes, explore the effect of DUP in antipsychotic naïve patients, and control for potential confounders, particularly interrelated outcome variables, mode of presentation and diagnosis, to allow clearer inferences on causation to be drawn.

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Validation of the new DSM-5-TR criteria for prolonged grief disorder and the PG-13-Revised (PG-13-R) scale

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Although the concept of pathological grief dates back at least as far as Freud's "Mourning and Melancholia", there has been opposition to its recognition as a distinct mental disorder. Resistance has been overcome by evidence demonstrating that distinctive symptoms of prolonged grief disorder (PGD) – an attachment disturbance featuring yearning for the deceased, loss of meaning and identity disruption – can endure, prove distressing and disabling, and require targeted treatment. In acknowledgement of this evidence, the American Psychiatric Association Assembly has recently voted to include PGD as a new mental disorder in the DSM-5-TR. We tested the validity of the new DSM criteria for PGD and of an adapted version of our PG-13 scale, the PG-13-Revised (PG-13-R), designed to map onto these criteria, using data from investigations conducted at Yale University (N=270), Utrecht University (N=163) and Oxford University (N=239). Baseline assessments were performed at 12-24 months post-loss; follow-up assessments took place 5.3-12.0 months later. Results indicated that the PG-13-R grief symptoms represent a unidimensional construct, with high degrees of internal consistency (Cronbach's alpha = 0.83, 0.90 and 0.93, for Yale, Utrecht and Oxford, respectively). The DSM PGD diagnosis was distinct from post-traumatic stress disorder (phi=0.12), major depressive disorder (phi=0.25) and generalized anxiety disorder (phi=0.26) at baseline. Temporal stability was remarkable for this diagnosis (r=0.86, p<0.001). Kappa agreement between a PG-13-R threshold symptom summary score of 30 and the DSM symptom criterion for PGD was 0.70-0.89 across the datasets. Both the DSM PGD diagnosis and the PG-13-R symptom summary score at baseline were significantly associated (p<0.05) with symptoms and diagnoses of major depressive disorder, post-traumatic stress disorder and/or generalized anxiety disorder, suicidal ideation, worse quality of life and functional impairments at baseline and at follow-up, in the Yale, Utrecht and Oxford datasets. Overall, the DSM-5-TR criteria for PGD and the PG-13-R both proved reliable and valid measures for the classification of bereaved individuals with maladaptive grief responses.

Key words: Prolonged grief disorder, DSM-5-TR, PG-13-R, ICD-11, pathological grief, bereavement, post-traumatic stress disorder

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Although the concept of pathological grief dates back at least as far as Freud's *Mourning and Melancholia*[1], there has been public and professional opposition to its recognition as a mental disorder[2-5]. For example, a 2015 international online survey of public attitudes revealed that approximately 25% of respondents did not endorse the position that grief could be a mental disorder[2]. More recently, an online survey on public opinion in China found that about 40% of participants did not agree that grief could be a mental disorder, even under circumstances such as threat of harm to self or others[4]. Concerns about "pathologizing" grief are reported to be rooted in the belief that all grief is normal and an expected response to the death of a loved one. Thus, a diagnosis of pathological grief is considered to be tantamount to stigmatizing, medicalizing and/or pathologizing love[2,4].

Himself wary of pathologizing grief, Freud conceptualized mourning (grief) as a normal, natural reaction to loss of a loved one, and even deemed working through grief as necessary to bereavement adjustment – the hard, often painful, work a mourner must do to withdraw emotional attachment to the deceased person. In fact, Freud considered medical interference in "grief work" to be "inadvisable if not even harmful"[1]. By contrast, he considered melancholia (i.e., depression) the pathological response to bereavement, and noted that this condition, not grief, posed a risk for suicide, and warranted medical attention.

Research over the past quarter century has shown not only that a small but substantial proportion of grief reactions can be severe, disabling, and endure beyond normal expectations, but that they may respond only to specialist treatment. Specifically, studies have documented that certain grief symptoms are distinct from those of bereavement-related depression[6-9], have idiosyncratic neurobiological[10] and clinical[11-13] correlates, can persist unabated for months or even years[8,14], prove distressing and dysfunctional[14-16], and may only respond to targeted intervention[17,18]. Thus, there exists a substantial and mounting body of evidence in support of a psychiatric syndrome of maladaptive grief.

The ICD-11 Workgroup on Stress-Associated Disorders found the available evidence for prolonged grief disorder (PGD) sufficiently compelling to recommend its recognition as a new mental disorder[19]. The DSM-5 had included "persistent complex bereavement disorder" (PCBD) in Section III (i.e., among "conditions for further study"). In response to the ICD's inclusion of PGD and the accumulated evidence, the DSM Steering Committee convened a workshop in June 2019. An invited panel of researchers presented their data to the Committee, who concluded that these data supported moving the disorder to Section II (i.e., among recognized mental disorders). A provisional PGD criteria set was then drafted, and the researchers were tasked with using the best data available to inform the parameters of the PGD diagnostic algorithm, and then to evaluate that algorithm's reliability and validity. The researchers submitted their reports, which found the same PGD diagnostic algorithm to be optimal. The Steering Committee then posted that PGD algorithm online on the American Psychiatric Association (APA)'s website and

opened a period for public commentary between April and May 2020. After reviewing the research reports and submitted comments, the Steering Committee released the proposed criteria, and on November 7, 2020, the APA Assembly approved the inclusion of PGD in the DSM-5-TR (see Table 1).

In order to be sensitive to the concern expressed in the public commentary about pathologizing normal grieving and diagnosing a grief-related disorder "too soon" after the death, the DSM-5-TR PGD criteria specify that 12 months must elapse since the death. This time frame contrasts with the ICD-11 diagnostic guidelines for PGD, requiring a period of 6 months[20]. Unlike the PCBD criteria, the DSM-5-TR criteria for PGD acknowledge the possibility of delayed onset of symptoms at or beyond 12 months post-loss. Furthermore, the PGD criteria require that three of eight C criteria (compared to PCBD's six of 12) be met for a diagnosis, and focus more on "yearning for" and preoccupation with the deceased person and less on "preoccupation with the circumstances of the death" – the latter of which could be captured by a post-traumatic stress disorder (PTSD) diagnosis. Lastly, the PGD diagnosis allows for fewer combinations of symptoms to meet the criteria compared to the PCBD diagnosis. An empirical analysis of the performance of these new DSM criteria for PGD has not been published, nor has the psychometric performance of a scale that maps onto these diagnostic criteria been evaluated.

The PG-13 scale[22] was introduced in the process of developing PGD diagnostic criteria proposed for inclusion in the DSM-5 and ICD-11[8]. The scale contains 13 items that can be used for the dual purposes of assessing grief intensity continuously on a dimensional scale and of diagnosing PGD according to the proposed criteria. Items in the PG-13 are a subset of those in the Inventory of Complicated Grief - Revised[23], which is a revision of the Inventory of Complicated Grief[7]. Included items were those that we found to be informative and unbiased with respect to gender, relationship to the decedent, and time from loss in item response theory-based item analysis, and which mapped onto our criteria for PGD proposed in 2009[8].

The present paper has two primary objectives. First, it aims to introduce and validate the PG-13-R, a revised version of the PG-13 scale that corresponds to the new DSM-5-TR criteria for PGD. Second, it aims to validate these new DSM criteria for PGD. Data from the US (the Yale Bereavement Study), the Netherlands (the Utrecht Bereavement Study), and the UK (the Oxford Grief Study) were used to evaluate the psychometric properties of the PG-13-R, determine its agreement with the new DSM criteria for PGD, assess the PG-13-R and DSM criteria's predictive validity, and establish a threshold PG-13-R score to identify syndromal level PGD.

METHODS

Datasets and measures

Data to evaluate the performance of PG-13-R items and the new DSM criteria for PGD came from the Yale Bereavement Study, the Utrecht Bereavement Study, and the Oxford Grief Study. In the Yale Bereavement Study, community-based bereaved individuals were recruited for a field trial of consensus criteria for PGD[8]. In the Utrecht Bereavement Study, community-based bereaved subjects were enrolled by mental health care providers to examine the role of cognitive behavioral factors in bereavement adjustment[24]. In the Oxford Grief Study, a community-based bereaved sample was recruited to investigate loss-related memories, appraisals and coping strategies relevant to the development and maintenance of PGD[25].

Across datasets, participants with at least one assessment at 12-24 months post-loss were included. Participants without

Table 1 DSM-5-TR criteria for prolonged grief disorder

A. The death, at least 12 months ago, of a person who was close to the bereaved (for children and adolescents, at least 6 months ago).

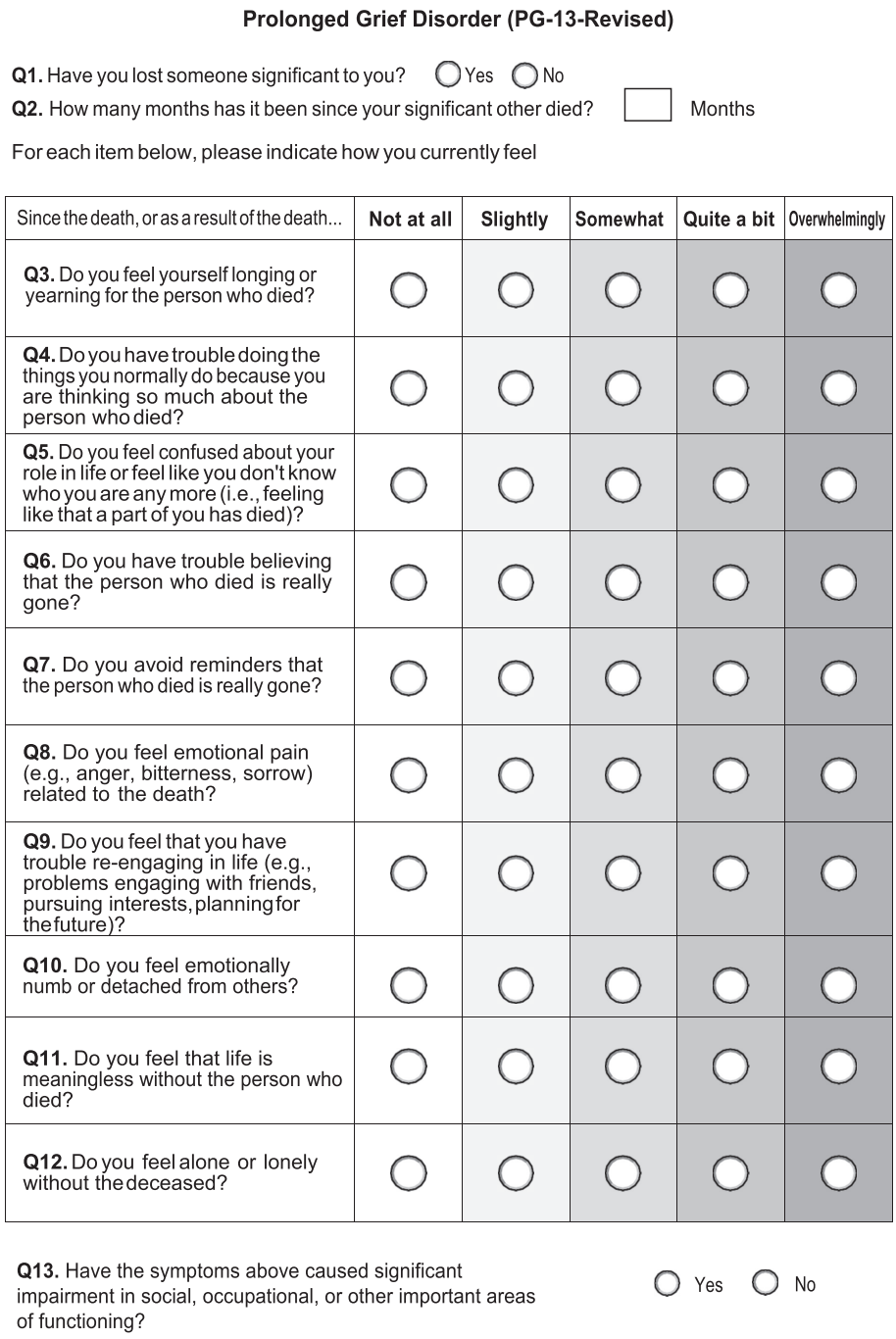
B. Since the death, there has been a grief response characterized by one or both of the following, to a clinically significant degree, nearly every day or more often for at least the last month:
   1. Intense yearning/longing for the deceased person
   2. Preoccupation with thoughts or memories of the deceased person (in children and adolescents, preoccupation may focus on the circumstances of the death)

C. As a result of the death, at least 3 of the following 8 symptoms have been experienced to a clinically significant degree since the death, including nearly every day or more often for at least the last month:
   1. Identity disruption (e.g., feeling as though part of oneself has died)
   2. Marked sense of disbelief about the death
   3. Avoidance of reminders that the person is dead (in children and adolescents, may be characterized by efforts to avoid reminders)
   4. Intense emotional pain (e.g., anger, bitterness, sorrow) related to the death
   5. Difficulty with reintegration into life after the death (e.g., problems engaging with friends, pursuing interests, planning for the future)
   6. Emotional numbness (i.e., absence or marked reduction in the intensity of emotion, feeling stunned) as a result of the death
   7. Feeling that life is meaningless as a result of the death
   8. Intense loneliness (i.e., feeling alone or detached from others) as a result of the death

D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The duration and severity of the bereavement reaction clearly exceeds expected social, cultural, or religious norms for the individual's culture and context.

F. The symptoms are not better explained by major depressive disorder, posttraumatic stress disorder, or another mental disorder, or attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.



Prolonged Grief Disorder (PG-13-Revised)

Q1. Have you lost someone significant to you? ◯ Yes ◯ No

Q2. How many months has it been since your significant other died? ☐ Months

For each item below, please indicate how you currently feel

Since the death, or as a result of the death...	Not at all	Slightly	Somewhat	Quite a bit	Overwhelmingly
Q3. Do you feel yourself longing or yearning for the person who died?	◯	◯	◯	◯	◯
Q4. Do you have trouble doing the things you normally do because you are thinking so much about the person who died?	◯	◯	◯	◯	◯
Q5. Do you feel confused about your role in life or feel like you don't know who you are any more (i.e., feeling like that a part of you has died)?	◯	◯	◯	◯	◯
Q6. Do you have trouble believing that the person who died is really gone?	◯	◯	◯	◯	◯
Q7. Do you avoid reminders that the person who died is really gone?	◯	◯	◯	◯	◯
Q8. Do you feel emotional pain (e.g., anger, bitterness, sorrow) related to the death?	◯	◯	◯	◯	◯
Q9. Do you feel that you have trouble re-engaging in life (e.g., problems engaging with friends, pursuing interests, planning for the future)?	◯	◯	◯	◯	◯
Q10. Do you feel emotionally numb or detached from others?	◯	◯	◯	◯	◯
Q11. Do you feel that life is meaningless without the person who died?	◯	◯	◯	◯	◯
Q12. Do you feel alone or lonely without the deceased?	◯	◯	◯	◯	◯

Q13. Have the symptoms above caused significant impairment in social, occupational, or other important areas of functioning? ◯ Yes ◯ No

Figure 1 PG-13-Revised (by H.G. Prigerson, J. Xu and P.K. Maciejewski)

complete responses to the new DSM PGD symptom items were excluded (total missing rate ~5%), resulting in sample sizes of N=270 (Yale), N=163 (Utrecht) and N=239 (Oxford), for a total of N=672. In participants with more than one assessment, the first evaluation within the time frame was used for item evaluation and threshold sensitivity analysis. The average time post-loss for the first assessment (T1) was 16.7±2.6 months for the Yale study, 16.3±3.7 months for the Utrecht study, and 14.1±1.7 months for the Oxford study. Participants' next available assessment (T2) was used for predictive external validity analysis, with a time lag of 7.4±2.0, 12.0±0 (fixed by design), and 5.3±1.3 months after T1 for Yale (N=48), Utrecht (N=90) and Oxford (N=35) subjects, respectively. All studies were approved by each university's institutional review board.

All three studies assessed the 10 symptom items included in both the new DSM criteria for PGD and the PG-13-R (yearning, preoccupation, identity disruption, disbelief, avoidance, intense emotional pain, difficulty with reintegration, emotional numb-

Table 2 Sample characteristics for the three bereavement studies

	Yale Study (N=270)	Utrecht Study (N=163)	Oxford Study (N=239)
Age, years (mean±SD)	61.8±13.5	56.2±13.3	46.9±13.3
Time from loss, months (mean±SD)	16.7±2.6	16.3±3.7	14.1±1.7
Gender, N (%)			
Male	67 (24.9)	44 (27.0)	50 (20.9)
Female	202 (75.1)	119 (73.0)	189 (79.1)
Highest education, N (%)			
Primary/secondary school	103 (38.3)	102 (62.6)	55 (23.0)
College/university	166 (61.7)	61 (37.4)	184 (77.0)
Relationship to the deceased, N (%)			
Partner/spouse	219 (83.6)	128 (78.5)	71 (29.7)
Other	43 (16.4)	35 (21.5)	168 (70.3)
Cause of death, N (%)			
Natural	251 (94.0)	151 (92.6)	218 (91.2)
Unnatural	16 (6.0)	12 (7.4)	21 (8.8)

ness, feeling that life is meaningless, and intense loneliness). These items (questions Q3 through Q12 in the PG-13-R) were rated using a 5-point Likert scale ranging from "1 = not at all" to "5 = overwhelmingly". In the PG-13-R, the symptom items are accompanied by three gatekeeper items exploring whether the respondent had lost a significant other (Q1), how long ago the death occurred (Q2), and impairment associated with the above symptoms (Q13) (see Figure 1).

In the Yale study, the occurrence of PTSD, major depressive disorder (MDD), generalized anxiety disorder (GAD) and panic disorder was further explored using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[26]; suicidal ideation was assessed using the Yale Evaluation of Suicidality (YES)[27]; and quality of life in eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) was evaluated using the SF-12 Health Survey[28].

In the Utrecht study, PTSD symptoms were assessed using the PTSD Symptom Scale Self-Report (PSS-SR)[29], and depressive symptoms by the Beck Depression Inventory (BDI-II)[30]. In the Oxford study, mental health problems were assessed using the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5)[31], the Patient Health Questionnaire (PHQ-9)[32] and the Work and Social Adjustment Scale (WSAS)[33].

Statistical analysis

The item performance of the PG-13-R symptom items (Q3-Q12) was evaluated within each dataset at T1. This included inspection of item means and variances, percentage of syndromal-level responses (score of 4 or 5), and item-total correlations. Cronbach's alpha of the PG-13-R symptom items was used to evaluate the internal consistency (reliability) of the scale.

A principal components factor analysis was conducted for each dataset at T1 to evaluate the dimensionality of the grief symptoms (Q3-Q12) construct. In each dataset, the eigenvalues obtained from actual PG-13-R symptom item data were compared with those obtained from simulated random data (parallel analysis)[34].

The external validity of the 10-item PG-13-R symptom score at T1, not including the impairment item (Q13), was assessed by its associations with other concurrent (T1, concurrent validity) and follow-up (T2, predictive validity) psychological and behavioral health measures within each dataset, including measures of depression, post-traumatic stress, suicidality, quality of life and functional impairments. Associations with dichotomous variables were estimated as odds ratios (ORs) using logistic regression; associations with continuous variables were evaluated with Pearson's correlation coefficients.

The summed PG-13-R score for the symptom items may range from 10 to 50. The optimal threshold was the symptom score that had the highest degree of agreement (kappa statistic) with fulfillment of B and C symptom criteria for PGD according to DSM within each dataset. The median maximum-agreement threshold score across the datasets was taken to be the overall optimal PG-13-R symptom threshold score.

The associations between the dichotomous PG-13-R diagnostic threshold score plus the three gatekeeper criteria (i.e., loss, timing, impairment) as well as the DSM PGD diagnosis with the mental and behavioral health outcomes at baseline and follow-up were estimated as ORs using logistic regression.

Phi coefficients were used to determine associations between PGD and other diagnosed mental disorders (e.g., MDD, PTSD,

Table 3 PG-13-R item performance and scale internal consistency

		Yale Study (N=270) Alpha=0.83				Utrecht Study (N=163) Alpha=0.90				Oxford Study (N=239) Alpha=0.93			
PGD-13-R symptom item		Rate	Score (mean±SD)	Deleted alpha	Corrected item-total correlation	Rate	Score (mean±SD)	Deleted alpha	Corrected item-total correlation	Rate	Score (mean±SD)	Deleted alpha	Corrected item-total correlation
Q3	Yearning	35.2%	2.9±1.3	0.81	0.59	68.1%	3.8±0.9	0.89	0.65	34.7%	3.1±1.2	0.92	0.75
Q4	Preoccupation	2.6%	1.3±0.8	0.82	0.53	26.4%	2.9±0.9	0.88	0.72	36.4%	3.2±1.2	0.92	0.74
Q5	Identity disruption	22.6%	2.2±1.4	0.81	0.58	42.3%	3.1±1.3	0.88	0.71	33.9%	2.7±1.4	0.92	0.76
Q6	Disbelief	6.3%	1.5±1.0	0.82	0.50	27.0%	2.9±1.2	0.89	0.56	33.9%	2.8±1.3	0.92	0.69
Q7	Avoidance	2.6%	1.3±0.7	0.84	0.25	5.5%	1.9±1.0	0.91	0.33	11.7%	1.8±1.2	0.93	0.52
Q8	Intense emotional pain	10.7%	2.1±1.0	0.82	0.51	49.7%	3.4±1.0	0.88	0.75	26.8%	3.0±1.1	0.92	0.74
Q9	Difficulty with reintegration	9.3%	1.8±1.1	0.82	0.52	26.4%	2.7±1.2	0.89	0.67	17.6%	2.1±1.3	0.92	0.76
Q10	Emotional numbness	7.4%	1.5±1.0	0.82	0.50	16.6%	2.4±1.1	0.88	0.70	21.8%	2.4±1.2	0.92	0.76
Q11	Life is meaningless	16.3%	2.0±1.2	0.81	0.61	39.3%	3.1±1.1	0.88	0.76	18.8%	2.1±1.3	0.92	0.80
Q12	Intense loneliness	33.3%	2.8±1.3	0.81	0.61	51.5%	3.4±1.1	0.89	0.65	26.4%	2.5±1.3	0.92	0.76

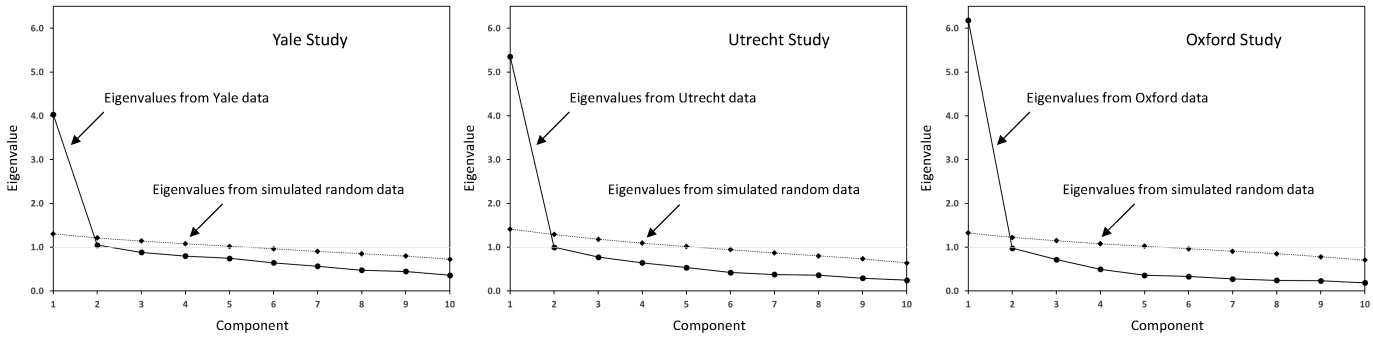


Figure 2 Eigenvalues from principal components factor analysis for PG-13-R symptom items and comparison to eigenvalues from parallel analysis (median of 100 replications of simulated random data) for the three studies

GAD in the Yale data). Pearson's correlation coefficients were used to determine stability of PGD and these other mental disorders between T1 and T2.

Statistical analyses for the Yale, Utrecht and Oxford studies were performed using SAS (version 9.4), R (version 3.6.2), and SPSS (version 24), respectively.

Table 4 Concurrent and predictive validity of PG-13-R symptom score (excluding impairment)

	PG-13-R symptom score (sum of 10 items) at T1							
	Concurrent (T1) outcome				Predictive (T2) outcome			
Yale Study	**N**	**%**	**OR**	**p**	**N**	**%**	**OR**	**p**
Post-traumatic stress disorder (PTSD)	270	1.5	1.23	0.007	48	2.1	n.e.	
Major depressive disorder (MDD)	270	5.9	1.16	<0.001	48	4.2	n.e.	
Generalized anxiety disorder (GAD)	270	3.3	1.24	<0.001	48	6.3	1.26	0.032
PTSD, MDD or GAD	270	8.1	1.18	<0.001	48	8.3	1.57	0.033
Yale Evaluation of Suicidality (YES): at least one positive response	269	17.5	1.18	<0.001	48	18.8	1.13	0.032
Yale Study	**N**	**mean±SD**	**r**	**p**	**N**	**mean±SD**	**r**	**p**
SF-12: Physical functioning	269	5.1±1.3	–0.10	0.109	48	4.7±1.7	0.10	0.518
SF-12: Role-physical	270	3.5±0.8	–0.12	0.048	48	3.3±0.9	–0.05	0.715
SF-12: Bodily pain	270	4.5±0.9	–0.24	<0.001	48	4.4±1.0	–0.10	0.513
SF-12: General health	270	3.6±1.0	–0.25	<0.001	48	3.6±1.1	–0.21	0.162
SF-12: Vitality	270	2.6±1.3	–0.42	<0.001	48	2.4±1.3	–0.23	0.110
SF-12: Social functioning	270	4.3±1.0	–0.41	<0.001	48	4.4±1.0	–0.13	0.373
SF-12: Role-emotional	270	3.6±0.7	–0.45	<0.001	48	3.6±0.7	–0.42	0.003
SF-12: Mental health	270	7.4±2.0	–0.60	<0.001	48	7.3±2.1	–0.61	<0.001
Utrecht Study	**N**	**mean±SD**	**r**	**p**	**N**	**mean±SD**	**r**	**p**
PSS-SR	158	31.4±8.4	0.77	<0.001	85	26.3±6.5	0.68	<0.001
BDI-II	153	34.6±8.8	0.75	<0.001	82	31.1±7.8	0.53	<0.001
BDI-II: Suicidality (item 9)	161	1.2±0.4	0.34	<0.001	90	1.2±0.4	0.29	0.005
Oxford Study	**N**	**mean±SD**	**r**	**p**	**N**	**mean±SD**	**r**	**p**
PCL-5	239	23.5±17.8	0.78	<0.001	35	20.7±16.8	0.53	0.001
PHQ-9	239	8.9±7.1	0.68	<0.001	35	7.8±7.1	0.60	<0.001
PHQ-9: Suicidality (item 9)	239	0.4±0.8	0.52	<0.001	35	0.3±0.8	0.55	0.001
WSAS	237	12.8±9.4	0.77	<0.001	35	11.5±9.7	0.64	<0.001

OR – odds ratio, SF-12 – Medical Outcomes Short-Form-12, PSS-SR – PTSD Symptom Scale Self-Report, BDI-II – Beck Depression Inventory, PCL-5 – Post-traumatic Stress Disorder Checklist for DSM-5, PHQ-9 – Patient Health Questionnaire-9, WSAS – Work and Social Adjustment Scale, n.e. – not estimated

Table 5 Concurrent and predictive validity of prolonged grief disorder (PGD) diagnosis using PG-13-R symptom threshold score of 30 and including impairment

	PG-13-R threshold score-based diagnosis of PGD at T1					
	Concurrent (T1) outcome			Predictive (T2) outcome		
Yale Study	**N**	**OR**	**p**	**N**	**OR**	**p**
Post-traumatic stress disorder (PTSD)	270	54.00	0.001	48	n.e.	
Major depressive disorder (MDD)	270	18.98	<0.001	48	n.e.	
Generalized anxiety disorder (GAD)	270	15.26	<0.001	48	28.00	0.014
PTSD, MDD or GAD	270	20.77	<0.001	48	63.00	0.002
Yale Evaluation of Suicidality (YES): at least one positive response	269	3.71	0.012	48	9.25	0.028
Yale Study	**N**	**r**	**p**	**N**	**r**	**p**
SF-12: Physical functioning	269	–0.05	0.433	48	0.10	0.509
SF-12: Role-physical	270	–0.08	0.216	48	0.03	0.857
SF-12: Bodily pain	270	–0.24	<0.001	48	0.00	0.992
SF-12: General health	270	–0.17	0.006	48	–0.14	0.351
SF-12: Vitality	270	–0.29	<0.001	48	–0.20	0.183
SF-12: Social functioning	270	–0.34	<0.001	48	0.00	0.992
SF-12: Role-emotional	270	–0.38	<0.001	48	–0.31	0.034
SF-12: Mental health	270	–0.30	<0.001	48	–0.38	0.007
Utrecht Study	**N**	**r**	**p**	**N**	**r**	**p**
PSS-SR	158	0.48	<0.001	85	0.39	<0.001
BDI-II	153	0.47	<0.001	82	0.39	<0.001
BDI-II: Suicidality (item 9)	161	0.18	0.024	90	0.19	0.070
Oxford Study	**N**	**r**	**p**	**N**	**r**	**p**
PCL-5	239	0.51	<0.001	35	0.58	<0.001
PHQ-9	239	0.45	<0.001	35	0.59	<0.001
PHQ-9: Suicidality (item 9)	239	0.54	<0.001	35	0.79	<0.001
WSAS	237	0.49	<0.001	35	0.52	0.001

OR – odds ratio, SF-12 – Medical Outcomes Short-Form-12, PSS-SR – PTSD Symptom Scale Self-Report, BDI-II – Beck Depression Inventory, PCL-5 – Post-traumatic Stress Disorder Checklist for DSM-5, PHQ-9 – Patient Health Questionnaire-9, WSAS – Work and Social Adjustment Scale, n.e. – not estimated

RESULTS

Table 2 summarizes the demographic characteristics of the three study samples. The Yale sample was older (mean age: 61.8±13.5 years) than the Utrecht (mean age: 56.2±13.3 years) and Oxford (mean age: 46.9±13.3 years) ones. All three samples were primarily female (73.0 to 79.1%), and most survived a death from natural causes (compared to unnatural causes such as suicide or homicide or accidental) (>90%). The Yale and Oxford samples had higher levels of educational attainment (college or above >60%) than the Utrecht sample (college or above <40%).

The mean scores for each PG-13-R symptom item at T1 are presented in Table 3. They ranged from 1.3 to 2.9 in the Yale study; from 1.9 to 3.8 in the Utrecht study; and from 1.8 to 3.2 in the Oxford study. In general, most item means were located around the center of the range, which is an indication of desirable variability. The avoidance (Q7) and preoccupation (Q4) items were infrequent in the Yale study, where mean scores in general were low. Variances for most items across the datasets were reasonably high, confirming the scale's discriminating ability.

Across studies, the PG-13-R symptom items cohered well (Cronbach's alpha = 0.83 for Yale, 0.90 for Utrecht, 0.93 for the Oxford study) (see Table 3). This analysis revealed that the deletion of the avoidance item in each of the three datasets resulted in either the same or an improved overall Cronbach's alpha (deleted alpha = 0.84, 0.91, 0.93 for the Yale, Utrecht and Oxford, respectively). Similarly, while all the other items had high item-total correlations ($r \geq 0.50$, 0.56 and 0.69 for the three datasets, respectively), the avoidance item was an exception, with lower item-total correlations (r=0.25, 0.33, 0.52, respectively).

As illustrated in Figure 2, principal components factor analysis in combination with parallel analysis for each dataset supported the conclusion that the PG-13-R grief symptoms represent a unidimensional construct. In fact, in each dataset, a single factor

Table 6 Concurrent and predictive validity of new DSM diagnostic criteria for prolonged grief disorder (PGD)

	DSM diagnosis for PGD at T1					
	Concurrent (T1) outcome			Predictive (T2) outcome		
Yale Study	**N**	**OR**	**p**	**N**	**OR**	**p**
Post-traumatic stress disorder (PTSD)	270	7.73	0.087	48	n.e.	
Major depressive disorder (MDD)	270	10.25	0.001	48	n.e.	
Generalized anxiety disorder (GAD)	270	14.00	0.001	48	43.00	0.008
PTSD, MDD or GAD	270	10.13	<0.001	48	129.00	0.002
Yale Evaluation of Suicidality (YES): at least one positive response	269	1.61	0.486	48	19.00	0.017
Yale Study	**N**	**r**	**p**	**N**	**r**	**p**
SF-12: Physical functioning	269	0.00	0.965	48	0.05	0.737
SF-12: Role-physical	270	–0.02	0.805	48	0.15	0.316
SF-12: Bodily pain	270	–0.14	0.024	48	0.03	0.828
SF-12: General health	270	–0.09	0.134	48	–0.25	0.086
SF-12: Vitality	270	–0.20	0.001	48	–0.31	0.032
SF-12: Social functioning	270	–0.32	<0.001	48	–0.05	0.760
SF-12: Role-emotional	270	–0.28	<0.001	48	–0.38	0.008
SF-12: Mental health	270	–0.19	0.002	48	–0.45	0.001
Utrecht Study	**N**	**r**	**p**	**N**	**r**	**p**
PSS-SR	158	0.48	<0.001	85	0.39	<0.001
BDI-II	153	0.47	<0.001	82	0.39	<0.001
BDI-II: Suicidality (item (9)	161	0.20	0.011	90	0.19	0.070
Oxford Study	**N**	**r**	**p**	**N**	**r**	**p**
PCL-5	239	0.48	<0.001	35	0.58	<0.001
PHQ-9	239	0.43	<0.001	35	0.59	<0.001
PHQ-9: Suicidality (item 9)	239	0.54	<0.001	35	0.79	<0.001
WSAS	237	0.48	<0.001	35	0.52	0.001

OR – odds ratio, SF-12 – Medical Outcomes Short-Form-12, PSS-SR – PTSD Symptom Scale Self-Report, BDI-II – Beck Depression Inventory, PCL-5 – Post-traumatic Stress Disorder Checklist for DSM-5, PHQ-9 – Patient Health Questionnaire-9, WSAS – Work and Social Adjustment Scale, n.e. – not estimated

emerged whose eigenvalue was substantially larger than 1 and greater than would be expected by chance. This primary factor explained 40.3%, 53.5% and 61.8% of the variance in the Yale, Utrecht and Oxford studies, respectively.

Results in Table 4 support the external validity of the PG-13-R symptom score, not including the impairment item (Q13). PG-13-R symptom scores at T1 were significantly associated with PTSD, MDD and/or GAD diagnoses or symptomatology and suicidal ideation, both concurrently ($p<0.001$) and predictively ($p<0.05$), in the Yale, Utrecht and Oxford data. PG-13-R symptom scores were significantly associated with poorer role-emotional and mental health domains of quality of life both concurrently and predictively in the Yale data ($p<0.005$), and with work and social adjustment difficulties both concurrently and predictively in the Oxford data ($p<0.001$).

PG-13-R symptom threshold scores of 29, 32 and 30 maximized agreement with meeting DSM symptom criteria for PGD in the Yale (kappa=0.77), Utrecht (kappa=0.86), and Oxford (kappa=0.89) study data, respectively. Overall, a symptom threshold score of 30 optimized agreement with meeting DSM symptom criteria for PGD across the three datasets (kappa ≥0.70 across the datasets).

Results in Table 5 illustrate that using a PG-13-R symptom threshold score of 30 in combination with the impairment criterion demonstrated excellent external validity. The prevalence of PGD using the PG-13-R score ≥30 at T1, including impairment, was 6.3%, 16.6% and 11.3% for the Yale, Utrecht and Oxford samples, respectively. The PG-13-R threshold-based diagnoses of PGD at T1 were significantly ($p<0.05$) associated with PTSD, MDD and/or GAD diagnoses or symptomatology and suicidality in the Yale, Utrecht and Oxford data, concurrently and predictively (except for suicidality in the Utrecht study, where the association was significant only concurrently). PG-13-R threshold-based diagnoses of PGD were significantly associated with poorer role-emotional and mental health domains of quality of life both concurrently and predictively in the Yale data ($p<0.05$),

and with work and social adjustment difficulties both concurrently and predictively in the Oxford data ($p \leq 0.001$).

Results in Table 6 illustrate that the DSM diagnosis of PGD demonstrated excellent external validity. The prevalence of PGD using DSM criteria at T1 was 4.4%, 15.3% and 10.9% for the Yale, Utrecht and Oxford samples, respectively. DSM diagnoses of PGD at T1 were significantly ($p<0.05$) associated with PTSD, MDD and/or GAD diagnoses or symptomatology concurrently and predictively in the Yale, Utrecht and Oxford data. Interestingly, in the Yale sample, DSM diagnoses of PGD were significantly associated with suicidality predictively (at T2) but not concurrently (at T1). DSM diagnoses of PGD were significantly associated with poorer vitality, role-emotional and mental health domains of quality of life both concurrently and predictively in the Yale data ($p<0.05$), and with work and social adjustment difficulties both concurrently and predictively in the Oxford data ($p \leq 0.001$).

In the Yale data (T1, N=270), the DSM PGD diagnosis was found to be distinct from PTSD (phi=0.12), MDD (phi=0.25) and GAD (phi=0.26). Temporal stability (T1, T2 correlation; N=48) was greatest for DSM PGD ($r=0.86$, $p<0.001$), significant for MDD ($r=0.31$, $p=0.030$), and not significant for GAD ($r=-0.07$, $p=0.653$). We could not estimate the temporal stability for PTSD because no participants with T2 data met criteria for PTSD at T1 (and only one study participant met criteria for PTSD at T2).

DISCUSSION

Results of analyses of data from independent Yale, Utrecht and Oxford bereavement studies suggest that both the PG-13-R and the DSM-5-TR PGD diagnostic criteria possess desirable performance characteristics. The symptoms were uniformly higher in the Utrecht sample, which is unsurprising given that this sample was recruited via mental health professionals. Across all three datasets, the preoccupation item was infrequently reported at syndromal levels. This was most noticeable in the Yale data, where syndromal level preoccupation was found in <3% of the sample. Such low prevalence is an undesirable property for a "gatekeeper" item, which suggests that it might have been preferable to have only "yearning" in the B criterion for PGD in the DSM.

The weakest performing item across all the datasets was "avoidance of reminders that the deceased is dead". Item-total correlations for this item were the lowest of all items examined, and Cronbach's alpha improved in the Yale and Utrecht datasets when the avoidance item was removed. It may be the case that avoidance is more a function of fear, with roots in psychological trauma, than a function of grief, with roots in an attachment disturbance. Alternately, there may be a need to revise the item to focus on what aspect of the loss is avoided (e.g., avoidance of reminders of the death as an event may be more a traumatic stress response, while avoidance of reminders that the deceased is truly gone may be the most relevant to disturbed grief). Future studies are needed to confirm whether the avoidance item should be retained, revised or discarded.

In accordance with the high internal consistency of the PG-13-R symptom items, factor analyses revealed that the scale is unidimensional. These results are consistent with those reported for the Inventory of Complicated Grief[7] and its Dutch version[35], and for the original PG-13[8] and its Swedish[36], Chinese[37], Portuguese[38] and many other translated versions[e.g.,39]. Though some studies have found multiple factors in this set of grief symptoms[40], these exceptions occurred only in highly comorbid treatment-seeking and treatment-receiving samples and a military family study, not in community-based samples. The preponderance of evidence supports the unidimensional nature of PGD symptomatology as found in the three studies examined here.

Because the Yale data alone included structured clinical interviews that yielded diagnoses of mental disorders, only these data could be used to assess PGD's overlap with other disorders and to compare diagnostic stability over time. The results demonstrated minimal overlap between PGD and competing diagnoses (i.e., PTSD, MDD and GAD) (phi=0.12-0.26), suggesting its distinctness from mental disorders already included in Section II of the DSM. In addition, the PGD diagnosis proved remarkably stable between the T1 and T2 assessments approximately 7.4 months apart ($r=0.86$, $p<0.001$) and much more stable than MDD ($r=0.31$, $p=0.030$) or GAD ($r=-0.07$, $p=0.653$). These results suggest that PGD fills a diagnostic gap left open by other mental disorders secondary to bereavement. Furthermore, they show that PGD is likely not to remit with the passage of time and to require specialized treatment.

With respect to concurrent and predictive validity, we first sought to determine if the intensity of PGD symptoms alone (excluding impairment, the DSM criterion D) would predict distress and dysfunction. The PG-13-R symptom score proved to be highly predictive of both concomitant and future distress and dysfunction, indicating that the severity of these symptoms themselves is pathological even without "stacking the deck" by requiring the fulfillment of an impairment criterion.

Next, we sought to determine the threshold score of these symptoms that optimized agreement with meeting the B and C symptom criteria for PGD in the DSM. We found that the PG-13-R symptom score of 30 was the optimal threshold score across the three datasets. Finally, we sought to evaluate and compare the concurrent and predictive validity of diagnoses for PGD using the PG-13-R threshold diagnostic score, and, separately, using the DSM criteria B and C, each in combination with meeting the impairment criterion. Results indicated that both performed extremely well in predicting substantial current and future maladaptive behaviors and outcomes.

A strength of this study was the use of three independent community-based bereavement cohort samples. A possible weakness was the fact that the wording for the PG-13-R questions was slightly different in the three studies. The Utrecht sample was uniformly more distressed than the Yale and Oxford samples, which is understandable given that Utrecht participants were recruited via mental health care providers, who are

more likely to encounter distressed bereaved individuals. The Yale and Utrecht samples were predominantly comprised of widowed persons, which was not the case for the Oxford sample (~80% to ~30%, respectively). With respect to ethnicity, all three samples nearly entirely consisted of people of Caucasian ethnicity.

In conclusion, three independent community-based samples showed that the PG-13-R is a reliable tool for assessing grief symptoms on a dimensional scale. A PG-13-R symptom score of 30 or greater identifies syndromal-level PGD symptomatology. The dimensional PG-13-R symptom score, the diagnosis of PGD using the PG-13-R threshold symptom score of 30 plus the impairment criterion, and the diagnosis of PGD using the new DSM-5-TR criteria all predict enduring distress and dysfunction. Thus, the PG-13-R and the new DSM-5-TR criteria for PGD appear to be reliable and valid measures for the classification of bereaved individuals with maladaptive grief responses. Future research is needed to confirm their psychometric performance in more ethnically diverse samples.

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Psychological processes mediating the association between developmental trauma and specific psychotic symptoms in adults: a systematic review and meta-analysis

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Experiencing psychological trauma during childhood and/or adolescence is associated with an increased risk of psychosis in adulthood. However, we lack a clear knowledge of how developmental trauma induces vulnerability to psychotic symptoms. Understanding the psychological processes involved in this association is crucial to the development of preventive interventions and improved treatments. We sought to systematically review the literature and combine findings using meta-analytic techniques to establish the potential roles of psychological processes in the associations between developmental trauma and specific psychotic experiences (i.e., hallucinations, delusions and paranoia). Twenty-two studies met our inclusion criteria. We found mediating roles of dissociation, emotional dysregulation and post-traumatic stress disorder (PTSD) symptoms (avoidance, numbing and hyperarousal) between developmental trauma and hallucinations. There was also evidence of a mediating role of negative schemata, i.e. mental constructs of meanings, between developmental trauma and delusions as well as paranoia. Many studies to date have been of poor quality, and the field is limited by mostly cross-sectional research. Our findings suggest that there may be distinct psychological pathways from developmental trauma to psychotic phenomena in adulthood. Clinicians should carefully ask people with psychosis about their history of developmental trauma, and screen patients with such a history for dissociation, emotional dysregulation and PTSD symptoms. Well conducted research with prospective designs, including neurocognitive assessment, is required in order to fully understand the biopsychosocial mechanisms underlying the association between developmental trauma and psychosis.

Key words: Developmental trauma, psychotic symptoms, childhood, adolescence, delusions, hallucinations, paranoia, post-traumatic stress disorder, dissociation, psychological processes

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Causative associations between psychologically traumatic experiences during childhood and/or adolescence – hereon referred to as "developmental trauma" (DT) – and adult psychopathology were proposed in the 19th century by Breuer and Freud[1]. These theories were elaborated by Ferenczi[2], who suggested that childhood sexual abuse could give rise to psychotic symptoms in adults. Following these early conceptualizations, and notwithstanding unmeasured confounds, consistent observational evidence indicates that people who experience DT have a higher risk of psychosis in later life[3-7].

Meta-analyses indicate that the odds of experiencing a psychotic disorder are approximately three times higher in adult survivors of DT, compared to those who have not experienced DT, with the overall population attributable risk for development of psychosis associated with DT being 33%[6,8]. Importantly, the association between DT and psychosis during adulthood is unlikely to be the result of reverse causality or passive gene-environment correlations[9]. Clinically, adult survivors of DT with psychosis have a more severe illness and are more likely to be hospitalized than people with psychosis who have not experienced DT, indicative of the urgent need to improve treatment outcomes in this population[10,11].

There is, therefore, clear evidence that DT is associated with an increased risk and severity of psychosis, but an understanding of the processes or pathways involved is lacking. Whilst recent progress has been made in our knowledge of the biopsychosocial sequelae of DT[12], there remains a gap in understanding how psychotic symptoms arise following DT. This is a barrier to the development of effective secondary preventive measures for adult survivors of DT and treatments for survivors with psychosis[13].

Several lines of evidence support the view that post-traumatic stress disorder (PTSD)-type phenomena are associated with psychotic symptoms in adult survivors of DT with psychosis[14-20]. Stress-induced changes in information processing during exposure to psychological trauma may result in fragments of highly emotionally salient memories being laid down which lack temporospatial and sensory contextual data that would normally be present in non-traumatic episodic memory processing[21]. The re-emergence of these poorly integrated memories may underlie trauma-related hallucinations.

Additional processes that may be involved include dissociation, hyperarousal, avoidance and mood instability. Dissociation is an umbrella term used to refer to reactions including detachment (e.g., depersonalization and derealization) and compartmentalization (i.e., suppression of thoughts and emotions)[22]. Dissociation has been proposed to have an initial adaptive (defensive) role in response to traumatic experiences as part of the

acute stress response[23,24]. However, peri-traumatic detachment is likely to interfere with encoding of material and therefore impair the quality of memory and distort meanings[22]. Furthermore, hyperarousal and avoidance have been proposed to increase vulnerability to psychosis through increased threat anticipation[25]. Mood instability may also create a mental environment in which psychotic beliefs and experiences emerge[26]. For example, bursts of anxiety occurring with otherwise neutral environmental stimuli may be viewed as signs of threat, prompting a search for meaning and attribution to external agents, resulting in paranoia.

There are also further factors that can complicate the processing of DT. These relate to schemata (i.e., mental constructs of meanings) learned through experiences of trauma, such as negative beliefs about the self and beliefs that the environment is dangerous and uncontrollable. They may be involved in the evolution of psychotic experiences, for example, by influencing the content of hallucinations and/or delusional beliefs[27-29].

Together, these processes are likely to further result in social isolation, potentially exacerbating suspicion of others and paranoid thinking through impaired social safety learning. Finally and importantly, additional complexities may arise from experiencing abuse from an attachment figure, which can be associated with difficulties in emotional regulation and interpersonal relationships[30].

Most research to date has investigated the relationships between trauma and psychotic symptoms in general, rather than specific psychotic symptom domains. Understanding the psychological processes associated with specific psychotic symptoms in the context of DT has the potential to lead to improved treatments, including both psychotherapies and pharmacotherapies.

We therefore sought to systematically review studies that have investigated psychological processes in relation to DT and specific psychotic symptom domains (i.e., hallucinations, delusions and paranoia) in adults. We also combined sets of findings using meta-analytic techniques in order to further contribute to this state-of-art review by indicating whether the psychological processes investigated are statistically significant across studies and quantifying the magnitude of their effects.

METHODS

This systematic review and meta-analysis was pre-registered on PROSPERO (registration no. CRD42018112883).

Inclusion criteria and search strategies

We included studies investigating the role of psychological processes potentially underlying the association between DT and specific psychotic symptom domains in adulthood. We included all types of clinical and community samples. We defined DT to comprise loss of a parent, childhood maltreatment and victimization (including sexual, physical and emotional abuse, and bullying) and neglect. We excluded studies if they: a) did not measure specific psychotic symptoms and/or experiences, but examined psychotic symptoms as a whole (e.g., total score on a measure of psychotic symptoms such as the Positive and Negative Syndrome Scale, PANSS); b) did not differentiate between trauma experienced in childhood and adulthood; c) solely examined neurobiological processes with no measure of psychological processes, or d) were not available in English.

We systematically searched PubMed, Web of Science and PsycINFO. We used search terms that were related to psychosis (e.g., "psychosis" and "schizophreni*") to identify studies investigating psychotic experiences in clinical, at-risk and non-clinical populations. We used search terms including "hallucinat*", "delusion*", "paranoi*" and "negative" to identify studies of specific psychotic symptoms. We used terms including "physical abuse", "emotional abuse", "psychological abuse", "sexual abuse", "neglect", "molest*", "bullied" and "bully" to identify studies of DT. We used terms including "mechanism", "mediat*", "process*", and "model" to identify studies examining potential mechanisms between DT and psychosis. No restrictions were placed on date of publications. The reference lists of suitable papers obtained from this search were hand-searched to identify further relevant studies.

After piloting the search and data extraction tool, the final search was conducted on August 26, 2020. Each stage of data screening and extraction was completed by two independent reviewers, and discrepancies were resolved with a third reviewer.

Quality assessment and strength of evidence

We used the Newcastle-Ottawa quality assessment scale to assess methodological quality and risk of bias[31]. In brief, each study is rated on three broad criteria: selection of the study groups; comparability of the groups; and the ascertainment of the exposure or outcome of interest. A score of 7 or more for case-control and cohort studies, and of 6 or more for cross-sectional studies, is indicative of "good" quality and bias control. Two reviewers independently applied the tool, and discrepancies were resolved through discussion with a third reviewer. As this is an under-researched area, all studies were included regardless of quality rating.

The Oxford Centre for Evidence-based Medicine – Levels of Evidence guideline was used to assign a level of evidence to each study, to facilitate the development of overall clinical recommendations[32]. This tool provides a hierarchy of study designs from 1 to 5, whereby a lower number indicates a higher level of evidence.

Meta-analyses

Where three or more studies investigating the same psychological mediating process for the same psychotic experience and/or symptom were available, we sought to combine sets of findings using meta-analytic techniques. Meta-analyses were

performed using the 'metan' command in Stata (version 15), which employs a random effects model.

The effect size for each study was estimated by calculating Cohen's d and 95% confidence intervals (CIs). Studies reporting effect sizes which cannot be converted to Cohen's d were excluded from the meta-analysis. Pooled effect sizes were weighted based on the sizes of CIs. We tested heterogeneity by examining χ^2 and I^2 statistics. Jack-knife sensitivity analyses were performed by individually removing each study and re-running the meta-analyses.

RESULTS

Systematic review

Study characteristics

We identified 22 studies investigating psychological phenomena associated with DT and psychotic symptom domains, published between 2011 and 2020. Every study assessed DT retrospectively during adulthood based on self-report, and all but one[33] were mediation studies. Details of the selection process are presented in our PRISMA flow chart in Figure 1.

The 22 studies included 24,793 participants in total, of which 1,639 were from clinical and 23,154 from non-clinical samples (see Table 1). Clinical populations included patients diagnosed with schizophrenia, schizoaffective disorder, psychotic disorder, bipolar disorder, depression, relapsing psychosis, first episode psychosis, and those categorized as at ultra-high risk for developing psychosis as well as voice-hearers with a psychosis-related diagnosis.

Of the included papers, one was a cohort study, seven were case-control studies, and fourteen were cross-sectional studies. Ten studies used clinical interviews along with self-report questionnaires[26,33,36,43-45,47,48,52,53], one used a signal detection task to assess hallucination proneness[52], and one used a virtual reality scenario to assess paranoia[46].

Quality and strength of evidence appraisal

A detailed description of the methodological quality of the studies as measured on the Newcastle Ottawa Scale is presented in Table 2. Amongst studies which met the criteria for "good" quality, there are two case-control studies[34,52], one cohort study[47], and two cross-sectional studies[33,43].

In terms of level of evidence, the included studies ranged from levels 2a to 3b. Two studies had the highest level of evidence. The first was a prospective study with good follow-up rates at three months (84.7%), that included a clinical sample recruited from mental health outpatient clinics and used validated clinical in-

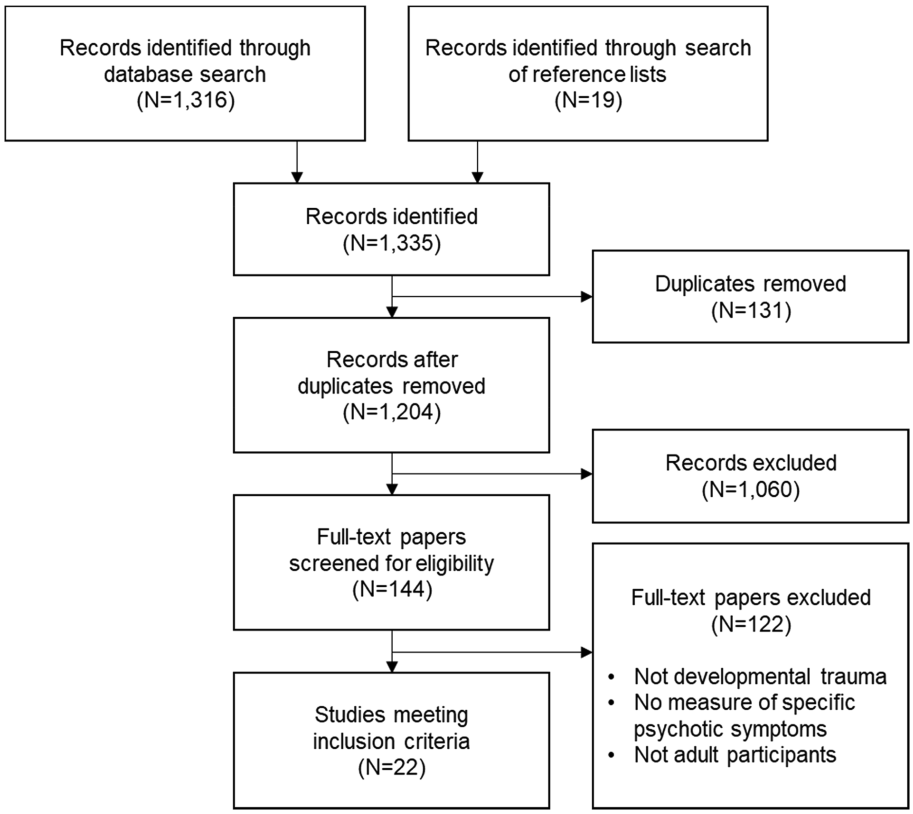

Figure 1 PRISMA flow chart

Table 1 Characteristics and main findings of included studies

Study	Study design	Level of evidence	Sample	Type of developmental trauma (DT)	Phenomenon investigated	Psychotic symptom focused on	Main findings
Appiah-Kusi et al[34]	Case-control	3a	30 individuals at ultra-high risk for psychosis and 38 healthy controls	Abuse (emotional, physical and sexual) and neglect (emotional and physical)	Negative self-schemata	Paranoid ideation	Negative cognitive schemata about the self partially mediated between emotional neglect in childhood and paranoia.
Ashford et al[35]	Cross-sectional	2b	135 undergraduate students	Bullying: indirect aggression, direct verbal aggression, direct physical aggression	Negative self- and other-beliefs, depression and anxiety, interpersonal sensitivity	Paranoid thoughts: persecution and social reference	Negative self-beliefs and depression mediated between childhood experience of indirect aggression and paranoia. Negative other-beliefs mediated between direct verbal aggression and paranoia.
Bendall et al[36]	Case-control	3a	44 individuals with first episode psychosis and 26 healthy controls	Abuse (emotional, physical and sexual) and neglect (emotional and physical)	External misattribution	Hallucinations	DT was not associated with external misattribution, which therefore did not mediate a relationship with hallucinations.
Bortolon et al[37]	Cross-sectional	2b	425 participants recruited online	Abuse (emotional, physical and sexual) and neglect (emotional and physical)	Dissociation and early maladaptive schemata	Auditory hallucinations	Dissociation mediated between DT and auditory hallucinations. Abandonment schema mediated between emotional abuse and auditory hallucinations.
Bortolon & Raffard[38]	Cross-sectional	2b	175 individuals from general population	Adverse childhood experiences, bullying victimization	Shame; trauma-related intrusions and avoidance	Hallucinations	Shame and intrusions mediated between DT and hallucinations.
Fisher et al[39]	Cross-sectional	3a	212 individuals from general population	Abuse (emotional, physical and sexual) and neglect (emotional and physical)	Negative beliefs about the self and others, depression and anxiety	Paranoia	Anxiety partially mediated between emotional abuse and paranoia. Negative self- and other-beliefs did not mediate between emotional or physical abuse and paranoia. Depression did not mediate either association.
Goldstone et al[40]	Case-control	3a	100 individuals with psychosis and 133 non-clinical participants	Physical and emotional trauma, sexual abuse	Experiential avoidance	Delusions	In non-clinical participants, experiential avoidance partially mediated between childhood emotional trauma, life hassles and subclinical delusions. In clinical participants, experiential avoidance partly mediated between childhood sexual trauma, life hassles and delusions.
Goldstone et al[41]	Case-control	3a	100 individuals with psychosis and 133 non-clinical participants	Physical and emotional trauma	Metacognitions and experiential avoidance	Hallucinations	In clinical participants, experiential avoidance and metacognitions partially mediated between DT and hallucinations. In non-clinical participants, metacognitions partially mediated between DT and hallucinations.

Table 1 Characteristics and main findings of included studies *(continued)*

Study	Study design	Level of evidence	Sample	Type of developmental trauma (DT)	Phenomenon investigated	Psychotic symptom focused on	Main findings
Gomez & Freyd[42]	Cross-sectional	2b	192 university students	Sexual abuse	Dissociation	Hallucinations	Dissociation partially mediated between childhood sexual abuse and hallucinations.
Hardy et al[43]	Cross-sectional	2b	228 individuals with relapsing psychosis	Direct, witnessed or vicarious: war, traffic accident, natural disaster, serious illness, sexual abuse, physical attack, threatened, bullying	Post-traumatic avoidance, hyperarousal and numbing, intrusive trauma memory, negative beliefs, depression	Auditory hallucinations and delusions (persecutory and referential)	Post-traumatic numbing, avoidance and hyperarousal mediated between childhood sexual abuse and auditory hallucinations. Negative other-beliefs mediated between childhood emotional abuse and persecutory delusions.
Isvoranu et al[44]	Cross-sectional	2b	552 individuals with psychosis	Childhood maltreatment; physical, emotional and sexual abuse; physical and emotional neglect	Symptoms of general psychopathology (somatic concern, anxiety, guilt, tension, mannerism and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, poor judgment and insight, disturbed willpower, poor impulse control, preoccupation, active social avoidance)	Positive and negative symptoms	Anxiety was the most significant mediator between sexual abuse and delusions, hallucinations and paranoia, as well as between physical abuse and paranoia.
Marwaha et al[26]	Cross-sectional (with a cohort component)	2a	7,403 non-clinical participants	Sexual abuse	Mood instability	Auditory hallucinations and paranoid ideation	Mood instability mediated a third of the association of child sexual abuse and persecutory ideation. Mood instability mediated a quarter of the association of child sexual abuse and auditory hallucinations.
McCarthy-Jones[45]	Cross-sectional	2b	5,788 individuals from the general population	Sexual abuse	Compulsions, obsessions, anxiety, depression, post-traumatic symptomatology (hyperarousal and re-experience of memories)	Auditory verbal hallucinations	Compulsions partially mediated between childhood sexual abuse and auditory verbal hallucinations. Post-traumatic symptomatology partially mediated between childhood sexual abuse and auditory verbal hallucinations.
McDonnell et al[46]	Case-control	3a	64 individuals at clinical high risk for psychosis	Bullying victimization	Interpersonal sensitivity	Paranoid ideation	Interpersonal sensitivity mediated between bullying severity and paranoid ideation.

Table 1 Characteristics and main findings of included studies *(continued)*

Study	Study design	Level of evidence	Sample	Type of developmental trauma (DT)	Phenomenon investigated	Psychotic symptom focused on	Main findings
Muenzenmaier et al[47]	Cohort study	2a	183 outpatients with schizophrenia, schizoaffective disorder, bipolar disorder or depression	Sexual, physical and emotional abuse, and stressful experiences related to the family environment (e.g., substance use, mental illness, witnessing abuse)	Dissociation	Delusions and hallucinations	Dissociation mediated between DT and hallucinations.
Moffa et al[33]	Cross-sectional	2b	General population data from Adult Psychiatric Morbidity Survey (2000 sample: N=8,580; 2007 sample: N=7,403)	Bullying victimization	Worry, mood instability, anxiety, depression	Persecutory ideation and hallucinations	Depression and persecutory ideation, as well as mood instability and worry (through depression), mediated between bullying and hallucinations.
Perona-Garcelan et al[48]	Cross-sectional	2b	71 individuals with psychosis	Sexual abuse, physical abuse, unexpected death of relative/friend, assault, transport accident	Dissociation	Delusions and hallucinations	Dissociation mediated between DT and hallucinations.
Pilton et al[49]	Cross-sectional	3a	55 voice-hearers with a psychosis-related diagnosis	Abuse (emotional, physical and sexual) and neglect (emotional and physical)	Adult attachment	Auditory hallucinations	Anxious attachment partially mediated between DT and auditory hallucination severity and voice-related distress.
Rosen et al[50]	Cross-sectional	2b	61 individuals with schizophrenia or psychotic bipolar disorder	Childhood adversity (abuse, neglect and household dysfunction)	Negative voice content and depression	Voice-related distress in auditory verbal hallucinations	DT had an indirect effect on voice-related distress through negative voice-content.
Sitko et al[51]	Cross-sectional	2b	5,877 non-clinical participants	Witnessed injury or killing, sexual assault, neglect, threatened with a weapon, held captive or kidnapped	Adult attachment and depression	Paranoia and hallucinations	Anxious and avoidant attachment mediated between childhood neglect and paranoia.
Varese et al[52]	Case-control	2b	45 patients with schizophrenia spectrum disorders and 20 healthy controls	Sexual abuse, punishment, negative home environment, emotional abuse	Dissociation	Hallucinations	Dissociation mediated between DT and hallucination proneness.
Wickham & Bentall[53]	Case-control	2b	72 patients with schizophrenia spectrum disorders and 72 healthy controls	Emotional, physical and sexual abuse; emotional and physical neglect; bullying	Beliefs in a "just world"	Hallucinations and paranoia	Personal, but not general, beliefs in a "just world" partially mediated between childhood neglect and paranoia.

terviews[47]. The second analyzed data from 2000 and 2007 UK national surveys of psychiatric morbidity, which included an 18-month follow up of a sub-sample of the 2000 survey, and used validated clinician-rated and self-report measures[26]. Only one of those two studies was rated as "good" quality using our criteria for quality assessment[47].

We identified several methodological limitations of the included studies. While four of them were prospective[26,43,44,47], all but one of these made assessments at single time points and therefore provided cross-sectional data. The remaining studies were all retrospective and made assessments only at one time point. Furthermore, all studies except one[47] had poor follow-up rates. Although all studies utilized validated psychometric instruments, more than half relied on self-report measures only. In addition, several studies used methods of recruitment which may limit generalizability: three recruited non-clinical samples using snowballing[40,41,53], three enrolled clinical samples through case managers[36,40,41], and three used convenience sampling including, for example, advertisements in clinics[35,36,39].

We categorized studies into higher-order groupings to allow examination of the role of different psychological processes in the associations between psychotic symptoms and DT. Based on our search, we used the following groupings: dissociation, PTSD symptomatology, schemata and belief systems, obsessive-compulsive phenomena, emotional dysregulation, attachment and social cognition. Results of studies were then further subdivided into the different psychotic experiences examined, namely hallucinations, delusions and paranoia. A visual overview of the findings can be found in Figure 2.

Statistical approaches used

Ten studies used mediation analyses[34,35,37,38,42,48-50,52,53], one used directed acyclic graphs[33], three studies adopted path models[40,41,46], four used regression models[26,39,43,45], and one applied a network analysis[44]. Of these, only six[35,39,43,45,50,53] accounted for potential confounders in their analyses.

Dissociation

There was converging evidence, also from high-quality studies, that dissociative processes mediate the relationship between childhood trauma and hallucinations during adulthood[37,42,43,47,48,52]. This finding was consistent across clinical[43,47,48,52] and non-clinical[37,42] samples. One high-quality study[43] looked at types of dissociative phenomena, highlighting depersonalization and derealization as particularly important, rather than dissociative amnesia, or absorption and imaginative involvement. This study was conducted as part of a larger longitudinal study which assessed symptoms at baseline and at 3-, 6-, 12-, and 24-month follow-ups. However, results were reported from the 3-month follow-up only, and follow-up rates and results for other sessions were not presented. When looking at specific DT experiences, there was evidence from clinical and non-clinical samples that dissociation mediated the relationship between childhood sexual abuse and auditory hallucinations in adulthood[42,43,52].

In terms of delusions, a high-quality prospective cohort study[47] with good follow-up rates found evidence of a dose-response relationship between DT and delusions in adulthood, and dissociation partially mediated this relationship. However, whilst other studies reported associations between DT, delusions and dissociation, mediating effects were not observed[43,48]. We did not identify studies that investigated the relationship between dissociation and paranoia.

PTSD symptoms

There was evidence from two studies that PTSD symptoms mediated the association between childhood sexual abuse and auditory hallucinations in adulthood[43,45]. One study used data collected as part of the 2007 UK national survey of psychiatric morbidity[45], while the other used data collected as part of a larger longitudinal study[43]. Avoidance, numbing and hyperarousal were found to mediate this association, but not intrusive trauma memories[43].

Other studies investigated experiential avoidance and external misattribution (a form of source monitoring error where internal sensations or thoughts are attributed to an external source, i.e. something seen or heard), although they had methodological limitations. Experiential avoidance partially mediated the relationship between sexual abuse and hallucinations[40,41]. The role of external misattribution of post-traumatic intrusive memories, such as flashbacks, in the relationship between DT and hallucinations in adulthood was observed in one study[36]. Adults with psychosis who had experienced DT did not show greater external misattribution than those without a DT experience, or healthy controls without trauma[36].

Emotional dysregulation and affect

Nine studies examined the potential mediating role of variables associated with emotional dysregulation[26,33,35,39,43-45,50,51], two of which used data from the same sample[26,33]. There was evidence, also from one high-quality study, that emotional symptoms including anxiety and depression mediated the association between DT experiences and hallucinations in adulthood[33,44,51], although this was not found in all studies[45,50]. In one study, there was an indirect effect of DT severity on voice-related distress through negative voice content[50].

The role of mood instability on auditory hallucinations specifically has also been investigated. One study[26] analyzed data collected from 2000 and 2007 UK national surveys of psychiatric morbidity. Mood instability was significantly predictive of hallucinations following childhood sexual abuse, and mediated a

Table 2 Quality and risk of bias assessment results using the Newcastle-Ottawa scale

Case-control studies										
	Selection				Comparability		Exposure			
Study	Adequate case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total score (out of 9)
Appiah-Kusi et al[34]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	7
Bendall et al[36]	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	6
Goldstone et al[40]	Yes	Yes	Yes	No	No	No	No	Yes	No	4
Goldstone et al[41]	Yes	Yes	No	No	No	No	No	Yes	No	3
Varese et al[52]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	7
Wickham & Bentall[53]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	5

Cohort studies										
	Selection				Comparability		Outcome			
Study	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of cases and controls on the basis of design or analysis		Ascertainment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	Total score (out of 9)
Muenzenmaier et al[47]	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7

Table 2 Quality and risk of bias assessment results using the Newcastle-Ottawa scale *(continued)*

Cross-sectional studies								
	Selection			Comparability		Outcome		
Study	Representativeness of the sample	Non-response rate	Ascertainment of the exposure (valid measure)	Subjects in different outcome groups are comparable, based on study design or analysis; confounding factors are controlled		Assessment of the outcome (blinded?)	Statistical test	Total score (out of 7)
Ashford et al[35]	No	No	Yes	Yes	Yes	No	Yes	4
Bortolon et al[37]	No	No	Yes	Yes	Yes	No	No	3
Bortolon & Raffard[38]	No	Yes	Yes	Yes	Yes	No	Yes	5
Fisher et al[39]	Yes	No	Yes	Yes	Yes	No	No	4
Gomez & Freyd[42]	No	No	No	No	No	No	Yes	1
Hardy et al[43]	Yes	Yes	Yes	Yes	Yes	No	Yes	6
Isvoranu et al[44]	Yes	No	Yes	Yes	Yes	No	Yes	5
Marwaha et al[26]	Yes	No	Yes	Yes	Yes	Yes	No	5
McCarthy-Jones[45]	Yes	No	Yes	Yes	Yes	No	Yes	5
McDonnell et al[46]	Yes	No	Yes	No	No	No	Yes	3
Moffa et al[33]	Yes	No	Yes	Yes	Yes	Yes	Yes	6
Perona-Garcelan et al[48]	Yes	No	No	No	No	No	Yes	2
Pilton et al[49]	Yes	No	Yes	No	No	No	Yes	3
Rosen et al[50]	Yes	No	Yes	Yes	Yes	No	Yes	5
Sitko et al[51]	Yes	No	No	Yes	Yes	No	Yes	4

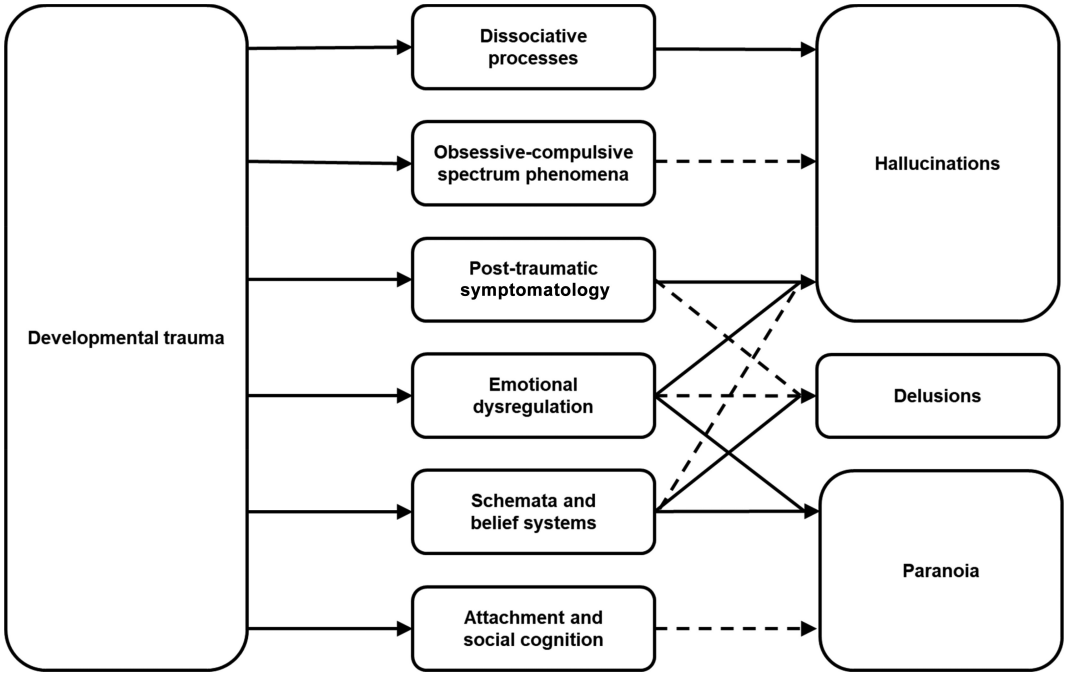

Figure 2 Overview of findings from the systematic review (solid arrows represent mediating paths supported by converging evidence from more than one study; dashed arrows represent mediating paths supported by one study only)

quarter of the association between childhood sexual abuse and auditory hallucinations in adulthood.

In terms of delusions, an affective pathway between childhood trauma and psychotic symptoms during adulthood was identified by a prospective study using a network analysis, and anxiety was the most significant mediator between childhood sexual abuse and delusions during adulthood, although follow-up rates were not given[44].

Two studies, one in a clinical[44] and the other in a sub-clinical sample[39], found that anxiety mediated the relationship between DT and paranoia later in life. These effects may be specific to adult-to-child maltreatment, as anxiety did not mediate the relationship between peer bullying and paranoia in a separate study, which was limited by its convenience sampling of undergraduate students[35]. Nonetheless, depression (and negative self-beliefs) did mediate specifically between experiences of indirect aggression in childhood and adulthood paranoia[35]. Evidence for the mediating role of depression between DT and paranoia has also been found by some other high-quality studies[39,43,51]. A recent study analyzing data from the 2000 and 2007 UK national surveys of psychiatric morbidity, using a Bayesian directed acyclic graph model, found no support for the mediating roles of depression, as well as anxiety or sleep disturbance, in the relationship between bullying victimization and persecutory ideation during adulthood, suggesting instead that these lie causally downstream from persecutory ideation[33]. A potential role for mood instability was found in another study for the association between childhood sexual abuse and adulthood persecutory ideation[26]. Taken together, these studies suggest that depression, anxiety and mood instability may be associated with increased risk of paranoia following certain types of DT.

Schemata, beliefs and metacognitive beliefs

A schema is a dynamic constellation of cognitions, feelings and motivations. In terms of delusions, there was evidence from one high-quality study[43] that the relationship between childhood emotional abuse and delusions in adulthood was mediated by negative other-beliefs, rather than negative self-beliefs. There was high-quality evidence that negative self and other schemata mediate the association between DT, particularly emotional abuse and neglect, and paranoia in adulthood[34,43,53]. There was lower-quality evidence for a role of beliefs in a "just world" in the development of paranoia[53].

In a non-clinical sample, abandonment schema mediated the relationship between childhood emotional abuse and auditory hallucinations in adulthood[37]. In the same study, subjugation and vulnerability schemata were involved in the association of emotional and sexual abuse with auditory hallucinations, although this was accounted for by dissociation[37].

Metacognitive beliefs, including those about the uncontrollability and danger of thoughts, as well as measures of cognitive confidence, need for control, and cognitive self-consciousness have also been investigated. When combined with subsequent stressors, these negative metacognitive beliefs partially mediated the relationship between DT and hallucinations[41]. However, these studies were of lower quality. We did not identify studies

that investigated the relationship between metacognitive beliefs and paranoia.

Obsessive-compulsive spectrum phenomena

Data collected by the 2007 UK national survey of psychiatric morbidity were used to investigate the relationship between childhood sexual abuse, obsessive-compulsive symptoms and auditory verbal hallucinations. In this study, compulsions, but not obsessions, partially mediated the relationship between childhood sexual abuse and auditory verbal hallucinations in adulthood[45]. Paranoia and delusions in adulthood were not investigated as outcomes in this study, nor in any of the other studies.

Attachment and social processes

There was some evidence that disrupted attachment plays a mediating role in the relationship between childhood trauma and psychotic experiences during adulthood[37,49,51], although these studies were not rated as high-quality. Anxious attachment has been associated with higher severity and distress related to auditory hallucinations[49]. Furthermore, abandonment schema, arguably related to early attachment, mediated the relationship between emotional abuse and auditory hallucination proneness in adulthood[37].

There was some evidence of specificity in the mediating role of attachment styles in the relationship between trauma types and hallucinations. For example, anxious attachment partially mediated the relationship between childhood sexual abuse and adulthood hallucinations, whereas avoidant attachment mediated the relationship between being held captive or threatened with a weapon during development and adulthood hallucinations[51]. However, when the statistical model included measurements of depression, the mediating effects of anxious and avoidant attachment were significantly reduced, and the effect of anxious attachment on the association between childhood sexual abuse and hallucinations in adulthood was no longer significant.

Avoidant and anxious attachment mediated the association between a range of DTs and adulthood paranoia[51]. The strongest association was found for anxious and avoidant attachment as a mediator between childhood neglect and paranoia in adulthood. These findings have also been extended to bullying, whereby bullying severity was significantly associated with paranoid ideation in later life, and this association was mediated by interpersonal sensitivity[46].

A more recent study with a non-clinical sample failed to find support for the rejection sensitivity model in the association between bullying and paranoid thinking in adulthood, instead finding that negative self-beliefs and depression mediated between childhood bullying experiences, specifically of indirect aggression, and adulthood paranoid thinking[35]. This study also found negative other-beliefs to mediate between direct verbal aggression in childhood and adulthood paranoid thinking.

Meta-analysis

We meta-analyzed the role of the following mediating relationships where three or more studies were available: dissociation and hallucinations[37,42,47,48,52], negative other-beliefs and paranoia[35,39,53], and emotional dysregulation and hallucinations[26,33,45,50]. Although five studies investigated the mediating role between PTSD symptomatology and hallucinations[36,39,41,43,45], effect sizes of individual mediators could not be extracted from two of the studies[36,41].

Due to the low number of publications, we included studies in our meta-analysis regardless of quality or risk of bias. A visual overview of the findings can be found in Figure 3.

Dissociation and hallucinations

All five studies investigating dissociation as a mediator of psychosis found that it positively predicted hallucinations following DT[37,42,47,48,52]. One high-quality study was excluded from the meta-analysis due to its reporting of effect sizes as incidence rate ratios, which could not be directly converted to Cohen's d based on information provided[47].

Meta-analysis indicated that dissociation is a statistically significant mediator of the relationship between DT and hallucinations in adulthood (pooled Cohen's d=0.35; pooled 95% CI: 0.25-0.45, see Figure 4). There was high heterogeneity between studies (I^2=71.8%). Sensitivity analysis revealed that no study significantly affected the pooled effect size.

Schemata, beliefs and paranoia

Among the three studies included in the meta-analysis[35,39,53], two reported findings that negative other-beliefs mediate the association between DT and paranoid ideation in adulthood[35,53]. Although one other high-quality study included in the systematic review[34] also supported the mediating role of negative schemata between childhood mistreatment and adulthood paranoia, it was excluded from meta-analysis due to its focus on self schemata rather than schemata about others.

Meta-analysis indicated that negative other-beliefs are not a statistically significant mediator between DT and paranoia in adulthood (pooled Cohen's d=0.02; pooled 95% CI: –0.04 to 0.09, see Figure 5), with relatively low heterogeneity between studies (I^2=48.1%).

Emotional dysregulation and hallucinations

Four studies investigated the mediating role of emotional dysregulation in the development of hallucinations following DT exposure. Findings that mood instability mediated the development of auditory hallucinations were reported in two studies[26,33]. One of these studies was excluded from the meta-analysis due to

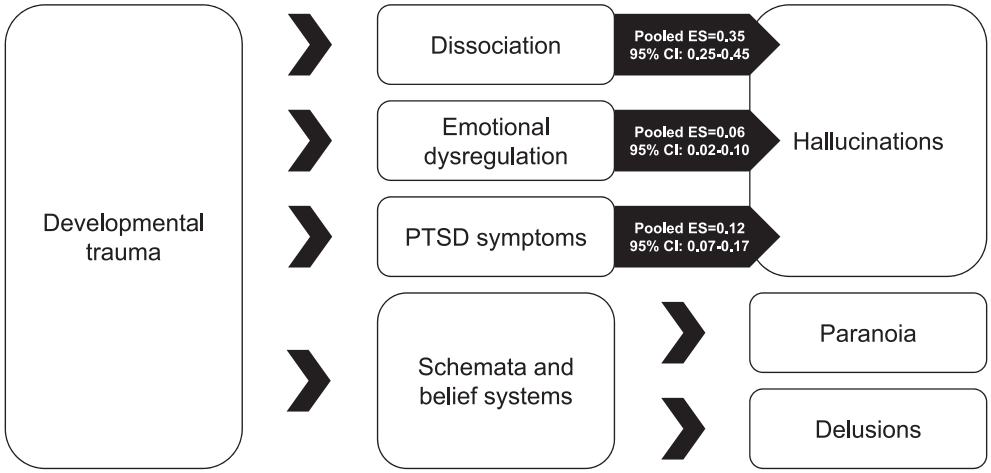

Figure 3 Overview of converging findings from high-quality studies and meta-analysis (thin arrows indicate paths supported by evidence from high-quality studies, thick arrows indicate paths supported by meta-analysis in addition to high-quality studies). Effect size (ES) is reported as Cohen's d.

employing directed acyclic graphs which estimated causal relationships in a form which could not be converted into Cohen's d effect size[33]. Two other studies found that depression had no mediating role between DT and auditory verbal hallucinations or voice-related distress in adulthood[45,50].

Meta-analysis indicated that emotional dysregulation is a statistically significant mediator between developmental trauma and auditory hallucinations in adulthood (pooled Cohen's d=0.06; pooled 95% CI: 0.02-0.10, see Figure 6). However, there was high heterogeneity between studies (I^2=85.8%). One study[45] had a substantially larger sample size (N=5,788) and smaller 95% CI than others and was assigned a weight of 75.84%. As a result, the pooled effect size was almost equal to that reported from this study. Sensitivity analysis revealed that one study affected the pooled effect size significantly[26]. Its removal altered the pooled effect size to become non-significant (pooled Cohen's d=0.022, pooled 95% CI: –0.021 to 0.066).

PTSD symptoms and hallucinations

Five studies investigated the mediating role of PTSD symptoms between DT and hallucinations in adulthood. Only one study investigated PTSD symptomatology as a whole[45]; four other studies investigated specific PTSD symptoms, including experiential avoidance[38,43], trauma-related intrusions[38,43], external misattribution[36,41], post-traumatic hyperarousal[43] and shame[38]. Effect sizes extracted from three studies[38,43,45] were included in the meta-analysis. One study was excluded due to its use of a path analysis model which combined life hassles with developmental trauma[41]. Another study was excluded because effect sizes were not reported[36].

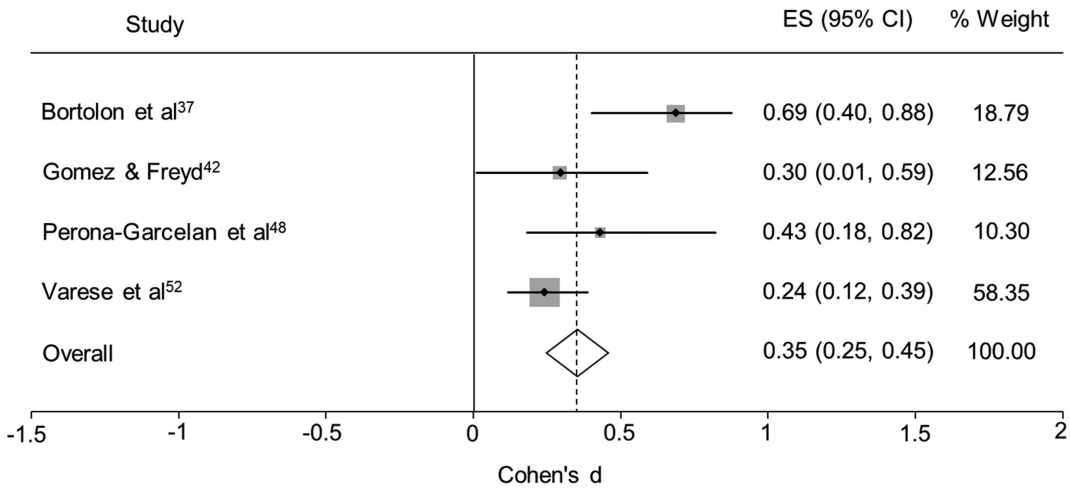

Figure 4 Meta-analysis of dissociation as a mediator between developmental trauma and hallucinations in adulthood. Sizes of grey squares represent weights of Cohen's d effect size (ES) according to sample size; horizontal lines indicate 95% CIs; the diamond represents the overall ES and 95% CIs.

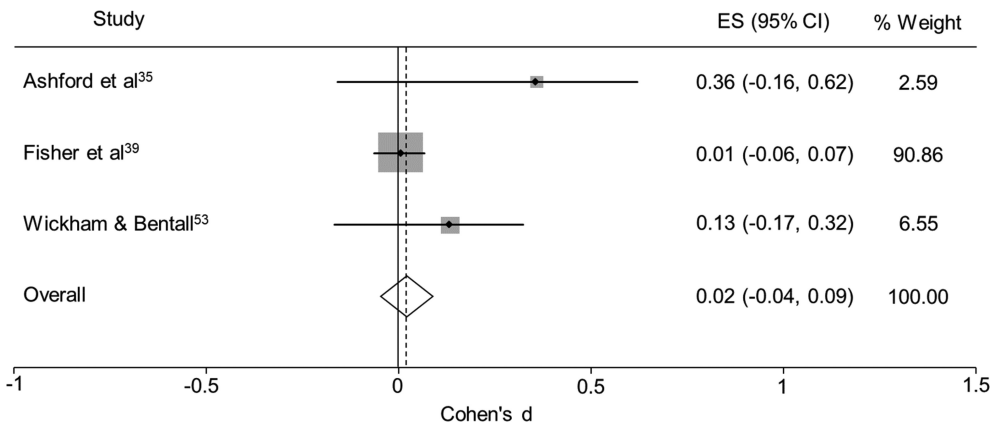

Figure 5 Meta-analysis of negative other-beliefs as a mediator between developmental trauma and paranoia in adulthood. Sizes of grey squares represent weights of Cohen's d effect size (ES) according to sample size; horizontal lines indicate 95% CIs; the diamond represents the overall ES and 95% CIs.

Meta-analysis indicated that PTSD symptoms, overall, are a statistically significant mediator between DT and hallucinations in adulthood (pooled Cohen's d=0.12; pooled 95% CI: 0.07-0.17, see Figure 7). However, there was high overall heterogeneity between studies (I^2=84.6%) and between subgroups. Sensitivity analysis revealed that no study significantly affected the pooled effect size.

DISCUSSION

In the first systematic review and meta-analysis of psychological phenomena potentially mediating the relationships between DT and specific psychotic symptom domains, we found evidence that dissociation, PTSD symptoms and emotional dysregulation are associated with hallucinations. We also found some evidence supporting associations of negative schemata with paranoia and delusions.

Major limitations of the existent literature include the reliance on self-report measures of DT obtained in adulthood, and self-report measures of psychopathology. Importantly, since the work presented here is based on cross-sectional studies, we are unable to make inferences regarding the temporality of phenomena investigated and causal effects between the variables. It is therefore still possible that specific psychotic symptoms may be mediating the effect of trauma on the psychological phenomena described. This highlights the need for longitudinal studies.

Interpretation of results

Our results extend previous models of the mechanisms underlying psychosis following trauma[54]. Experiencing psychological trauma is associated with dissociation, which is thought

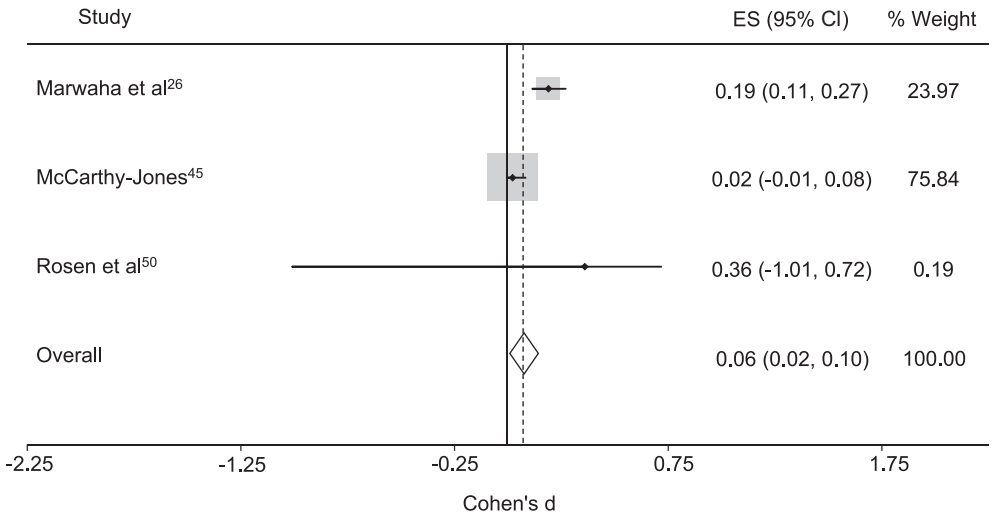

Figure 6 Meta-analysis of emotional dysregulation as a mediator between developmental trauma and auditory hallucinations in adulthood. Sizes of grey squares represent weights of Cohen's d effect size (ES) according to sample size; horizontal lines indicate 95% CIs; the diamond represents the overall ES and 95% CIs.

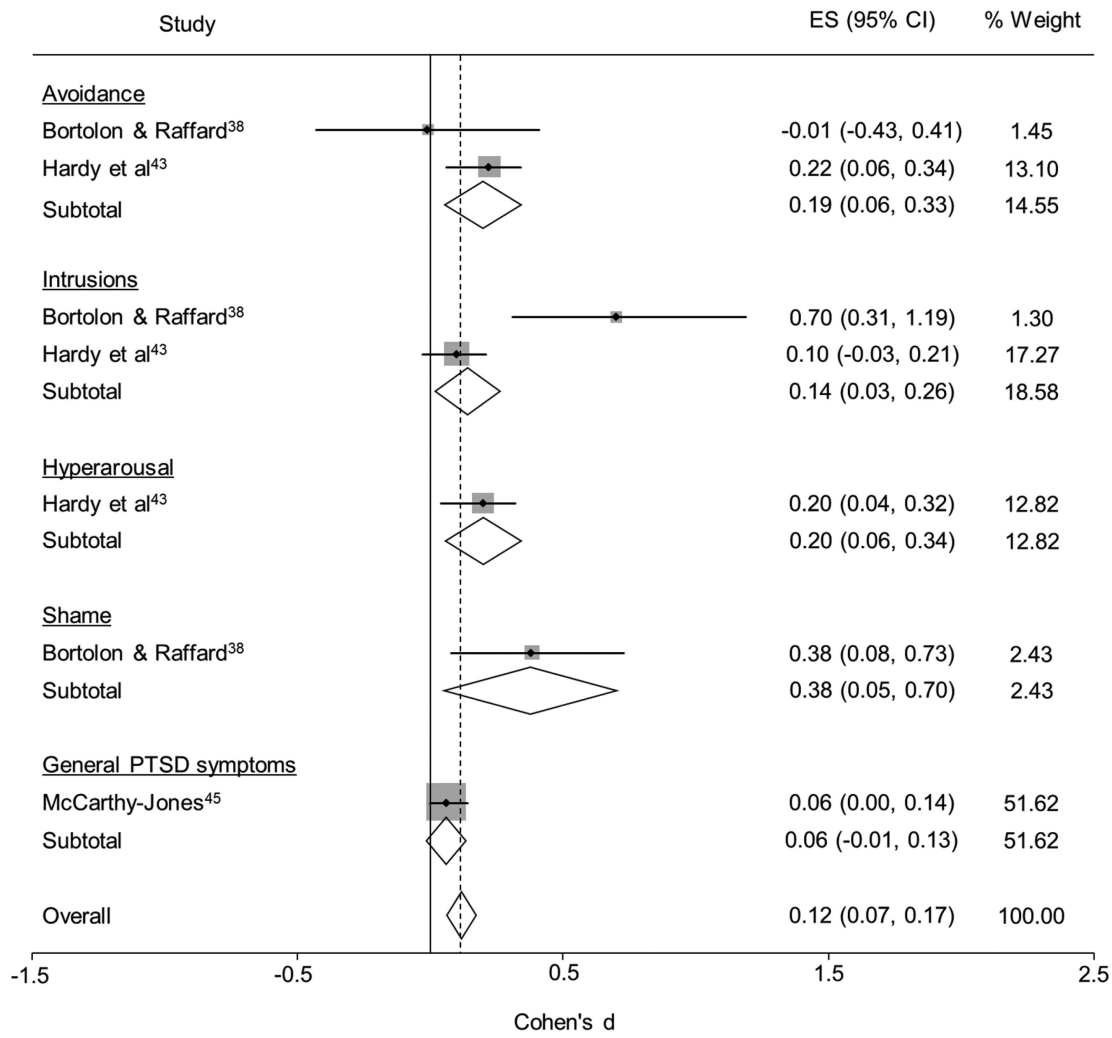

Figure 7 Meta-analysis of post-traumatic stress disorder (PTSD) symptoms as a mediator between developmental trauma and hallucinations in adulthood. Sizes of grey squares represent weights of Cohen's d effect size (ES) according to sample size; horizontal lines indicate 95% CIs; diamonds represent the overall ES and 95% CIs.

to function as an automatic coping (defence) mechanism[55]. The finding that dissociation may be a mediating factor between DT and hallucinations is in keeping with work on trauma and voice-hearing[5,56-59], although not all authors agree[60]. Indeed, there is longitudinal evidence that childhood dissociative experiences are associated with subsequent auditory hallucinations[61]. It has been suggested that dissociation may contribute to the development of hallucinations through decreasing an individual's ability to judge the reality of internal experiences, arguably a form of source attribution error[48,62]. Within this context, non-integrated trauma memories may be externally attributed as "voices" rather than "memories"[63]. In fact, there is recent evidence that dissociation may be a marker of comorbidity of psychosis with PTSD[64]. A further possibility is that voice-hearing in the context of trauma is dissociative rather than psychotic in nature. Within this account, experiences of voices are dissociated or disowned components of the self that result from trauma[65].

DT can alter emotion regulation and stress reactivity, including in individuals experiencing psychosis[66-68]. Our finding that emotional dysregulation plays a mediating role in hallucinations and paranoia is in line with the threat anticipation model[58,59]. Plausible mechanisms include sensitization to environmental stressors[69] and hyperactivity of hypothalamic-pituitary-adrenal (HPA) axis. Increased stress sensitivity is observed across the psychosis spectrum, including non-clinical populations[70], individuals at ultra-high risk of psychosis[71]; and clinical populations with psychotic disorder[67]. HPA axis hyperactivity has been found to precede onset of psychotic disorder[72], and is associated with both abnormal dopaminergic activity and structural changes in the brain[73]. There is also converging evidence that DT causes structural and network connectivity alterations in and between key regions involved in memory and emotional processing, including the hippocampus, the amygdala and anterior cingulate cortex[12]. These accounts are consistent with information processing models, whereby DT-induced brain changes result in greater amygdala-driven processing, im-

paired integration of information processing and more anomalous experiences[74].

Our finding that PTSD symptoms are implicated in the relationship between DT and hallucinations can be interpreted in the light of dominant models of PTSD[21,75]. Under normal conditions, perceptual, emotional and spatiotemporal information is encoded as an integrated contextual engram (representation), which is then perceived as having occurred in the past when the memory is recalled. Under traumatic conditions, perceptual and emotional information is encoded as sensory representations that have not been integrated and lack spatiotemporal information. Trauma memories are stored as unintegrated fragments, which are prone to involuntary retrieval and are re-experienced in an emotionally raw (unprocessed) form in the here and now. Such an account is consistent with findings that hallucinatory content is thematically linked to experiences of trauma[5,54,76-78]. Within this framework, an intrusive trauma memory may be misinterpreted in a psychotic way (i.e., the trauma memory is the anomalous experience that is mis-appraised). Failure of reality testing is a common sequel in PTSD patients[79], and hallucinations and delusions are considered a sign of this[80].

The possibility that PTSD and psychosis in the context of DT have shared underlying mechanisms is consistent with evidence from neuroimaging studies that brain regions including the hippocampus, amygdala and prefrontal cortex are implicated in PTSD[81], and that the structure and functioning of these regions differ between adult DT survivors with psychosis and individuals with psychosis who have not experienced DT[82].

Experiencing DT can understandably result in negative beliefs about the self and others. It has consistently been hypothesized that paranoia and delusions result from disrupted belief systems[83], and our study lends some support to this. Further high-quality research in this area is needed to confirm the view that paranoia and delusions may arise from internalized (learned) negative schemata. It is likely that DT induces alterations in the threat system[12], so that individuals may anticipate threat and danger at significantly lower thresholds than their peers.

Clinical implications

People with psychosis are frequently not asked about their DT histories[87]. This may contribute to low service engagement amongst adult DT survivors with psychosis[87-89]. The situation is compounded by poor responses to initial disclosures of DT, including low referral rates for trauma-related interventions[90]. Clinicians should screen psychotic patients for PTSD, dissociative symptoms and emotional difficulties, and refer them for specialist treatment where available. Clinician leaders should develop effective treatment pathways for people with comorbid PTSD and psychosis. The relationship between psychosis in adult DT survivors and the new ICD-11 diagnosis of complex PTSD (i.e., PTSD plus persistent and pervasive disturbances in affect regulation, self-concept and relational functioning)[91,92] should be investigated.

Several psychotherapeutic and pharmacological interventions are available which target the processes outlined in this review. There is an evidence base for addressing emotional regulation through a range of psychotherapies, including mentalization-based therapy, cognitive-behavioral therapy (CBT) and dialectical-behavioral therapy. Evidence is emerging on successful psychotherapies that can target dissociation[93]. Further work is needed to evaluate these interventions in adult DT survivors with psychosis. There is a growing interest in trauma-focused CBT for psychosis, and the results of currently ongoing multicentre trials are awaited[94]. Regarding pharmacotherapy, medicines already exist that have an evidence base for the treatment of PTSD and are capable to address negative emotional processing biases[95]. Work is needed to investigate whether these agents are effective in reducing psychotic symptoms in this group of patients. Research is also warranted into pharmacological treatments for dissociation.

Strengths and limitations

This study has a number of strengths. It is the first study to systematically examine psychological mechanisms mediating between DT and specific symptoms of psychosis. Furthermore, our search terms were broad, and we did not restrict studies to specific forms of child abuse, leading to the inclusion of a broad range of studies in this area. We also did not limit participant diagnoses, resulting in a transdiagnostic view of psychological processes associated with psychotic experiences.

However, it must be acknowledged that our review has some limitations. Included studies predominantly implemented cross-sectional mediation analyses, precluding inferences on causation. Most studies did not account for confounders when examining the associations between DT, the mediator (psychological phenomena of interest) and the outcome (psychotic experiences). There is a paucity of research using experimental vs. (observational) clinical psychological measures, and work is urgently needed into underlying neurocognitive mechanisms. A number of studies did not specify the type of DT experienced, and we were not able to account for the co-aggregation of experiences of trauma[96]. Furthermore, the majority of the studies relied on questionnaires as trauma measures rather than clinician rated tools. As with other research in the field, given the scarcity of phenomenological rigour in many of the included studies, a limitation lies in clinical diagnostic challenges and difficulties in classifying symptoms (e.g., psychotic vs. dissociative). Finally, our meta-analyses were limited by not including an assessment of publication bias, due to the insufficient number of studies available.

CONCLUSIONS

Our review has found evidence of mediating roles of dissociation, emotional dysregulation and PTSD symptoms between DT and hallucinations. There was also evidence of mediating roles of negative schemata between DT and delusions as well as paranoia. These findings suggest that there may be distinct psycho-

logical pathways from DT to psychotic phenomena in adulthood. However, the existing evidence is mostly based on cross-sectional studies, and more prospective research is needed.

There is a pressing need to elucidate the neurocognitive mechanisms involved and to further phenomenologically understand the subjective experience of DT survivors. Further work is needed to understand the relationships between psychosis in adult DT survivors and the new diagnostic construct of complex PTSD. Understanding the temporal dynamics of the relationships between DT, underlying mechanisms and psychotic symptoms is likely to be key to the development of new treatments and secondary preventive interventions.

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Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States

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Concerns have been expressed that persons with a pre-existing mental disorder may represent a population at increased risk for COVID-19 infection and with a higher likelihood of adverse outcomes of the infection, but there is no systematic research evidence in this respect. This study assessed the impact of a recent (within past year) diagnosis of a mental disorder – including attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, depression and schizophrenia – on the risk for COVID-19 infection and related mortality and hospitalization rates. We analyzed a nation-wide database of electronic health records of 61 million adult patients from 360 hospitals and 317,000 providers, across 50 states in the US, up to July 29, 2020. Patients with a recent diagnosis of a mental disorder had a significantly increased risk for COVID-19 infection, an effect strongest for depression (adjusted odds ratio, AOR=7.64, 95% CI: 7.45-7.83, p<0.001) and schizophrenia (AOR=7.34, 95% CI: 6.65-8.10, p<0.001). Among patients with a recent diagnosis of a mental disorder, African Americans had higher odds of COVID-19 infection than Caucasians, with the strongest ethnic disparity for depression (AOR=3.78, 95% CI: 3.58-3.98, p<0.001). Women with mental disorders had higher odds of COVID-19 infection than males, with the strongest gender disparity for ADHD (AOR=2.03, 95% CI: 1.73-2.39, p<0.001). Patients with both a recent diagnosis of a mental disorder and COVID-19 infection had a death rate of 8.5% (vs. 4.7% among COVID-19 patients with no mental disorder, p<0.001) and a hospitalization rate of 27.4% (vs. 18.6% among COVID-19 patients with no mental disorder, p<0.001). These findings identify individuals with a recent diagnosis of a mental disorder as being at increased risk for COVID-19 infection, which is further exacerbated among African Americans and women, and as having a higher frequency of some adverse outcomes of the infection. This evidence highlights the need to identify and address modifiable vulnerability factors for COVID-19 infection and to prevent delays in health care provision in this population.

Key words: COVID-19, mental disorders, risk of infection, mortality, hospitalization, depression, schizophrenia, ADHD, bipolar disorder, ethnic disparity, gender disparity, access to care, discrimination

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COVID-19 infection has rapidly escalated into a global pandemic, with more than 33 million cases and one million deaths worldwide as to September 30, 2020[1]. Socioeconomic deprivation, older age, and several medical conditions are associated with increased risk for severe COVID-19 disease[2-5].

Mental disorders are estimated to affect 20-25% of the adult population (450 million globally, 47 million in US)[6], and their incidence is likely to have increased during the pandemic, due to a variety of factors[7,8]. Concerns have been expressed that persons with a pre-existing mental disorder may represent a population with an increased risk for COVID-19 infection, and in which the outcomes of the infection are worse[7-10].

Multiple factors have been described that could increase the risk of persons with mental disorders to get COVID infection, or make the outcomes of the infection worse. These include challenges in appraising health information and complying with preventive behaviors, limitations in access to health care, homelessness or living in settings where the risk for contagion is higher[10], and the higher prevalence of comorbid medical conditions that are associated with increased risk for COVID-19 severe illness (such as cardiovascular diseases, cancers, and chronic obstructive pulmonary disease). Despite the recognition of these multiple vulnerability factors, the risk for COVID-19 infection and its outcomes among patients with mental disorders have not been investigated systematically.

Ethnic disparities in mental health and mental health care have been repeatedly documented, especially among minority populations in the US, such as African Americans[11-13]. Gender is also a critical determinant of mental health, due to the differential power and control of men and women over the socioeconomic determinants of their lives, and the different exposure and susceptibility to specific mental health risks[14].

Data from the general population across the US have revealed that COVID-19 infection disproportionately affects African Americans and people with poorer socioeconomic status[15]. Men might have a higher COVID-related mortality, whereas women might be more vulnerable to the socioeconomic and emotional effects of the infection[16-18].

In this study, we analyzed a nation-wide database of electronic health records of 61 million adult patients in the US, aiming to assess the impact of a recent (within past year) diagnosis of a mental disorder – including attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, depression and schizophrenia – on the risk for COVID-19 infection and related mortality and hospitalization rates. We also evaluated how these risks were affected by ethnicity and gender.

METHODS

Design and study population

We conducted a case-control study using de-identified population-level electronic health records data collected by the IBM

Watson Health Explorys from 360 hospitals and 317,000 providers across 50 states in the US, representing 20% of US population[19].

The electronic health records were de-identified according to the Health Insurance Portability and Accountability Act, and the Health Information Technology for Economic and Clinical Health Act standards, so that the approval by an institutional review board was not needed. After the de-identification process, curation process normalized the data through mapping key elements to widely-accepted biomedical terminologies and standards[20], including the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) for disease coding[21,22].

More than 160 published studies have used this large-scale and standardized database and the cloud-based Explorys Cohort Discovery informatics tools to study a variety of conditions, including cardiovascular diseases, cancers, neurological diseases, infectious diseases, and substance use disorders[23]. Recently, we have used this database for drug discovery[24,25] and for COVID-19 research in patients with substance use disorders[26].

In the present study, the status of COVID-19 was based on the concept "coronavirus infection (disorder)" (SNOMED-CT code 186747009), while that of mental disorder was based on the diagnosis of "mental disorder (disorder)" (74732009). The status of type of disorder was based for ADHD on the diagnosis of "attention deficit hyperactivity disorder (disorder)" (406506008); for bipolar disorder on the diagnosis of "bipolar disorder (disorder)" (13746004); for depression on the diagnosis of "depressive disorder (disorder)" (35489007); and for schizophrenia on the diagnosis of "schizophrenia (disorder)" (58214004). The SNOMED-CT concept "hospital admission (procedure)" (32485007) was used to obtain hospitalization status. The status of "death" was based on the Social Security Death index that Explorys regularly imports.

We examined the impact of mental disorders on the risk of COVID-19 infection, adjusted for age, gender, ethnicity, and common medical comorbidities. The exposure groups were patients diagnosed with a mental disorder; the unexposed groups were patients without the mental disorder; and the outcome measure was the diagnosis of COVID-19.

We then explored how demographic factors affected COVID-19 infection risk among patients with mental disorders. The case groups were patients with a mental disorder and one of the following factors: female, senior (i.e., >65 years), African American. The comparison groups were patients with a mental disorder and one of the following corresponding factors: male, adult (i.e., 18 to 65 years), Caucasian. The outcome measure was the diagnosis of COVID-19.

We finally investigated the rates of death and hospitalization among patients with COVID-19 infection and a mental disorder, compared to patients with COVID-19 infection but no mental disorder, and to patients with a mental disorder but no COVID-19 infection.

Statistical analysis

The adjusted odds ratio (AOR), 95% CI and p values were calculated using the Cochran-Mantel-Haenszel method[27], controlling for age groups (adults, seniors), gender (female, male), ethnicity (Caucasian, African American), and medical comorbidities such as cancers, cardiovascular diseases, type 2 diabetes, obesity, chronic kidney diseases, chronic obstructive pulmonary disease, asthma, and substance use disorders.

Two-sided, two-sample tests for equality of proportions with continuity correction were used to compare outcomes. Statistical tests were conducted with significance set at $p<0.05$ (two-sided). All analyses were done using R, version 3.6.3.

RESULTS

Patient characteristics

The demographic characteristics of the study population are presented in Table 1. Among 61,783,950 patients (age ≥18), 11,240,580 had a lifetime diagnosis of a mental disorder (within past year or prior) and 1,307,720 had a recent diagnosis (within past year) (lifetime diagnosis: 18.2%, recent diagnosis: 2.1% of study population).

The specifics for lifetime and recent diagnosis were as follows: lifetime 1,030,790, recent 99,230 (1.7% and 0.2% of study population, respectively) for ADHD; lifetime 930,280, recent 87,270 (1.5% and 0.1%, respectively) for bipolar disorder; lifetime 6,237,350, recent 610,710 (10.1% and 1.0%, respectively) for depression; lifetime 275,950, recent 26,510 (0.5% and 0.04%, respectively) for schizophrenia.

Among 15,110 COVID-19 patients in the database, 5,450 had a lifetime diagnosis of a mental disorder (past year or prior, but prior to COVID-19 diagnosis), and 3,430 had a recent diagnosis of a mental disorder (past year, but prior to COVID-19) (lifetime: 36.1%, recent: 22.7% of COVID-19 population). Lifetime and recent diagnosis for specific disorders in the COVID-19 population were highest for depression (lifetime: 18.0%, N=2,720; recent: 9.7%, N=1,460); followed by ADHD (lifetime: 2.7%, N=400; recent: 1.5%, N=220); bipolar disorder (lifetime: 2.1%, N=310; recent: 1.2%, N=180); and schizophrenia (lifetime: 0.8%, N=120; recent: 0.5%, N=80).

Associations between mental disorders and COVID-19

Patients with a recent diagnosis of a mental disorder had significantly higher odds of COVID-19 infection than patients without a mental disorder, after adjusting for age, gender and ethnicity, with the strongest effect for depression (AOR=10.43, 95% CI: 10.10-10.76, $p<0.001$) and schizophrenia (AOR=9.89, 95% CI: 8.68-11.26, $p<0.001$) (see Figure 1). The trend was similar for patients with a lifetime diagnosis of a mental disorder, but the risk associations were lower (e.g., AOR=2.01, 95% CI: 1.96-2.06, $p<0.001$ for depression; AOR=1.48, 95% CI: 1.33-1.65, $p<0.001$ for schizophrenia). For the rest of the analyses, we focused on patients with a recent diagnosis.

After adjusting for medical comorbidities (cancers, cardiovascular diseases, type 2 diabetes, obesity, chronic kidney diseases, chronic obstructive pulmonary disease, asthma, and substance use disorders), in addition to age, gender and ethnicity, the odds

Table 1 Characteristics of the sample

	Study population	With mental disorder (lifetime)	With mental disorder (recent)	With COVID-19	With COVID-19 + mental disorder (lifetime)	With COVID-19 + mental disorder (recent)
Total	61,783,950	11,240,580	1,307,720	15,110	5,450	3,430
Gender						
Female	33,654,480 (54%)	6,899,010 (61%)	838,380 (64%)	8,980 (59%)	3,730 (68%)	2,380 (70%)
Male	27,758,960 (45%)	4,301,060 (38%)	449,290 (34%)	6,090 (40%)	1,710 (32%)	1,040 (30%)
Unknown	371,040 (<1%)	40,590 (<1%)	20,060 (2%)	30 (<1%)	10 (<1%)	0
Age						
Adult (18-65 years)	43,933,300 (71%)	7,684,520 (68%)	934,500 (71%)	11,290 (75%)	3,680 (68%)	2,240 (65%)
Senior (>65 years)	17,896,950 (29%)	3,570,470 (32%)	374,950 (29%)	3,820 (25%)	1,770 (32%)	1,190 (35%)
Ethnicity						
Caucasian	35,096,550 (57%)	8,506,170 (76%)	990,000 (76%)	7,550 (50%)	3,150 (58%)	1,980 (58%)
African American	6,389,510 (10%)	1,238,820 (11%)	160,480 (12%)	6,310 (42%)	2,030 (37%)	1,280 (37%)
Asian	1,008,180 (2%)	139,810 (1%)	14,260 (1%)	150 (1%)	40 (1%)	20 (1%)
Hispanic/Latino	859,970 (1%)	101,120 (1%)	7,970 (<1%)	10 (<1%)	0	0
Unknown	7,959,570 (12%)	1,361,290 (12%)	111,090 (8%)	790 (5%)	330 (6%)	230 (7%)

of COVID-19 infection among patients with a mental disorder decreased, but remained highly significant (see Figure 2). Once again, the strongest effect was for depression (AOR=7.64, 95% CI: 7.45-7.83, p<0.001), followed by schizophrenia (AOR=7.34, 95% CI: 6.65-8.10, p<0.001), ADHD (AOR=5.82, 95% CI: 5.46-6.20, p<0.001), and bipolar disorder (AOR=5.72, 95% CI: 5.35-6.10, p<0.001).

Demographic disparity of risk for COVID-19 infection among patients with recent diagnosis of a mental disorder

Among patients with a recently diagnosed mental disorder, African Americans had a higher risk for COVID-19 than Caucasians, after adjusting for age, gender and medical comorbidities, with the strongest ethnic disparity for depression (AOR=3.78, 95% CI: 3.58-3.98, p<0.001), followed by schizophrenia (AOR=2.33, 95% CI: 1.84-2.97, p<0.001), bipolar disorder (AOR=2.23, 95% CI: 1.90-2.61, p<0.001), and ADHD (AOR=2.00, 95% CI: 1.64-2.43, p<0.001) (see Figure 3).

Women with a recent diagnosis of a mental disorder had higher odds of COVID-19 infection than men after adjusting for age, ethnicity and medical comorbidities, with the strongest gender disparity for ADHD (AOR=2.03, 95% CI: 1.73-2.39, p<0.001), followed by schizophrenia (AOR=1.53, 95% CI: 1.21-1.94, p<0.001), bipolar disorder (AOR=1.34, 95% CI: 1.14-1.58, p<0.001) and depression (AOR=1.29, 95% CI: 1.22-1.37, p<0.001).

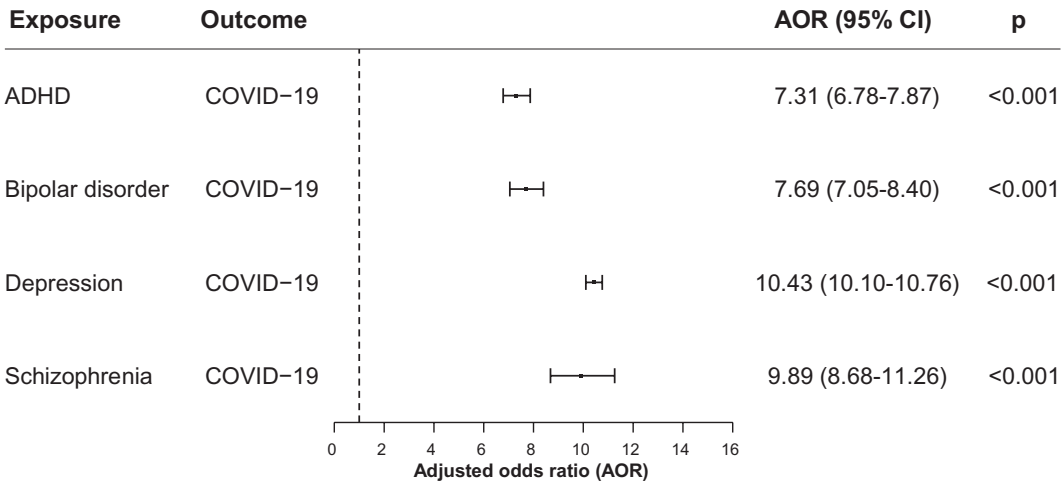

Figure 1 Association of recent (within past year) diagnosis of a mental disorder and COVID-19 infection after adjusting for age, gender and ethnicity. ADHD – attention-deficit/hyperactivity disorder

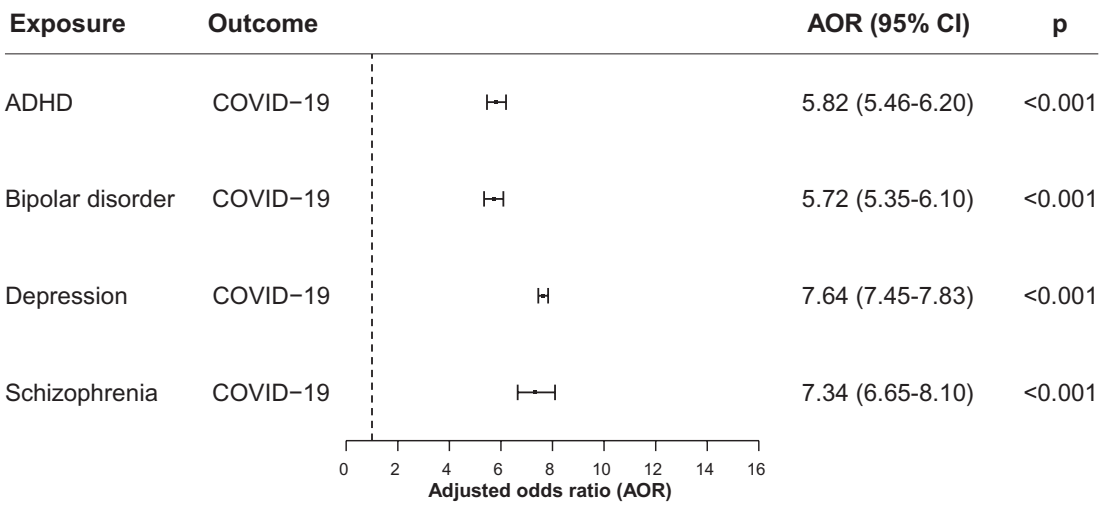

Figure 2 Association of recent (within past year) diagnosis of a mental disorder and COVID-19 infection after adjusting for age, gender, ethnicity, and medical comorbidities (cancers, cardiovascular diseases, type 2 diabetes, obesity, chronic kidney diseases, chronic obstructive pulmonary disease, asthma, and substance use disorders). ADHD – attention-deficit/hyperactivity disorder

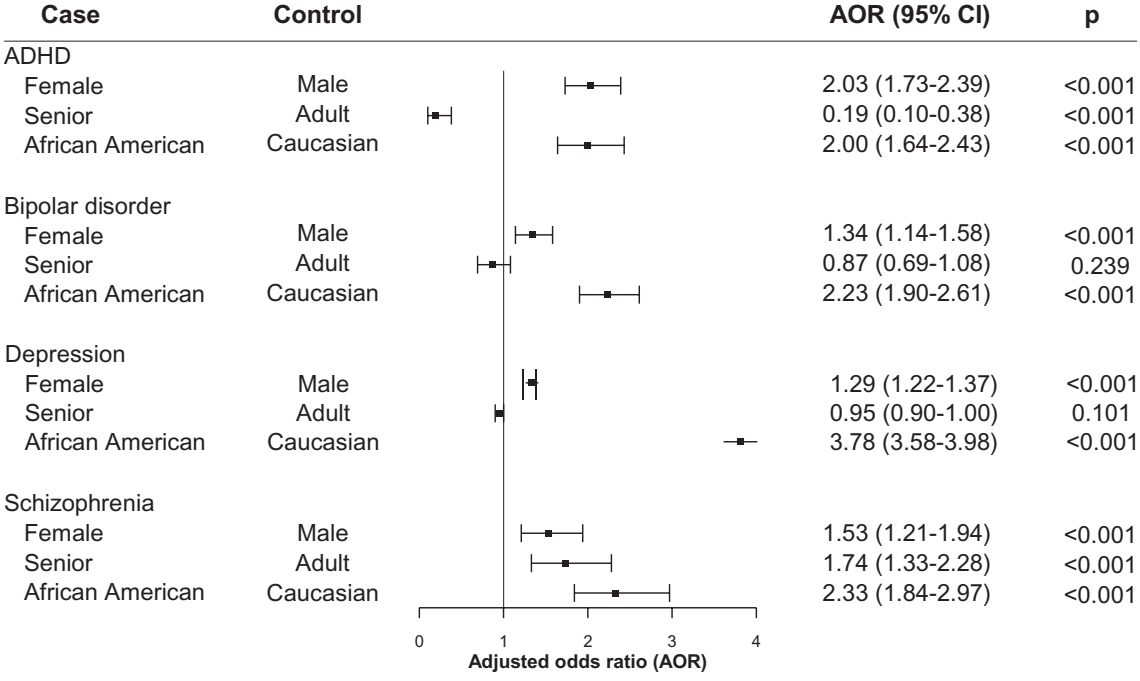

Figure 3 Effects of demographics on odds of COVID-19 infection among patients with a recently diagnosed mental disorder after adjusting for medical comorbidities (cancers, cardiovascular diseases, type 2 diabetes, obesity, chronic kidney diseases, chronic obstructive pulmonary disease, asthma, and substance use disorders). ADHD – attention-deficit/hyperactivity disorder

Age had significant effects on COVID-19 risk, after adjusting for gender, ethnicity and medical comorbidities, among patients with a recent diagnosis of ADHD (patients >65 years had a lower risk than those aged 18-65 years; AOR=0.19, 95% CI: 0.10-0.38, p<0.001), and schizophrenia (patients >65 years had a higher risk than those aged 18-65 years; AOR=1.74, 95% CI: 1.33-2.28, p<0.001) (see Figure 3).

Rates of death and hospitalization among COVID-19 patients with a recent diagnosis of a mental disorder

The death rate in the 15,120 COVID-19 patients was 5.7%, being higher for African Americans (6.2%) than for Caucasians (3.7%) (p<0.001), and higher for men (6.6%) than for women (3.4%) (p<0.001).

Among the 3,430 adults with both COVID-19 and a recent diagnosis of a mental disorder, 290 died (death rate of 8.5%), with similar rates for African Americans (8.6%) and Caucasians (8.6%), but higher rates for men (12.5%) than for women (6.7%) (p<0.001).

Among the 1,460 patients with both COVID-19 and a recent diagnosis of depression, 120 died (death rate of 8.2%), with similar rates for African Americans (9.6%) and Caucasians (8.1%), and higher rates for men (13.9%) than women (6.4%) (p<0.001).

The death rate for patients with both a recent diagnosis of a mental disorder and COVID-19 infection (8.5%) was higher than for patients with COVID-19 infection but no mental disorder (4.7%) (p<0.001), and for patients with a mental disorder but no COVID-19 infection (1.4%) (p<0.001).

The overall hospitalization rate in the 15,120 COVID-19 patients was 20.8%, being higher for African Americans (27.3%) than Caucasians (12.7%) (p<0.001), and higher for men (21.6%) than women (16.5%) (p<0.001).

Among the 3,430 patients with both COVID-19 and a recent diagnosis of a mental disorder, 940 were hospitalized (27.4%). The rate was higher for African Americans (33.6%) than for Caucasians (24.8%), and for men (36.5%) than for women (23.5%) (p<0.001).

Among the 1,460 patients with both COVID-19 and a recent diagnosis of depression, 380 were hospitalized (26.0%), and the rate was higher for African Americans (32.7%) than for Caucasians (23.3%) (p<0.001), and for men (33.3%) than for women (23.6%) (p<0.001).

Overall, the hospitalization rate for patients with both a recent diagnosis of a mental disorder and COVID-19 infection (27.4%) was higher than for patients with COVID-19 infection but no mental disorder (18.6%) (p<0.001) and for patients with a mental disorder but no COVID-19 infection (13.8%) (p<0.001).

DISCUSSION

Based on an analysis of a nation-wide database of electronic health records in the US, we document that patients with a recent (within past year) diagnosis of a mental disorder have a significantly higher risk for COVID-19 infection as compared to patients without mental disorders, and also present a worse outcome as evidenced by higher rates of hospitalization and death. The risk for COVID-19 infection among those with a recent diagnosis of a mental disorder is further increased among African Americans and women, though death and hospitalization rates are higher in men. These findings identify individuals with mental disorders as a highly vulnerable population for COVID-19 infection and its adverse outcomes, and confirm the ethnic and gender disparities already observed in the general population.

A variety of factors are likely to contribute to the higher risk for COVID-19 infection and worse outcomes of the infection in people with mental disorders. These people may have problems to appraise health information and to comply with preventive behaviors[10]. Their life circumstances place them at higher risk for living in crowded hospitals or residences, or even in prisons, and these are environments where infections can disseminate rapidly[10]. People with serious mental illness are likely to be socioeconomically disadvantaged, which might force them to work and live in unsafe environments. Homelessness and unstable housing may affect their ability to quarantine. Stigma may result in barriers to access health care for patients who are infected with COVID-19, or make them reluctant to seek medical attention for fear of discrimination[28].

Specific manifestations of individual mental disorders might influence risk differently. For example, in the case of patients with ADHD, their inattention might place them at higher risk for forgetting to wear face masks or maintaining social distancing, whereas in individuals suffering from depression their amotivation might lead them to neglect protecting themselves or seeking medical attention when indicated, and in a patient with schizophrenia the delusional thinking might lead him/her to reject the use of a face mask. On the other hand, the higher sensitivity to stress, which is common among patients with mental disorders, will make it harder for them to cope with the uncertainties, isolation and economic challenges linked with the COVID-19 pandemic, increasing their risk for relapse and disease exacerbation[7,10].

Individuals with mental disorders are also at higher risk for taking drugs and for suffering from a substance use disorder than the general population. In particular, tobacco smoking is highly prevalent among those with schizophrenia, bipolar disorder and depression compared to the general population[29,30]. Moreover, patients with mental disorders who are smokers smoke more heavily than those who do not have a mental disorder[31], which accentuates their risk for pulmonary pathology, making them more vulnerable to severe COVID-19 disease. Indeed, a higher risk for adverse outcomes related to the association of COVID-19 and smoking has been reported[32,33]. In a recent study based on an analysis of electronic health records data, we documented that patients with a recent history of tobacco smoking had increased odds (AOR=8.22) for COVID-19 infection[26].

People with severe mental disorders are more likely to suffer from comorbid medical conditions associated with higher risk for severe COVID-19 illness[10]. Indeed, our analyses showed that medical comorbidities (cancers, cardiovascular diseases, obesity, chronic kidney diseases, asthma, chronic obstructive pulmonary disease, type 2 diabetes, and substance use disorders) contributed to the higher COVID-19 infection risk in patients with a recent mental disorder, as evidenced by the reduction of risk after adjusting for these comorbidities. However, even after this adjustment, the risk for COVID-19 infection in patients with recent mental disorders was still increased, indicating that these disorders directly affect COVID-19 susceptibility.

Overlapping biological factors among mental disorders and COVID-19 infection could also be implicated. An example of a common biological factor that contributes to various mental disorders and to COVID-19 pathology is inflammation, which is reported to play a role in the pathogenesis of depression[34], schizophrenia[35] and bipolar disorder[36], as well as in the systemic manifestations of COVID-19 infection[37].

Our analyses revealed that African Americans with depression, bipolar disorder, schizophrenia and ADHD had higher risk for COVID-19 infection than Caucasians even after controlling for medical comorbidities, indicating that social, behavioral and lifestyle factors also contribute to this profound ethnic inequality. Women with ADHD, bipolar disorder, depression and schizophrenia had higher risk for COVID-19 infection, though lower rates of death and hospitalizations than men, which could reflect either a higher risk for infection or a higher likelihood of being tested. However, socioeconomic factors contribute to gender disparities in health and are likely to have also influenced gender disparities in COVID-19 infection rates. The much higher risk of death for men than women in general, but prominently for patients with depression and COVID-19 infection, could similarly reflect biological as well socioeconomic factors.

Patients with both COVID-19 infection and a recent diagnosis of a mental disorder had an increased risk of death (8.5% versus 5.7% for all COVID-19 patients and 4.7% for COVID-19 patients without a recent mental disorder), which again may result from delays in getting medical attention, medical comorbidities, and a variety of socioeconomic and disease-related factors. The difference in death rate of COVID-19 patients with mental disorders compared to all COVID patients (48% higher) is similar in magnitude to the difference we recently reported for COVID-19 patients with substance use disorder (45% higher)[26]. However, in that prior study, using electronic health records data up to June 15, 2020, we reported a higher death rate from COVID-19 infection than in the current study, which used data up to July 29, 2020 (6.6% vs. 5.7%), which is likely to reflect the decline in COVID-19 mortality attributed in part to better disease management, increased testing and shifts in the patient population[38].

Patient electronic health records data may have limitations when used for research purposes, including limited information on time-series, socioeconomic and lifestyle determinants[39-41]. Moreover, COVID-19 is regularly tested at drive-up and pop-up sites, so it is likely that many cases, particularly asymptomatic ones, were not captured by electronic health records. Third, findings from this study are correlational, not causal, and need to be validated in other patient databases or populations.

Despite these limitations, our analysis of a large nation-wide database provided evidence of an increased COVID-19 infection risk among patients with mental disorders, exacerbated by ethnic and gender disparities, and of higher mortality and hospitalization rates in COVID-19 patients with a recent diagnosis of a mental disorder. Our results identify mental disorders as a health risk factor for COVID-19 infection and its adverse outcomes, emphasizing the need to recognize and address modifiable vulnerability factors and to prevent delays in health care provision in this population.

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Challenges to mental health services for refugees: a global perspective

Considerable progress has been made over recent decades in formulating models of care and implementing mental health and psychosocial support (MHPSS) services for refugees worldwide[1]. The challenges in providing services to this population are being greatly increased by the COVID-19 crisis. At the same time, the World Health Organization has provided impetus to supporting refugees, including in the MHPSS field, by adopting a Global Action Plan extending over the next four years[2]. It is timely, therefore, to draw on the lessons of past decades to consider what steps will assist in advancing MHPSS services for refugees around the globe.

The principles underpinning all MHPSS activities in this field are well established, including a commitment to human rights, cultural integrity and right to regain autonomy of all refugees. Moreover, communities need to be empowered to participate in, and where possible lead, MHPSS programs, a principle that focuses central attention on capacity building and skills development in all MHPSS activities.

Guidelines in place for over a decade also direct attention towards the subpopulations in need of special MHPSS attention, including those with severe and disabling mental disorders, and those with more common forms of traumatic stress, mood and anxiety disorders. Also well documented are the core MHPSS activities, including the provision of generic community mental health services, structured psychotherapy programs, and non-clinical psychosocial programs aimed at promoting self-help and resilience in the community as a whole[3].

The immediate challenge facing the field, however, revolves around the issue of scarcity of resources, a constraint that requires careful matching of selective components to the most urgent MHPSS needs of each population. The size of the population need underscores this principle. A record 80 million persons currently are displaced, representing one percent of the world's population. The majority are internally displaced or asylum seekers in countries where MHPSS services are at a low level of development.

Pooled epidemiological data indicate that, on average, 30% of these populations experience ongoing symptoms of depression, anxiety and/or post-traumatic stress disorder (PTSD)[4], and one in 10 meet criteria for moderate or severe forms of mental disorder[5]. Even discounting these numbers based on natural remission, the size of the population in need of MHPSS services far exceeds the skills base and material resources available to provide equitable interventions at a global level.

Systematic baseline assessments facilitate the process of priority-setting and include consideration of the community's exposure to persecution, violence and loss; the point in the trajectory of displacement where the population is located; the inherent cultural and social strengths and skills base of each group; the threats, assets and enablers for social and economic recovery in the immediate context; and the availability of external support for MHPSS services.

The difficulty is that, in real life situations, many influences dictate the choice of interventions in any setting, including the idiosyncratic preference of donors, lobby groups or implementing agencies. Standardization of assessments, systematic decision-making and transparency in the process would greatly facilitate a more rational allocation of resources in each setting.

In the early aftermath of humanitarian crises, persons with mental illness manifesting bizarre or disorganized behaviour are at high risk of abandonment and neglect, falling physically ill, being injured or assaulted, or experiencing abuse and exploitation. Psychiatric diagnosis is only a broad indicator of need, given that individuals with a wide range of problems may reach a point of social crisis in these settings. As a consequence, services need to be prepared to deal with a range of people, including those with psychotic disorders; delirium or dementia; depression and other emotional disorders; medically unexplained somatic complaints; and adjustment disorder associated with self-harm or dangerous behaviours[6]. In some settings, mental health services are also the only source of intervention for persons with epilepsy, alcohol and substance use disorders, and intellectual disability or developmental disorders.

Low-cost mobile emergency teams led by psychiatrists and other mental health professionals, supported by community health teams of workers provided with intensive training and ongoing supervision, can provide psychotropic medications and social and family support in these unstable settings, averting the need for inpatient care except in the extreme instances.

In more stable environments, such as refugee camps or urban settings, it may be feasible to introduce more systematic programs of psychological therapies for PTSD, complicated grief reactions, and other common mental disorders such as depression. Models of psychotherapy tend to apply overlapping techniques derived from cognitive behavioural and other evidence-based strategies used in high-income countries, although adapted to the local culture and context[7]. Some programs are based more explicitly on cultural concepts of mental health and/or psychosocial models that are specific to refugees[8]. The use of operationalized training and treatment manuals, and the recruitment of indigenous lay or primary health care workers to administer therapies under supervision, add to the logistic feasibility and cost-containment of these programs. Typically, supervision is provided on site and continued via remote, digital communication by expatriate professionals.

In general, these interventions have produced positive outcomes in the short term[8], but less is known about whether these effects are maintained over time. The capacity to embed these programs securely within routine community services also needs to be demonstrated. However, the early success of these programs represents a milestone in demonstrating the potential for MHPSS services to make a major contribution to the overall

humanitarian relief effort.

In high-income countries, refugees constitute two distinct populations based on immigration policy: permanent refugees, who receive full access to public mental health and resettlement services, and asylum seekers without permanent residency status, who are subjected to restrictions and, in some cases, held in detention for prolonged periods of time[9]. In some settings, only permanent refugees have access to MHPSS services provided by specialist refugee agencies. An extensive body of research has demonstrated that the post-migration living difficulties experienced by asylum seekers exert a detrimental effect on their mental health, both in the short and medium term. Moreover, practitioners in the field confront major obstacles and ethical challenges in attempting to provide optimal care to this group.

It is vital that the field ensures that the basic principles of human rights and equity are upheld in planning MHPSS services in the future. A global focus requires that careful decisions are made regarding the allocation of resources, in order to provide equitable access to MHPSS services. Given the vagaries of funding, there is a temptation to focus on populations and contexts that most readily garner support by donor countries and other sources. As an exemplar of practice in the humanitarian field, the MHPSS community needs to counteract this tendency, by arguing assertively for the equitable distribution of resources to all those in need. At the front-line, it is vital to uphold the principles of ethical practice, and support colleagues in so doing, especially when working in politically charged situations.

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Public attitudes towards migrants: understanding cross-national and individual differences

Immigration has become an enduring feature of many societies in the world. Additionally, during the recent refugee crisis, countries in the Middle East accommodated millions of people, and Europe received around 1.5 million new asylum claims. Although there are important legal differences among categories of migrants, in public perception the term typically is viewed to also include refugees and asylum seekers.

Public attitudes towards immigration have become a major societal issue. These attitudes can influence policy makers, and settling into a supportive or rather more hostile environment makes a difference for immigrants' adjustment and mental health. Countries and individual citizens vary widely in their views about immigration and immigrants[1]. In social sciences, an increasing number of empirical studies on these attitudes are being conducted, although predominantly in Western societies.

A host of factors appear to drive people's attitudes towards immigration. They are difficult to isolate and also tend to affect each other. In general, however, public attitudes differ depending on contextual factors, migrant characteristics, and personal characteristics.

First, countries differ in their average support to immigration and their level of polarization. For example, people in North America tend to hold more positive views towards immigration than Europeans, and East Europeans tend to be more negative than West Europeans[1]. Furthermore, the public in some countries is consensually rather hostile toward immigration (i.e., Czech Republic, Hungary), while other countries are internally quite divided (e.g., The Netherlands, Norway), or consensually rather supportive (Canada, New Zealand)[2].

There are various reasons for these country differences, including the country's immigration and emigration history, the political context, the immigration and integration policies, the size of the immigrant population, and its composition in terms of country of origin, religion, and level of educational and work skills[3].

Second, in their immigration policies, countries often make distinctions between types of migrants – e.g., Western and non-Western; European Union (EU) and non-EU immigrants – and the public tends to do the same. Public attitudes are, for example, more negative towards immigrants who are culturally less similar, such as Muslims in Europe[4].

Additionally, newcomers who are considered to have migrated voluntarily (i.e., labor migrants) face more negative public attitudes than involuntary migrants (i.e., refugees). Migrants who have chosen themselves to migrate often elicit feelings of threat and anger, and therefore more negative reactions, whereas refugees may elicit humanitarian concerns and feelings of empathy, and therefore more positive responses[5].

Third, some sections of the population are supportive of immigrants and refugees, while other sections are rather negative or even hostile. In general, more positive attitudes are found among the higher educated and political liberals, who tend to have a more cosmopolitan orientation, experience little competition and threat from migrants, and more strongly value open-

ness, change and cultural diversity. Furthermore, the perception that migrants make a valuable contribution to society and the experience of positive contacts with migrants are predictors of more favorable attitudes[3,5].

In contrast, stronger national attachment, feelings of relative deprivation, perceived economic competition and cultural threats, and an authoritarian predisposition in which conformity to social norms is central, explain anti-immigrant sentiments[3]. Additionally, the perception that immigrants are a burden on society and challenge the *status quo*, and the direct exposure to massive increase in arrivals of refugees, increase hostility towards newcomers.

From a person x context interaction perspective, it can be expected that the role of these personal factors be not uniform. Psychological characteristics will matter more under some conditions than others. For example, people with an authoritarian predisposition are particularly prone to react with increased negativity towards culturally dissimilar immigrants (non-Western, Muslims), who are perceived as normative threatening, rather than towards culturally similar immigrants (Western, Christian). Another example is that people who have economic concerns and worries about crime are more negative towards Eastern European immigrants, whereas those who perceive cultural or terrorism-related threats have more negative views towards Muslim immigrants[6].

Additionally, individual differences matter more for anti-immigrant attitudes when the proportion of immigrants is higher, the economic situation is declining, and the ideological climate in society is dominated by hierarchy enhancing and *status quo* preserving norms and values[7]. Further, stronger national attachment tends to be associated with stronger anti-immigrant attitudes in non-settler countries, but not in settler countries in which cultural diversity is a constitutive norm of the national identity. Information about immigrants can invoke both feelings of threat and countervailing humanitarian concerns, whereby the former can override the latter, but also the latter can override the former[8]. System justification motivations can be used by politicians and policy makers to garner support for refugees (e.g., "Open hearts and welcoming communities: it's the Canadian way"[9]).

In general, research has demonstrated that people tend to overestimate the number of immigrants and refugees entering their country, and that subjective perceptions are much more important for people's attitudes than actual changes and events. This means that how public policies are being framed and how immigrants are depicted in the media and by politicians is important. It matters whether newcomers are described as a potential threat to the host society or rather as making a valuable contribution and being in need of help.

Apart from those with very strong positive or negative views about immigration, most people are struggling with the challenges and uncertainties that the arrival of large numbers of newcomers imply. Taking their concerns and doubts seriously is critical for broadening public support for immigration and refugee settlement.

Public opposition to immigration can be a major social and political disruptive force and has negative implications for the opportunities of newcomers. Understanding what drives individuals to be positive or rather negative towards immigrants, and when and how the various psychological determinants become less or more important for their attitudes, is crucial for trying to avoid the divisive consequences of migration and increase the successful accommodation of newcomers.

Mass immigration is a global phenomenon affecting most countries, and there is much at stake for societies, communities and individuals, including the mental health of newcomers.

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The impact of social network sites on mental health: distinguishing active from passive use

Social network sites are part of modern life. With over 2.7 billion monthly active users, Facebook is the most popular social network site, though Instagram is rapidly catching up (particularly among adolescents and young adults), with over one billion monthly active users. Other widespread social network sites include Twitter and LinkedIn. Worldwide, people spend on average more than two hours on social network sites each day, sharing billions of messages[1].

Social network sites are a subcategory of social media, which are characterized by three features[2]. Specifically, social network sites allow users to: a) create a personal profile, b) generate a list of online connections, and c) traverse a stream of frequently updated information (e.g., Facebook's News Feed). Many social network sites combine these features with a range of other functions, allowing their users to play games, chat, purchase goods, join groups, or advertise.

The massive adoption of social network sites and the many functions they offer may suggest that using them only has benefits. However, the rapid adoption of social network sites has been accompanied with a growing public concern that these sites undermine rather than enhance people's mental health. In response, a large number of studies examined whether this concern is justified.

Initial research provided mixed evidence, with some studies showing positive effects of social network sites on mental health indicators, while others revealed negative or non-significant effects. However, these studies adopted cross-sectional designs, which do not speak to how social network sites impact mental health indicators over time.

To overcome this hurdle, we conducted an experience sampling study[3]. Experience sampling involves text-messaging participants multiple times per day for several days, asking them to report on their current thoughts, feelings or activities (e.g., use of social network sites). This method is considered the golden standard to measure behavior and emotional experiences over time within the context of everyday life. Using this approach, we demonstrated that Facebook use predicts declines in mental health over time[3].

Follow-up longitudinal studies, large-scale experimental research and meta-analyses converged on the conclusion that use of social network sites has a negative, albeit small and possibly reciprocal, relationship with mental health[4]. Unfortunately, these results have led some media to conclude that social network sites are inherently bad and should be avoided at all costs.

Social network sites allow for a wide range of activities, and evidence is accumulating that their impact critically depends on how the technology is used. A key distinction pertains to active versus passive use[5]. Active use refers to activities that facilitate direct exchanges with others, and encompasses both targeted one-on-one exchanges (i.e., direct communication) and non-targeted exchanges (i.e., broadcasting). Passive use refers to monitoring the online life of other people without engaging in direct exchanges with them. While active use is mainly about information production (e.g., posting a status update or sending private messages on Facebook), passive use deals with information consumption (e.g., scrolling through news feeds or looking at other users' profiles).

We conducted an experience sampling study to examine the possible differential impact of active and passive Facebook use on mental health[5]. We found that passive use predicted a decline in affective well-being over time, while active use did not influence well-being. Follow-up studies provided further evidence for a negative (possibly reciprocal) relationship between passive use of social network sites and mental health, and revealed that certain subcategories of active usage can have a positive effect on mental health[6].

Overall, these findings illustrate that social network sites are not "good" or "bad". Their mental health consequences critically depend on how these sites are used. Unfortunately, usage statistics reveal that passive use is more frequent than active use, which implies that many people use social network sites in a suboptimal manner[5].

Why do active and passive use differentially impact mental health? Many psychological mechanisms have been proposed, but social comparison and social capital accrual are the two mechanisms that have been implicated most frequently[7].

Social comparison refers to upward (i.e., other is better) and downward (i.e., self is better) comparisons with other people on a particular dimension (e.g., appearance or success). People tend to portray a rosy picture of themselves on social network sites, by predominantly sharing their successes rather than their failures[3,5]. Passively consuming this so-called success theatre often results in upward social comparisons, and associated feelings of envy or inferiority. A large number of studies has confirmed that the negative impact of passive use of social network sites on mental health is indeed driven by damaging social comparisons[7].

Social capital accrual is often proposed to underlie the positive impact of active use of social network sites on mental health. Social capital accrual is further broken down in bridging (i.e., access to new information and perspectives typically provided by weak ties) and bonding (i.e., emotional and instrumental support typically provided by strong ties). Facebook's mission statement to "give people the power to build community and bring the world closer together" reflects the potential of social network sites to increase social capital. Consistently, a number of studies show that the positive consequences of active use on mental health are driven by increases in social capital[7].

In sum, do social network sites threaten our mental health? The literature suggests that much depends on whether their use is active or passive, unless there are signs of social network site addiction[8], or cyberbullying is involved. When engaging actively with social network sites, one may feel more connected, which positively influences mental health. In contrast, passive use of social network sites is negatively related to mental health, especially when this use results in feelings of envy or inferiority rather than social connection.

Future research examining subcategories of active and passive use, as well as research on additional explanatory psychological processes (e.g., distraction, multi-tasking, information overload, and social displacement)[9] is needed to further refine our understanding of the impact of social network sites on mental health.

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PHQ-9: global uptake of a depression scale

Depression is the most prevalent mental disorder, a greater cause of disability than any other disease, and a major contributor to direct and indirect health care costs[1]. In the absence of a laboratory or imaging test, eliciting patient symptoms by clinical interview or a self-report scale is the principal way to detect depression and monitor its response to treatment.

First published in 2001, the Patient Health Questionnaire 9-item depression scale (PHQ-9) has had global dissemination, with over 11,000 scientific citations and translations into more than 100 languages. It has been used in hundreds of clinical and population-based studies, incorporated into numerous depression guidelines, and implemented in many clinical practice settings. Depression screening is far from universal; however, where it occurs, the PHQ-9 is a leading scale[2].

The international spread of the PHQ-9 is likely due to multiple factors[3]. Its nine items comprise the DSM criteria for depressive disorders, making it both a severity and potentially diagnostic measure. The total score is a simple summation of item scores, and cut-points are easy to memorize: 5, 10, 15, and 20 represent thresholds for mild, moderate, moderately severe, and severe depressive symptoms, respectively. Unlike some depression scales, the PHQ-9 is free to use as a public domain measure, and the many translations make it accessible to populations around the world.

The PHQ family includes several abbreviated versions and companion scales[4]. The PHQ-2 is an ultra-brief screener that comprises the first two items (depressed mood and anhedonia), which are core criteria for depressive disorders. The PHQ-8 omits the ninth item that asks about thoughts of "being better off dead or of hurting yourself in some way". Although conventionally considered a screening question for suicidal ideation, most positive responses represent endorsement of the first part of this compound item (i.e., being better off dead) rather than active thoughts of self-harm[5,6]. Because the ninth item is the least frequently endorsed one, PHQ-8 and PHQ-9 scores are nearly identical, as are severity cut-points[7].

The PHQ-8 is sometimes used in studies where depression is a secondary outcome and not the focus of the investigation, in population-based studies where interviews are administered by non-mental health professionals, or in clinical settings where patient-reported outcomes (PROs) are captured outside of an office visit, causing delays in clarifying positive responses to the ninth item.

Companion scales evaluate common fellow travelers of depression. The P4 is a 4-item measure that evaluates suicidal ideation in individuals who endorse the ninth item of the PHQ-9[6]. The Generalized Anxiety Disorder 7-item (GAD-7) measures anxiety symptoms that co-occur in a third to half of patients with depression. Although initially developed for generalized anxiety disorder, the GAD-7 is also an effective screener for panic, social anxiety, and post-traumatic stress disorders[4]. The PHQ-15 and its abbreviated version (the Somatic Symptom Scale-8, SSS-8) assess the presence and severity of physical symptoms that are the complaints with which depressed patients most frequently present, and may denote concurrent somatic symptom disorder and other somatizing conditions[8]. Finally, the PHQ-4 consists of the PHQ-2 and the GAD-2 (abbreviated version of the GAD-7) and serves as an ultra-brief screener for depression and anxiety as well as general psychological distress. The PHQ family of scales, including many translations, are available at www.phqscreeners.com.

Practical issues still constrain use of depression and other PRO measures in some clinical settings. Routine administration by the clinician or ancillary staff and manual entry of scores into the health records require time that is typically unreimbursed. The PHQ-9 and other PROs generally do not require an interview but rather can be self-administered using a variety of modes (e.g., paper or web-based forms, iPads, apps) before an office visit or while at home. Completed PROs can then be electronically imported or scanned into the records.

Whereas universal depression screening is advocated by some guidelines, the optimal frequency of screening is not established. One approach is to screen all new patients and then annually in established patients. Because screening every patient at every visit is excessive, reminders of when screening is due are required.

Another key role of depression measures is to monitor outcomes in response to active treatment of depression or, in some cases, watchful waiting. Again, flagging which patients require follow-up PHQ-9 administration must be operationalized.

One critique of scales like the PHQ-9 is that depression is not simply a number. Certainly, a depression score alone should not generate a reflexive depression diagnosis or antidepressant prescription, but requires clinical evaluation to determine if the threshold for clinical action has been reached. The length of time symptoms have been present, the degree of functional impairment, and patient treatment preferences, combined with the severity of symptoms as denoted by the depression score, collectively inform treatment decisions, be it psychotherapy, medications, or watchful waiting.

When following depression longitudinally, it is useful to couple the PHQ-9 score with a question about global change: "Are your symptoms the same, better, or worse?". Discordance between the depression score and global impression of change may have several explanations, including residual somatic symptoms such as insomnia or fatigue; co-occurring symptoms such as anxiety or pain; other medical or psychiatric comorbidity; stress or interpersonal factors; or a lag in functional improvement.

Is a universal depression measure necessary? The PHQ-9 has generally been shown to be similar or superior in performance to competing depression scales, including in special populations such as older adults, adolescents, pregnant or postpartum women, diverse racial/ethnic groups, patients with various medical and psychiatric diseases, and across clinical settings. Nonetheless, a number of depression scales are available and have their proponents, and methods for cross-walking depression scores

across measures are increasingly available[9].

Incorporating PROs into practice is less about the specific measure (presuming it is well validated) than the act of measuring; it is more about the verb than the noun. On the other hand, using a common measure may facilitate communication across clinical settings and avoid the Tower of Babel phenomenon wherein different "languages" (i.e., metrics) are used for the same condition.

Uptake of the PHQ-9 in the past two decades has paralleled the increasing recognition of depression as an international public health priority, and the discovery that measurement is the first step towards detection and improved management. In the words of M. Chan, former director of the World Health Organization, "accountability means counting; what gets measured gets done". Ditto for depression.

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Estimating the real-world usage of mobile apps for mental health: development and application of two novel metrics

Mobile apps for health and wellness (mHealth apps) have the potential to expand access to information and support, especially for people who are unable to access face-to-face care. The role of these apps is becoming especially salient during the ongoing COVID-19 crisis. According to recent estimates, there are over 325,000 mHealth apps, with 78,000 added in 2017 alone[1]. Estimating the effectiveness of these apps has become a topic of great interest[2,3].

Few studies have examined the extent to which mHealth apps reach real-world users. Some recent work suggests that mHealth app marketplaces may be highly skewed, with a small number of apps attracting a large share of users[4]. To rigorously test this assumption, an empirical characterization of asymmetry in mHealth markets is needed. Existing approaches, while useful, often lack an intuitive or easily interpretable meaning[5]. This presents a challenge that is especially important in the context of mental health research, which requires communication between experts from a variety of disciplines (e.g., psychiatry, clinical psychology, digital health, economics, public policy).

We examined the dissemination of mHealth apps for a variety of mental health conditions, searching the Apple App Store and Google Play Store in March 2020. We applied the following search terms: "addiction", "anxiety", "depression", "eating disorders", "fitness", "mood tracking", "schizophrenia", and "sleep". Consistent with previous work, apps within the top 50 search hits on either app store were screened[4]. We included apps designed to offer treatment, support or information.

We collected monthly active user (MAU) data from Mobile Action, a mobile app market research firm, for a one-month period from March 14, 2020 to April 13, 2020. Total MAUs per category ranged from 264,763 (addiction) to 47,133,801 (fitness), with a median of 6,254,650. We then developed two novel metrics to characterize the mHealth app marketspaces: the market share index-n (MSI-n) and the number needed to reach-p (NNR-p).

The MSI-n refers to the percentage of MAUs in a category (e.g., depression apps) that is accounted for by the top n apps. For example, "MSI-3" refers to the percentage of MAUs that is accounted for by the three most popular apps. Higher MSI values indicate that the top apps are responsible for a greater proportion of active users.

The NNR-p refers to the minimum number of apps that are needed to account for p percentage of active users. For example, "NNR-90" refers to the number of apps that are required to account for 90% of MAUs in a category. Lower NNR values indicate that the top apps are responsible for a greater proportion of active users.

For each of the above-mentioned categories, we calculated the MSI-3, MSI-10 and NNR-90.

In six of the eight categories, the top three apps were responsible for more than 50% of MAUs. The MSI-3 values were 41.5% for fitness (indicating that the top three apps accounted for 41.5% of MAUs in the fitness category), 45.6% for addiction, 66.2% for depression, 66.4% for sleep, 75.7% for anxiety, 79.2% for mood tracking, 88.9% for eating disorders, and 98.1% for schizophrenia, with a median MSI-3 value of 71.1%. The median MSI-10 value was 91.4% (ranging from 67.6% for fitness to 99.97% for schizophrenia).

The NNR-90 values were 2 for schizophrenia (indicating that the top two schizophrenia apps accounted for 90% of MAUs), 4 for eating disorders, 6 for mood tracking, 7 for anxiety, 11 for depression, 12 for addiction, 16 for sleep, and 25 for fitness. The median NNR-90 value was 9.

Thus, app marketplaces for mental illnesses (e.g., schizophrenia, eating disorders) were more asymmetrical than those for overall health and wellness (e.g., fitness, sleep).

These findings have important implications for the study and evaluation of mHealth apps. To better characterize the content that real-world users encounter through these apps, we recommend that usage data be incorporated to adjust the findings of mHealth app reviews[6]. Additionally, there are over 45 app evaluation frameworks, and there has been enormous interest in developing tools that help consumers sift through crowded app marketplaces[7,8]. However, the reliability and validity of such tools has been criticized, as many of them yield different and sometimes conflicting conclusions[8].

Due to overwhelming volume of mHealth apps and app evaluation methods, it is not surprising that such issues arise: investigators commonly evaluate hundreds or thousands of apps, a labor-intensive process that can yield cursory or unreliable evaluations. Given the skewness of mHealth app marketplaces, consumers may benefit more from highly detailed and reliable evaluations of a much smaller number of apps – those that they are most likely to encounter and use[9].

The exact number of popular apps may vary by mHealth category. To account for this, investigators could apply the MSI-n and NNR-p metrics. For example, using the NNR-p metric, investigators can determine how many apps, in a given category, should be evaluated in order to account for those that reach a certain proportion of active users.

We collected MAU data in March-April 2020. This allowed us to characterize patterns of use during the COVID-19 pandemic, a period in which mHealth apps are playing an essential public health role. Future research could examine if these trends generalize during other time periods.

Merging research on the efficacy of mHealth apps with that on usage will be appropriate to accurately estimate the real-world impact of these apps, determine research priorities, and inform the public about benefits and risks. Such a body of research could meaningfully change the way we study and evaluate mHealth apps, advancing a key priority in the digital health field that is likely to affect millions of consumers in the years ahead.

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The retention challenge in remote therapy and learning seen through the lens of the COVID-19 pandemic

What does the popularity of social media "unfriending", "blocking" and "ghosting" communicate about the success potential for online psychological treatment and online education? This question has been brought to the fore by the COVID-19 pandemic and the resultant transition to remote delivery for much of clinical care and teaching.

Online psychotherapy and education platforms represent rapidly adaptable, convenient substitutes and are playing an important role in helping stressed communities traverse the trauma. As we increasingly rely on these remote alternatives, however, it is crucial to anticipate and mitigate against a recurrent problem suggested by pre-pandemic scholarship: very poor retention.

Although this challenge has been borne out in studies of both online therapy[1] and online education[2], these fields have been mutually insular and have not benefited from each other's experience in addressing this common foe. This issue has been recently highlighted in the specialized education literature[3]. Here, we explore it for a mental health audience, since, besides learners and educators, countless online patients and therapists also stand to gain from retention-enhancing design.

Telemental health services vary greatly, including by specific technology used, intervention type, degree of provider involvement, and target population and diagnosis. During the pandemic, video-mediated consultations have become particularly common. Up until that point, the best studied telemental health intervention had been digitally-enabled self-help, typically inspired by cognitive behavioral therapy and incorporating little or no therapist involvement. The poor retention associated with the latter has been widely documented, including in one early[4] and one more recent[5] landmark studies that showed disappointing completion rates of 0.5% and 18%, respectively.

The same limitation is borne out in studies of remote learning. When massive open online courses (MOOCs) first appeared nearly 10 years ago, they were heralded as the long awaited antidote to education disparities. Through low-cost courses delivered online by renowned educators to a worldwide audience, they promised to democratize high-quality education like never before and challenged the very premise of location-bound learning, regardless of topic or discipline. Universities would become obsolete, went the optimistic prediction[6]. This echoed the older promise that therapist-optional digitally-enabled self-help would dramatically increase access to care by correcting provider shortages, especially in underserved areas and communities.

The euphoria – 2012 was dubbed "the year of the MOOC"[6] – was short-lived, in no small measure due to a stubborn retention problem that has been revealed in several studies. Among them, a landmark analysis of 565 MOOCs delivered by the Massachusetts Institute of Technology and Harvard University to 5.63 million learners showed completion rates that ranged from 3.13% to 5.91% across academic years[7]. Also disappointing was the finding that MOOC completers tended to be socio-economically advantaged, not the in-need learners at the margins of global education that MOOCs hoped to reach[6]. Already by 2013, the world was declared "MOOC'd out"[6].

Retention, of course, is not the only metric by which to measure the success of online therapy and education; even if retention is poor, a massively popular intervention or course still means that many users can benefit[3]. Also, today's pandemic-dictated platforms are typically much smaller, less impersonal, more interactive and better coached than the typical self-paced online therapy or MOOC of yore, suggesting that retention may be a less relevant problem with current offerings. Still, there is reason to be concerned about user engagement on today's platforms, due to characteristics that seem inherent to broader online psychology.

Online, regardless of the specific activity, inattention and distractibility seem like perennial obstacles and ever present personality features. Already in 2008, a British Library investigation of scholars' online reading behavior described it as "promiscuous", "horizontal", "volatile" and "squirrelling"[8]. Given today's obsession with such analytics as "visitor conversion", "page views", "bounce rate" and "scroll depth", it would be safe to assume that this problem has worsened as Internet-related technologies have grown more sophisticated and distractions have multiplied[3].

A weak attachment to content has parallels in the weak bonds that characterize many online relationships, further suggesting a

medium-wide commitment shortage present across online platforms and pursuits. In that sense, online information-seeking may not be fundamentally different from online befriending. From "blocking" to "unfollowing", "unfriending" and "ghosting", the abundance and popularity of online relationship-terminating functions and behaviors speak to this phenomenon.

Relatedly, attention-deficit/hyperactivity disorder is very commonly diagnosed in individuals with pathological Internet use, variably defined[9]. However, with the pace of online life, competition from countless sites, visual and auditory stimuli meant to drive traffic, and difficult-to-ignore "alerts" and "notifications", one need not suffer from pathological Internet use to appreciate an Internet-inattention link that seems like an intrinsic characteristic of online psychology.

The difficulty sustaining attention online, the weakness of online bonds and the weak commitment to online content suggest an environment-wide retention challenge that would be crucial to address in two activities where focus and commitment are indispensable: psychotherapy and education. To that end, various mitigating factors that have been proposed[3] in the mental health and education literature to enhance retention would seem very relevant in the COVID-19 era.

These include nurturing a medium-defying bond between patient/student and therapist/teacher; participative goal-setting that views users as collaborative partners; a hybrid or blended approach that integrates some in-person contact into remote delivery; underscoring the credentials of remote therapists/teachers so they may be taken more seriously by users; inclusive design elements that reflect the diversity of platform users; and "gamification", which borrows from video game development to increase platform engagement.

Moving therapy and education out of their traditional, time-honored settings in response to the pandemic has allowed the continued provision of mental health care and saved the academic year. But our knowledge of Internet psychology, as well as data from studies into digital self-help platforms and MOOCs, suggest that online mental health treatment and teaching cannot yet be considered an interchangeable, quality-assured alternative to conventional practice. Well-documented challenges with retention highlight this as a real obstacle to be fully investigated and addressed before online therapy and education can be embraced as reliable long-term solutions.

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Mental health problems among COVID-19 survivors in Wuhan, China

The COVID-19 pandemic is profoundly impacting mental health worldwide[1-3]. Wuhan, China has been the first city to experience the emergency of COVID-19 and its high hospitalization and casualty rates, as well as the mandatory curfews that were strictly enforced for infection control, with their significant mental health implications[4]. Although a large number of hospitalized COVID-19 patients recovered and met the clinical criteria for discharge, we hypothesized that mental health problems would occur as major sequelae among COVID-19 survivors.

A total of 4,328 hospitalized COVID-19 patients who met relevant clinical criteria[5] were discharged between January 18 and March 29, 2020 from five hospitals in Wuhan, China (Wuhan No.1 Hospital, Wuhan Wuchang Hospital, Hubei Provincial Hospital of Traditional Chinese Medicine, Hubei Provincial Hospital of Integrated Chinese and Western Medicine, and Wuhan Pulmonary Hospital).

All these COVID-19 survivors (median age: 59 years, interquartile range, IQR: 47-68 years; 54.1% female) were followed up and assessed by mental health care specialists. The evaluation period started on the date of hospital discharge and continued through July 28, 2020. Among the survivors, 156 (3.6%) dropped out at some point of the follow-up.

The validated Chinese versions of the Patient Health Questionnaire-9 (PHQ-9)[6] and the Generalized Anxiety Disorder-7 (GAD-7)[7] were administered to evaluate post-discharge depression and anxiety.

As a reference group, 1,500 randomly selected individuals from the general population of Hubei province were assessed using the same instruments during the same time frame. Chi-square tests were used to compare the prevalence of mild-to-severe mental health problems in the two samples. Among COVID-19 survivors with depression or anxiety, logistic regression analysis was applied to test whether several variables (including age, gender, education, income level, comorbid chronic physical diseases, and retesting positive for SARS-CoV-2) influenced the severity of the mental health condition.

The study was approved by the institutional ethics board of Tongji Medical College, Huazhong University of Science and Technology. All participants provided their informed consent.

The median duration of the follow-up period was 144.0 days

(IQR: 135-157). During this period, 615 COVID-19 survivors (14.2%) were found to have clinically defined depression (i.e., a score of at least 5 on the PHQ-9) and 528 (12.2%) to have clinically defined anxiety (i.e., a score of at least 5 on the GAD-7). Four survivors attempted suicide. Compared to the reference group, the risk of both depression and anxiety in COVID-19 survivors was significantly higher (relative risk, RR=1.2, 95% CI: 1.1-1.4, p=0.002; and RR=1.4, 95% CI: 1.2-1.7, p=0.001, respectively).

Among the 615 survivors with depression, the risk for a severe condition (i.e., a score of at least 10 on the PHQ-9) was significantly higher in individuals living alone (odds ratio, OR=5.2, 95% CI: 3.6-7.1, p<0.001), in females (OR=3.4, 95% CI: 2.8-5.3, p<0.001), in those with a low income level (OR=2.4, 95% CI: 1.8-3.5, p=0.012), in those with a comorbid chronic physical disease (OR=2.8, 95% CI: 2.1-3.7, p=0.032), and in those who retested positive for SARS-CoV-2 (OR=10.4, 95% CI: 8.3-12.5, p<0.001). Age did not significantly influence the severity of depression.

Among the 528 COVID-19 survivors with anxiety, the risk for a severe condition (i.e., a score of at least 10 on the GAD-7) was significantly higher in individuals with a low educational level (OR=3.5, 95% CI: 3.1-4.2, p<0.001), in unmarried subjects (OR=1.7, 95% CI: 1.2-2.8, p=0.025), and in those who retested positive for SARS-CoV-2 (OR=4.7, 95% CI: 3.7-5.8, p<0.001). Age, gender and other social status indices did not influence the severity of anxiety.

All the four COVID-19 survivors who attempted suicide were elderly, had retested positive for SARS-CoV-2, and had experienced severe levels of depression and anxiety.

In summary, this follow-up study documents that mental health problems among COVID-19 survivors in Wuhan are significantly more common than in the general population of the Hubei province. Risk factors for more severe mental health problems include retesting positive for SARS-CoV-2, living alone, female gender, comorbid chronic physical diseases, and low education and income levels. Clinicians and policy makers should be aware of the risk of mental health sequelae in COVID-19 survivors and implement appropriate preventive and treatment measures.

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Differential impact of COVID-related lockdown on mental health in Germany

The World Health Organization declared COVID-19 outbreak a global pandemic on March 11, 2020. Following the rapid and uncontrollable course of the pandemic, many governments decided to massively restrict public and private life to prevent further spread of the virus. Especially the measures to enforce "physical distancing" during the "lockdown" can be seen as a global macrostressor affecting a major part of mankind in an unprecedented manner.

Lockdown can have manifold psychosocial consequences, including unemployment and precarious economic situations, marital and familial discord, and domestic violence. Subsequent psychological responses, such as feelings of loneliness, anger or preoccupation about the future, are likely. This was picked up by mass media as well as experts[e.g.,1], warning the public about possible negative effects of the lockdown on mental health.

While many speculations and hypothetical considerations arose, there is a paucity of empirical real-world data. Initial *ad-hoc* studies have been conducted quickly, reporting high incidence of negative mental health outcomes, such as depression and anxiety[e.g.,2]. Thereby, reports inferred detrimental consequences for the mental state of the general population.

However, those studies have several shortcomings. Most of them applied cross-sectional designs, which may capture very transient symptoms rather than long-lasting fluctuations in mental states, and do not allow comparison with pre-lockdown measures. Also, the questionnaires that were used are often only screening tools rather than in-depth assessment instruments. In contrast, more meaningful insights can be gathered from longitudinal studies built on continuous, detailed assessments of mental health before and during the lockdown.

We present here extensive data on behavioral and mental health changes in relation to the lockdown of public life in Germany. We capitalize on a population-based, prospective, longitudinal cohort study termed LORA (Longitudinal Resilience Assessment[3]), conducted in the Rhine-Main region since 2017. Its main aim is investigating resilience – i.e., the ability to maintain mental health despite difficult life circumstances – in initially healthy adults (assessed by the Mini International Neuropsychiatric Interview[4]). After an extensive baseline evaluation, major life events, micro-stressors in the form of daily hassles, and mental

health status (primary outcome, assessed by the German version of the General Health Questionnaire, GHQ-28[5]) are recorded every three months using an online monitoring system.

The pandemic and the lockdown during the ongoing study provided a unique natural experiment for investigating how initially mentally healthy subjects respond to a major macro-stressor. Lockdown started in Germany on March 22 and was gradually relaxed from May 6 onwards. We immediately increased the sampling rate of our LORA study to once per week, the first assessment taking place on March 31. Ethical approval was obtained from the ethical review boards of the University Hospitals of Mainz and Frankfurt.

Data presented here are from the first eight weeks of the weekly assessments, compared to the last measurement time point in LORA prior to lockdown. Almost half of the overall sample (N=523) contributed data; this sample was not significantly different from the complete initial one.

The sample consisted of 69% females, and had a mean age of 31.5±8.4 years. Among participants, 47.8% were cohabitating with a partner and 22.8% had children under 18 years; 40.9% were working full-time and another 34.8% were studying or undergoing a professional training. Six participants were positively tested for SARS-CoV-2 since mid-March, and 57 had to undergo strict quarantine. As much as 362 participants worked and studied from home during lockdown.

Overall, the number of daily hassles per week *decreased* from an average of 60.0±27.2 prior to the lockdown to 41.2±22.3 at week 8. This decrease was significant when comparing pre-lockdown values to those at weeks 1-4 (t_{508}=13.5, p<0.001) and weeks 5-8 (t_{475}=17.7, p<0.001). Parallel to this, mental health status significantly *improved* over the entire post-lockdown period, indicated by a decrease of GHQ-28 mean values from 20.5±9.7 before lockdown to 16.8±7.6 averaged across weeks 1-4 (t_{508}=7.8, p<0.001), and to 16.2±7.1 averaged across weeks 5-8 (t_{474}=8.8, p<0.001).

A quadratic latent growth mixture model revealed the existence of three subpopulations among the study sample, with distinct mental health trajectories from pre-lockdown through week 8 of the assessment. Group 1 (8.3% of the sample, mean age 28.0±5.9 years, 86.8% female) showed high initial mental dysfunction values, that increased until week 3 and then decreased, returning to the baseline level by week 6 of the assessment. Group 2 (83.6% of the sample, mean age 31.7±8.5, 66.7% female) maintained or improved their mental health during the entire assessment period. Group 3 (8.1% of the sample, mean age 32.7±9.2, 73.7% female) significantly deteriorated in mental health from week 3 onwards.

The overall reduced amount of daily hassles and increase of mental health scores is, at first sight, counterintuitive. However, our analyses revealed subpopulations differentially affected by the pandemic. For Groups 1 and 2, the lockdown measures resulted in reduced mundane stress-inducing factors, such as less commuting or reduced workload. Thus, these groups experienced a short-term reduction of micro-stressors. However, in our sample of initially mentally healthy participants, we identified a susceptible group, whose mental health deteriorated over the course of the assessment. The existence of this "vulnerable group" may explain the rise in mental disorders seen in some cross-sectional studies: while the majority of people cope well with the consequences of the pandemic (at least if the economic impact is buffered against), a subgroup of individuals is susceptible to adversities and develops mental health problems.

Vulnerability towards such lockdown effects might be higher in people already suffering from psychiatric disorders, or in elderly populations with impoverished social networks. Indeed, Group 1 of our study had significantly younger participants than the other two ($F_{2,520}$=4.0, p=0.02). Further, it is likely that socioeconomic challenges and risk factors such as unemployment or poverty, less powerful in Germany than in many other countries, will have later negative influences.

Our results indicate that unspecific, general interventions may not be the optimal response to lockdown measures. Resources should rather be allocated to early identification and support of particularly vulnerable individuals in times of crisis. Future studies should quantify risk and especially protective factors playing a role in coping with the stressors of the current pandemic, followed by tailored interventions targeting the identified factors in susceptible individuals to prevent the manifestation of mental disorders.

In sum, we refute the undifferentiated view that lockdown *per se* has a negative effect on mental health. Rather, it affects a vulnerable group of individuals, while the vast majority of people remain healthy or even improve their mental well-being, as everyday stressors are reduced.

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Glucocorticoid use and risk of suicide: a Danish population-based case-control study

Suicide is an important public health problem, with nearly 800,000 people dying worldwide every year. The World Health Organization has declared suicide prevention an international priority[1]. Glucocorticoid treatment is prevalent and beneficial for many chronic diseases[2], but also associated with severe psychiatric adverse effects[3].

Evidence on an association between glucocorticoid treatment and suicide is sparse[4,5]. A study conducted in patients registered at UK general practices[4] pooled suicides and suicide attempts, although acknowledging that they represent two different phenomena that may or not be related. Persons treated with oral glucocorticoids were 7-fold more likely to attempt or die from suicide shortly after initiation of treatment, compared to persons with the same underlying conditions who did not receive these medications. A Canadian case-control study[5], focusing on people aged 66 years or more, found an unadjusted odds ratio of 1.33 (95% CI: 0.88-2.00) for the association of glucocorticoid use and suicide. There is a need to confirm the association between glucocorticoid use and suicide in a large sample representative of the general population, and to evaluate whether the association depends on glucocorticoid administration form, time since initiation of glucocorticoid treatment, and underlying medical conditions and comorbidities.

We examined the association between glucocorticoid use and suicide in a registry-based population-based case-control study in Denmark in the period between January 1, 1995 and December 31, 2015 (cumulated population of 7,559,392 persons). From the Danish Register of Causes of Death[6], we identified 14,028 suicide cases, and from the Civil Registration System[7] we sampled 140,278 population controls using risk-set sampling and matching by birth year and sex. The suicide date served as the index date for cases and controls.

We used the Danish National Prescription Registry, covering all Danish pharmacies[8], to identify all prescriptions for glucocorticoids redeemed by cases and controls before their index date, and defined present, recent and former users of glucocorticoids as individuals who redeemed their most recent glucocorticoid prescription 0 to 90 days, 91 to 365 days, and more than 365 days before the index date, respectively. We further divided present users into new (individuals who redeemed their first-ever prescription ≤90 days before their index date) and prevalent (individuals who redeemed their most recent prescription ≤90 days before their index date and had a prior prescription redemption ever). The cumulative dose of most recent oral glucocorticoid prescription was calculated to assess a dose-response effect based on prednisolone equivalents.

We examined oral glucocorticoids as well as injectable glucocorticoids, inhaled glucocorticoids, and glucocorticoids administered topically in the intestine. For the locally acting glucocorticoids, we considered only exclusive use of each type. As regard covariates, we used the Danish Health Registries[7] to obtain information on treatment indications (obstructive pulmonary disease, rheumatic diseases, renal diseases, inflammatory bowel disease, skin diseases, other autoimmune diseases, and cancer), comorbidities (psychiatric diseases, cardiovascular diseases, diabetes, osteoporosis, alcohol-related disorders), and co-medication use (opioids and antiepileptic medications).

We used logistic regression to estimate crude and adjusted incidence rate ratios (IRRs) for suicide among present, new, prevalent, recent and former users of glucocorticoids compared to never users. As we used risk-set sampling, the estimated odds ratios from the logistic regression provided unbiased estimates of the IRRs[9]. We found that cancer modified the association and therefore stratified our analyses by cancer. We further estimated incidence rate differences using a back-calculation method.

Median age for both cases and controls was 53 years, and 72% were men; 10% of cases and 7.3% of controls had a prior cancer diagnosis, and 67% of cases and 20% of controls had a prior psychiatric disease.

New use of oral glucocorticoids was associated with a 7-fold increased risk of suicide in individuals with cancer (adjusted IRR=7.2, 95% CI: 5.0-11), and with a 2-fold increased risk in individuals with other treatment indications (adjusted IRR=2.0, 95% CI: 1.5-2.8), compared to never use. The rate differences were 7.6 per 10,000 person years (95% CI: –1.7 to 17) and 1.4 per 10,000 person years (95% CI: –8.9 to 12), respectively.

The median cumulative dose of most recent oral glucocorticoid prescription was higher among individuals with cancer than without (2,000 mg vs. 500 mg prednisolone equivalents), and we found a dose-response effect. Adjusted IRRs for suicide according to the prednisolone-equivalent cumulative dose of most recent prescription were 1.2 (95% CI: 0.36-4.0) for dose <250 mg; 3.0 (95% CI: 1.2-7.8) for 250-499 mg; 3.4 (95% CI: 1.9-6.2) for 500-999 mg, and 20 (95% CI: 10-41) for doses ≥1000 mg, compared to never use.

The association was consistent across treatment indications and comorbidities, stronger among people below 30 and above 50 years of age, and similar among men and women. Recent and former use of oral glucocorticoids, as well as other administration forms (inhaled, injectable, and topically in the intestine), were not associated with suicide. Other administration forms have lower bioavailability, lower systemic absorption and are often used in lower doses compared to systemic glucocorticoids, which may explain these findings.

We conducted several sensitivity analyses. Residual confounding by disease severity cannot be entirely ruled out. However, our results remained robust to confounding by cancer stage and timing. We calculated E-values to examine the impact of potential unmeasured confounding. The E-value indicated that an unmeasured confounding factor needed to be associated with both glucocorticoid use and suicide with a relative risk of 14 and 3.4,

in cancer and non-cancer patients respectively, to fully explain our findings (i.e., only strong confounding could explain our data).

We concluded that oral glucocorticoid initiation was associated with suicide in a dose-dependent manner, with findings of a 7-fold increased risk in cancer patients and a 2-fold increased risk in patients treated for other medical conditions. The particularly strong association in individuals with cancer may be explained by high-dose treatment.

Given the widespread use of glucocorticoids, our study deserves clinical and public health attention. Awareness of the association between new use of oral glucocorticoids and suicide may enhance prevention efforts for an extremely serious global public health problem.

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Suicide-related Internet search queries in India following media reports of a celebrity suicide: an interrupted time series analysis

On June 14, 2020, media reported that Sushant Singh Rajput, a 34-year-old male Bollywood star, had died by suicide. He had starred in television and cinema for over a decade, with highly prominent roles that reached a broad cross-section of the community, including playing the Indian cricket team captain M.S. Dhoni in a blockbuster 2016 biographical film.

This suicide has generated widespread media coverage, including reports about hanging as the suicide method and the actor's struggle with depression. The event has sparked immediate concerns about possible imitation suicides. Due to the long delays in the release of suicide data, it may take some time before we are able to assess any impact on suicidal behaviour. However, it is possible to assess how the public responded in terms of online searching behaviours.

Social learning plays an important role in suicide. The Werther effect hypothesizes that a suicide can become a stimulus for subsequent imitation suicides, which can be exacerbated in cases of celebrity suicide and by irresponsible media reporting. A recent meta-analysis[1] estimated that the risk of suicide increased by 13% in the period after media reports of celebrity suicide; when the suicide method was reported in the media, there was an associated 30% increase in deaths by the same method, highlighting that media ought to be highly cautious in this regard.

On the other hand, the Papageno effect hypothesizes that media can report on suicide in ways that stimulate protective effects. Research has primarily examined the protective effects of reporting on people who have been suicidal and have drawn on internal or external resources to avoid progressing to an attempt[2], but it is recommended that media can assist in more ways, such as highlighting the role that mental ill-health can play in suicide crises and the supports that are available[3].

A substantial amount of social learning now happens online, and suicide research has recently been focusing on Internet search queries as one component of understanding online social learning exposures and interest in a topic[4]. For example, one study observed a 19% increase in worldwide Google suicide queries in the 19 days following the release of the TV series *13 Reasons Why*[5], and that event was associated with a 13% increase in youth suicides in the US[6]. Given these findings, we might expect that Internet search query volumes could yield insights into suicide trends over time in the context of celebrity suicides that receive a high level of media coverage.

We examined changes in Internet search queries in India in the three weeks following the suicide, compared to the two preceding years. We obtained weekly data on relative search volumes from Google Trends (https://trends.google.com/trends) for a series of search terms for the time period from June 13, 2018 to July 4, 2020. English search terms were adapted from those documented in a review of suicide-related Google Trends studies[4]. We included putatively harmful search terms ("suicide", "commit suicide", "how to suicide", "hanging", "how to hang") as well as protective terms that may reflect a stimulation of suicide/depression awareness ("suicide prevention", "depression", "suicide helpline", "depression doctor", "psychiatrist", "antidepressants"). We also collected data for a selection of Hindi search terms, including "aatmahatya" (suicide), "khudkushi" (suicide) and "avsaad" (depression).

Due to small day-to-day variations in data obtained through Google Trends, we followed validated methods[4] and repeated our search on seven consecutive days between August 3 and 9, 2020

and used the average for our analyses. To investigate whether weekly search volumes had changed since the suicide of Sushant Singh Rajput, relative to the two preceding years, we conducted interrupted time series regression for each search term. The outcome was the relative weekly search volume for the search term, which is generated in Google Trends as an index ranging between 0 and 100[4], and analyses were repeated using binary predictor variables representing each of the three weeks since the suicide.

Models were fit using a generalized linear model from the Poisson family, with a loglink function and a scale parameter to account for overdispersion. Models controlled for long-term trends (entered as a fractional polynomial to account for non-linearity) and short-term seasonality trends (entered as Fourier terms).

At week 1, we observed large relative risk (RR) increases for "suicide" (RR=11.53, 95% CI: 10.01-13.27), "commit suicide" (RR=16.46, 95% CI: 14.20-19.07), "how to suicide" (RR=10.15, 95% CI: 7.38-13.97), "hanging" (RR=2.08, 95% CI: 1.65-2.62), "how to hang" (RR=10.80, 95% CI: 6.33-18.44), "suicide hanging" (RR=2.53, 95% CI: 2.00-3.19), "aatmahatya" (RR=2.70, 95% CI: 1.76-4.14) and "khudkushi" (RR=7.56, 95% CI: 5.02-11.38).

Significant increases persisted at week 2 for the search terms "suicide" (RR=3.11, 95% CI: 2.55-3.80), "commit suicide" (RR=2.96, 95% CI: 2.39-3.67), "how to suicide" (RR=6.50, 95% CI: 4.58-9.22), "hanging" (RR=1.43, 95% CI: 1.09-1.88), "how to hang" (RR=4.00, 95% CI: 1.95-8.17), and "suicide hanging" (RR=1.67, 95% CI: 1.27-2.20), and at week 3 for the search terms "suicide" (RR=1.61, 95% CI: 1.25-2.08), "commit suicide" (RR=1.48, 95% CI: 1.13-1.95), "how to suicide" (RR=3.05, 95% CI: 1.98-4.69) and "suicide hanging" (RR=1.82, 95% CI: 1.39-2.37).

At week 1, we also observed large increases for the putatively protective search terms "suicide prevention" (RR=12.64, 95% CI: 5.01-31.89), "suicide helpline" (RR=5.63, 95% CI: 4.57-6.94), "depression" (RR=6.40, 95% CI: 5.93-6.92), "depression doctor" (RR=4.99, 95% CI: 3.10-8.03), "psychiatrist" (RR=1.86, 95% CI: 1.65-2.10), "antidepressants" (RR=1.47, 95% CI: 1.19-1.81) and "avsaad" (RR=5.79, 95% CI: 3.22-10.39). Significant increases persisted at week 2 for the search terms "suicide helpline" (RR=1.86, 95% CI: 1.36-2.54), "depression" (RR=1.79, 95% CI: 1.59-2.02), and "psychiatrist" (RR=1.41, 95% CI: 1.23-1.62), and at week 3 for "depression doctor" (RR=2.61, 95% CI: 1.74-3.93) and "avsaad" (RR=2.87, 95% CI: 1.16-7.13).

The suicide of Sushant Singh Rajput and the subsequent widespread media coverage appears to have activated large increases in both harmful and protective Google search queries in India. This may have been exacerbated by the COVID-19 lockdown, with more time spent at home on online devices resulting in increased media exposure and greater opportunities to search online.

Whether Sushant Singh Rajput's death and these search trends will be associated with an increase in suicides should be investigated when data become available. Regardless, the current analysis clearly shows that his suicide was associated with strong increases in suicide-related Internet search behaviours, highlighting the need to promote media recommendations[3]. Furthermore, the monitoring of Internet search queries after celebrity suicides and other large-scale media phenomena could inform suicide prevention.

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The global impact of celebrity suicides: implications for prevention

Actor and entertainer Robin Williams died by suicide on August 11, 2014. Three studies conducted in the US, Canada and Australia have shown population level increases in suicide in the months after Williams' death. Across the three countries, the excess in suicide – beyond what is expected given the long-term trend and seasonal fluctuation – was between 10 and 16%, amounting to thousands of excess suicide deaths. The increases were primarily concentrated in those who used the same suicide method as Williams, and were demographically similar in terms of age and gender. Moreover, Williams' death elicited a strong reaction of suicidal crisis, suggesting that the excess suicides reflect the reactions to Williams' death.

Decades of data confirm that irresponsible media coverage of high-profile suicides can contribute towards a population-level increase in subsequent suicides insofar as vulnerable individuals identify with the decedent. Graphic depictions and in-depth discussions of the methods used or state of mind of the decedent are specific vectors that increase risk for subsequent suicide deaths using similar methods and among those with similar demographic characteristics as the decedent. Portrayals of suicide as fixing a problem or providing a solution may also increase risk in vulnerable individuals. Because of this well-documented ef-

fect, national and international best practice suicide reporting guidelines for media professionals have been established.

Williams' death received considerable international media coverage, which varied in tone and content, with major differences in adherence to suicide reporting guidelines. In Australia, the major national program Mindframe released suicide reporting guidelines in 2014, and information and briefings on how to handle the reporting of Williams' death were disseminated immediately and largely followed throughout the country. In Canada, a similar program known as Mindset released suicide reporting guidelines in 2014, which were disseminated to newsrooms throughout the country, and largely followed after Williams' death.

In addition to the need for moderation in reporting of celebrity death, these guidelines often include messaging around where individuals can obtain mental health and suicide prevention support if needed, as well as messages of hope for mental health recovery. Indeed, the media can be a source of information about suicide prevention after a high-profile event.

While guidelines from several authoritative health organizations were available in the US, the graphic nature of the reporting indicates that they were largely not followed in the case of Williams' death. Seemingly no detail was spared in the US media presentation of Williams' suicide, including a well-covered press conference that described not only the method of death but what Williams was wearing, where he was seated, and lurid details of his final hours. News cameras broadcast from the location of the death for days, and the 24-hours news cycle included seemingly endless discussions of Williams' state of mind and mental health. This may have increased risk among vulnerable individuals in the US, but could have spread to other areas as well.

Indeed, suicides also increased after Williams' death in Canada and Australia, where at least some reporting guidelines were largely followed. One hypothesis is that dissemination of content regarding high-profile suicide deaths are not confined to national boundaries. Our information landscape is one in which obtaining minute-by-minute global news from many places in the world (especially the US) is a major mode of information transfer.

Social media are replacing traditional media as a source of news and information. Citizen journalists (often without journalistic training, and largely unaware of media guidelines) are now contributing greatly to the media landscape through user-generated content in blogs, vlogs and social media channels. To our knowledge, no study has been conducted on the content of citizen journalists' or average social media users' postings after a high-profile suicide. However, it is reasonable to hypothesize that such postings will frequently violate best practice guidelines in writing about suicide.

The globalization of the media and unfiltered dissemination of content via social media and citizen journalists as a new risk factor for suicide after a high-profile suicide death is concerning, especially as high-profile suicides and depictions of suicide continue to proliferate. Fictional depictions of suicide such as *13 Reasons Why* on Netflix have now been documented to adversely affect adolescent suicide in the US, and the impact of this program beyond borders is likely.

As Netflix, Youtube, Facebook, Snapchat and Instagram increasingly are easily available in many places across the world, public health attention to suicide prevention education needs to expand and move beyond local and traditional media. The fan base and reach of celebrities is increasingly global as well, indicating that future celebrity deaths may have a broader impact than previous events.

The solutions to the globalization of information for suicide prevention are not obvious, and will require thoughtful collaboration between public health, psychiatry, journalism, and policy stakeholders. There are massive efforts underway to build online platforms that provide guidance regarding how to discuss suicide safely and informatively online.

Suicide prevention should attend to new modes of information transfer, innovate the dissemination of safe reporting and suicide prevention messaging on online platforms, and actively serve to prevent suicide through scientifically accurate messaging around recovery and support. Such efforts are currently underway in several countries, and can be extended as well.

Research and action on popular citizen journalists are also needed, as well as research on "average" social media users. While these groups are already incorporated into some guidelines, the extent to which guidelines are followed outside of some traditional media remains questionable. Social media platforms are both an opportunity and a threat, with incredible reach to mobilize individuals to discuss mental health and reduce stigma, as well as to be unwieldly amplifiers of misinformation and harm.

The accumulating evidence of the widespread impact of a singular celebrity suicide death across countries, despite improved traditional media coverage, is an acute and tragic warning that we are in a new age for which the thoughtful and well-informed efforts to reduce suicide contagion need to be reimagined.

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Setting priority areas for WPA's new triennium

The WPA General Assembly held on October 16, 2020 elected the Association's new office bearers and approved the WPA Action Plan for the 2020-2023 triennium[1]. This plan defines emerging needs and priorities for the work of the WPA from a worldwide perspective.

Looking at the global situation, only a minority of people with mental disorder receive any help or intervention for their mental health difficulties. There is, thus, an outstanding need to improve access to high quality mental health care in all countries and to support psychiatrists and other mental health professionals in their important roles as direct service providers, trainers, supporters of health care workers in primary and community health care systems, and policy makers.

The key goals of the WPA Action Plan 2020-2023 include: promoting psychiatry as a medical specialty in clinical, academic and research areas; emphasizing public mental health as a guiding principle; highlighting the specific role of psychiatrists in working with other professionals in health, public health, legal and social aspects of care; and ensuring the WPA's positive engagement with Member Societies and other components of the Association, mental health professionals and general health care workers[2].

The WPA Action Plan 2020-2023 also looks at targeted areas that need attention, with input from various components of the Association, during the next triennium. It will work within an international perspective focusing specifically on improving coverage of interventions to treat mental disorders, prevent these disorders and promote mental well-being, including through relevant training of mental health and other professionals. It will also build on the previous Action Plans to ensure continuity in the WPA's work[3,4]. Focused attention will be given to public mental health; child, adolescent and youth mental health; comorbidities in mental health and developing partnerships for joint collaborative work in this area; strengthening partnerships with organizations working in the entire field of mental health; and continuation and completion of previous WPA Action Plans.

The public health population approach to mental health is particularly important to reduce the global burden of mental disorders, along with an emphasis on positive mental well-being[5]. Improving coverage of effective interventions to treat mental disorders; prominent coverage of child and adolescent mental health, including for higher-risk groups such as those with learning disability, autism, early onset of psychosis; addressing comorbidities in mental health care and training; capacity building and engagement with other mental health professionals are other salient features of this aspiring plan.

All the areas covered in the proposed Action Plan are of high priority. However, due to time limitations and scarcity of resources, there will be greater focus on specific areas. The WPA has established working groups that have started formulating plans and pilot projects in different areas outlined in the document. Once the findings of these pilot projects are available, we will share these reports and seek funding to implement these ideas in different settings and countries. It is hoped that the reports of these groups will set updated directions for all WPA components to develop further guiding principles and strategies for future work[6-8].

The WPA is mindful that the rapid spread of COVID-19 infection around the world is further increasing risk of developing mental disorders, relapse of existing mental disorders and poor mental well-being, which requires action at a population level[9]. The current coronavirus pandemic has changed the world as we knew it. Unlike many pandemics, COVID-19 has not only affected the health sector, but has had several implications for the social and financial sectors as well. Looking at the health implications, there is no group that is immune to this infection, but there are more significant concerns for vulnerable populations, including persons with severe mental illness[10]. The mental health field is significantly hit by this pandemic and in many ways it is at the frontline in addressing emotional and social aspects of this scourge[11-13].

Most mental health services are under-resourced and unfortunately under-prepared to cope with this pandemic. There is a dire need to use this lesson to reform our health and care services substantially[14]. Furthermore, response to COVID-19 is involving a prominent attention to the establishment of telehealth as an integral component of our future services. Psychiatry is still waiting for standards guiding the implementation of this component. The WPA plans to establish a working group to look at such opportunities and produce guidelines for online mental health services[15].

It is hoped that the WPA Action Plan 2020-2023 will generate interest among all WPA components to develop further strategies for future work. The WPA is optimistic that it will receive support, active input, and advice from its membership in addressing these priorities and making a real difference in mental health.

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The WPA responds rapidly to a mental health crisis: the Ukrainian example

On April 1, 2020, the Ukrainian government implemented the second phase of a health reform plan restructuring the funding of specialized health care, including psychiatric services[1]. As a result, many psychiatric services in the country reported serious levels of under-financing, leading to the discharge of many patients, dismissal of large numbers of personnel and closure of several departments.

This sudden reduction in financial support for services was worryingly reminiscent of recent crises in other parts of the world, with grave consequences for life, health and service responses[2]. It arose in the context of limited communication in recent years between the psychiatric profession and government departments. It also coincided with the COVID-19 pandemic as it began to take hold in Ukraine, reaching several psychiatric hospitals and social care homes in the country.

In April 2020, the Ukrainian Psychiatric Association (UPA) approached the WPA with a request for assistance in its efforts to resolve the crisis in mental health care, subsequently joined by the Kharkiv-based Association of Neurologists, Psychiatrists and Narcologists of Ukraine. In early May, the WPA commissioned the formation of an international Expert Committee to assist the two associations, both of them long-standing Member Societies of the WPA.

The Expert Committee was established in collaboration with the Federation Global Initiative on Psychiatry (FGIP). The main task of the Committee was to analyze the situation in Ukraine following the implementation of the second phase of the health reform plan, advise the associations on how to deal with the situation, and assist the Ministry of Health in finding a solution to the crisis and work towards the successful reform of services.

This paper documents the manner in which the Expert Committee was formed and functioned, and the outcomes and results of its work. This can serve as a model for future requests of a similar nature. It also exemplifies how organizations of a different profile, in this case a multinational association of psychiatric societies such as the WPA and a human rights based foundation such as the FGIP, can work together successfully to help improve treatment and care for people living with mental disorders.

E. Chkonia of the Georgian Psychiatric Association was invited to chair the Expert Committee. She had been involved in the reform process in Georgia (which has the same historical legacy as Ukraine, having been part of the Soviet Union) and speaks both English and Russian fluently. Other members of the Committee were chosen because of a combination of specific expertise and knowledge of the situation in Ukraine. R. van Voren was selected as Secretary of the Committee because of his contacts with people working in Ukraine and his knowledge of the Ukrainian situation. A small supervisory group was appointed, including the WPA and FGIP leadership, to advise on the process and review the draft document before its finalization.

E. Chkonia and R. van Voren discussed the objectives and strategy of the Expert Committee with members of the supervisory board. A series of conference calls was then arranged between E. Chkonia and R. van Voren with I. Pinchuk, Director of the Institute of Psychiatry at the Taras Shevchenko Nation University of Ukraine in Kyiv and Vice-President of the UPA. The data needed for the Committee to function were gathered by I. Pinchuk and her colleagues in Ukraine, based on reports from mental health facilities from all parts of the country. These were sourced by I. Pinchuk and subsequently translated into English.

The Expert Committee met weekly by videoconference. Several of the meetings were joined by members of the supervisory board. In addition, E. Chkonia and R. van Voren continued their communication with I. Pinchuk between these meetings, sometimes joined by other members of the Committee.

The situation in Ukraine continued to unfold. New persons were appointed to the Ministry of Health, including a new First Deputy Minister of Health, who was commissioned to solve the crisis in psychiatry, and a new Minister of Health, who was determined to avoid a collapse of the psychiatric system. As a result, it was vital that the outcome of the Expert Committee's work be delivered as soon as possible, and that the recommendations be such that they could immediately contribute to the mitigation of the existing situation. It was also important that these recommendations be consistent with those of other advisory bodies, including the World Health Organization. In order to assure this, constant communication was maintained with other parties in the mental health field.

An extensive and comprehensive policy brief was produced in the course of several weeks and subsequently reviewed by the supervisory board and several other selected experts. Once finished, the document was translated into the Ukrainian and Russian languages. Russian was chosen not only because many professionals in the eastern part of the country have it as their mother tongue, but also because the document could subsequently be used as an example for other countries in the region.

On June 29, 2020, the policy brief was sent to the two WPA Member Societies and the Ministry of Health in Ukraine. The next day the document was handed over to the First Deputy Minister of Health of Ukraine by I. Pinchuk. The President of the UPA, S. Gluzman, sent the document electronically to the Minister of Health M. Stepanov.

The Ukrainian associations are using this policy brief as a basis for discussion with the Ministry of Health. The recommendations include the necessity to enhance collaboration with all stakeholders within the country and restore the relationship between the Ministry and the

psychiatric profession. The Ministry of Health is leading the dialogue about the reform process with engagement of the psychiatric associations as well as civil society and other ministries. The UPA adopted the recommendation to approach international bodies that monitor the implementation of Ukraine's obligations as a signatory to international conventions. In July 2020, the UPA sent letters to the United Nations (UN) Special Rapporteurs on the Right to Health and the Rights of Persons with Disabilities, hoping that their involvement will strengthen the motivation of the Ukrainian authorities to solve the current psychiatric crisis.

The work of the Expert Committee illustrates the way in which the WPA can help to develop an effective and rapid response to a request for support from its Member Societies. The work of the Committee also exemplifies the collaboration between the WPA and the FGIP, which facilitated responding to a crisis with the help of leading experts.

The experience gained on this occasion will be helpful in responding to similar crises. It will also help in design of a training program to provide skills for addressing such situations. Success in these circumstances requires working in partnership with policy makers and community groups. Among the skills are those essential in advocacy, communication with media, the management of professional organizations, the application of the basic principles of the UN Convention on the Rights of Persons with Disabilities[3], and the implementation of alternatives to coercion in mental health care[4-6].

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International classification systems: views of early career psychiatrists

Classification systems are an important part of medical education and clinical practice. A classification system that is reliable, clinically useful, and globally applicable provides an essential foundation for the diagnosis of mental disorders, helping to identify the patients with higher mental health needs, and ensuring the best care provision[1]. A system that is not clinically useful will likely not be implemented by clinicians[2].

The World Health Organization (WHO) developed the Clinical Descriptions and Diagnostic Guidelines (CDDG) for ICD-10 Mental and Behavioural Disorders[3] for clinical, educational and service use. Surveys undertaken as a part of the development of ICD-11 suggested that many clinicians regularly use this material, reviewing it systematically when making an initial diagnosis[4].

The WPA-WHO Global Survey of Psychiatrists' Attitudes Towards Mental Disorders Classification was an international study published in 2011, reporting responses by 4,887 psychiatrists from 44 countries[5]. Respondents regarded communication among clinicians as the most important purpose of a diagnostic classification system, followed by informing treatment and management decisions. The use of classification systems was very common, and the ICD-10 was by then the most widely used classification system across the world. Since one of the inclusion criteria of the survey was that participating psychiatrists had completed their training, the study did not cover the views of those still in training. This is particularly important, as much of the clinical practice worldwide is done by psychiatrists in training, who are responsible for making clinical diagnoses for their patients to the best of their knowledge.

The WPA Early Career Psychiatrists (ECPs) Section developed an online survey based on questions from a prior WHO survey[6] and asked ECPs across the world to respond about their experience and opinions on classification systems. The survey was circulated through the online platforms of the WPA ECPs Section to its members between August and September 2019. The included questions explored: the frequency of providing direct mental health services to patients, the responsibility for assigning a psychiatric diagnosis to patients, the frequency of using different classification systems, the purpose of such usage and its usefulness, as well as their interest in classification systems, and suggestions for the involvement of ECPs in the implementation of ICD-11.

Responses were collected from 52 countries across Europe, Asia, Africa, Americas and Australia. The sample consisted of 202 ECPs (52.5% female; mean age: 33 years, range 25-59 years). Of the respondents, 41.1% were psychiatrists in training, and the rest were still in their early career.

An overwhelming majority of 86.6% of respondents reported that they usually assign psychiatric diagnosis themselves, 0.5% that they assign it together with their supervisor, 9% that diagnosis is assigned by another health professional, and 0.5% that a consultant psychiatrist assigns it in a weekly meeting.

During a typical work week, the majority of respondents (33.7%) spent 40 hours or more providing direct mental health services to patients, while 18.3% spent between 30 and 39 hours, 14.9% 20 to 29 hours, 12.4%

10 to 19 hours, 13.9% 4 to 9 hours, 5.4% 1 to 4 hours, and 1.5% less than one hour.

The majority of respondents (63.9%) used ICD-10 routinely; the DSM-5 was sometimes used by 35.6% of participants. When inquired about the main purpose of use of classification systems, the ICD-10 ranked first with respect to assigning diagnoses for administrative purposes (81.7%) and clinical practice (74.3%), whereas the DSM-5 ranked first for teaching and education (66.4%) and research (56%).

Most ECPs were interested (47.0%) or very interested (41.6%) in classification systems, with only very few (0.5%) not at all interested. ECPs were very interested (55.0%) or interested (36.1%) in the ICD-11, and very interested (38.1%) or interested (48.5%) in the DSM-5. Many ECPs reported their wish and availability to be involved in the implementation of and training for the ICD-11, and suggested the use of technology (e.g., smartphone apps, videos and webinars) for these purposes.

These findings document the important role of ECPs in assigning psychiatric diagnosis in routine clinical practice worldwide. When developing the ICD-11 CDDG, the importance of clinical utility has been emphasized as a core principle[1], and field studies conducted in 13 countries in clinical settings reported that clinicians considered the clinical utility of ICD-11 to be high[7]. While the Global Clinical Practice Network, through Internet-based field studies, allowed mental health and primary care professionals worldwide to contribute to the development of the ICD-11[2], there was little involvement of ECPs.

The WHO is now working with its Member States, health professionals, academic centers, and professional organizations such as the WPA on ICD-11 implementation and training. Based on the findings of this survey, the WPA Secretary for Education will convene a new Task Force with members from the WPA ECPs Section and the International Federation of Medical Student Associations, who will advise on the key strategic implementation steps in enabling competent use of ICD-11 classification.

With the launch of the new WPA learning management system in the WPA website[8,9], online training and discussion forums can be conducted and disseminated to ECPs working in any part of the world. We hope that voicing the views of ECPs will raise awareness of their critical role in clinical practice, and support them in utilizing current and future psychiatric classification systems across the world.

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Updates from the WPA Section on Education in Psychiatry

The WPA Section on Education in Psychiatry, which is one of the oldest sections in the WPA, having been established in the 1970s, is committed to improve the quality of education in psychiatry.

In particular, the aims of the Section are the following: a) to improve psychiatric care provided to patients and their carers; b) to update training curricula for residents in psychiatry worldwide, and in particular in low- and middle-income countries; c) to develop educational materials about mental health and mental disorders for clinicians, researchers and academic professionals involved in teaching activities for undergraduate students, trainees in psychiatry, and primary care workers; d) to increase the attractiveness of psychiatry as a profession among medical students; e) to promote the public image of psychiatry among the general population; f) to improve the mental health literacy of the general public.

In many countries, education in psychiatry is still based on a knowledge formed in the last century, while the recent scientific, clinical, social and economic changes require the update of psychiatric training curricula[1]. In fact, psychiatry is now a modern medical specialty that deals with the structure and function of the brain, the operations of mind (i.e., thoughts, feelings and consciousness), human behaviours and social relationships. Accordingly, the target of psychiatry has also changed, and very often psychiatrists are called to deal with conditions which are not proper mental disorders, but mental health problems associated with high levels of personal burden and reduced social functioning, thus requiring professional help[2]. New diagnostic and therapeutic approaches are continuously proposed, and these should be integrated in training curricula. At the same time, some classical psychiatric disorders, which seem almost disappeared from daily practice, should not be disregarded[3]. The Section on Education in Psychiatry has participated in the development, update and revision of the WPA core curriculum for medical students[4-6].

The post-graduate training curricula of

modern psychiatrists should include skills in leadership, administrative and economic management, dealing with media, conflicts of interests, and academic development. The Section has recently carried out a web-based survey with more than 600 participants from 60 countries in order to assess the levels of training on academic skills and leadership competencies in residency curricula. Respondents reported to have low levels of academic skills, which are not usually taught during residency courses. These findings have been discussed at several international meetings, including the annual meeting of the American Psychiatric Association.

The WPA Section on Education in Psychiatry has contributed to the revision of educational materials on depression targeted to the general population, which are now available on the WPA website (wpanet.org)[7], and has participated in the development of educational packages for the general public in order to address misconceptions on people with mental disorders.

Several textbooks have been published in the field of education in psychiatry with the involvement of several members of the Section (e.g., *Teaching psychiatry: putting theory into practice* edited by L. Gask, B. Coskun and D. Baron; *A new era in psychiatric education, a new era for education in the WPA* edited by A. Tasman; *New directions in psychiatry* edited by A. Fiorillo and N. Sartorius). The fifth edition of the *Tasman's Psychiatry* is currently in preparation and will be ready by the year 2021, with the involvement of several members of the Section.

Our Section has also recently contributed to the international debate on the need to increase the attractiveness of psychiatry among medical students. In fact, a shortage of medical students choosing a career in psychiatry is consistently reported, which is frequently due to the misconception that psychiatry is unscientific compared to other medical disciplines. This bad image of our discipline negatively impacts on the decision to choose a career in psychiatry. Moreover, in many parts of the world, the skills of psychiatrists are often confused with those of psychologists and other mental health professionals, further reducing the attractiveness of our discipline.

The Section on Education in Psychiatry has participated in several campaigns to erase the stigma of mental health, which have been carried out in different parts of the world in order to improve the public image of psychiatry among the general population. Positive messages on mental health and people with mental disorders have been proposed and conveyed through seminars, informative materials and books, which have been developed and disseminated worldwide[8,9]. The Section aims to make this material available, in particular in low- and middle-income countries, where the levels of stigma are much higher compared to other countries.

Finally, members of the Section have participated in the development of informative and educational materials for patients, carers and family members, or have contributed to the adaptation of those already existing, also in collaboration with international associations of users and/or carers[10,11].

The WPA Section on Education in Psychiatry has organized symposia, workshops and educational courses in collaboration with other national and international bodies involved in education. It actively collaborates with other WPA Scientific Sections[12,13], in particular with the Sections on Early Career Psychiatrists and on Psychotherapy, in order to fulfil the educational needs of early career psychiatrists and to fill the educational gaps in crucial areas, such as that of training in psychotherapy.

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