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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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Physical health of people with severe mental disorders: leave no one behind

The 2030 United Nations Agenda for Sustainable Development seeks to ensure that, over the next 15 years, countries make concerted efforts towards economic, social and environmental development that is sustainable and inclusive. In order to achieve the goal of universal health and well-being (Goal 3), an important target is "to reduce premature mortality from non-communicable diseases (NCD) through prevention and treatment and promote mental health and well-being"[1]. While this goal applies to all, there is a need for making special efforts to the populations that are vulnerable to be left behind. One such population is people with severe mental disorders (SMD).

SMD and NCD are related in complex ways. The major modifiable risk factors for NCD, such as physical inactivity, unhealthy diet, tobacco use and harmful use of alcohol, are exacerbated by poor mental health. Mental illness is a risk factor for NCDs; its presence increases the chance that an individual will also suffer from one or more chronic illnesses. In addition, individuals with mental health conditions are less likely to seek help for NCDs, and symptoms may affect adherence to treatment as well as prognosis.

The physical health of people with SMD is commonly ignored not only by themselves and people around them, but also by health systems, resulting in crucial physical health disparities and limited access to health services. This impacts the life expectancy of people with SMD. The facts are clear: people with severe mental disorders die, on average, 15 to 20 years earlier than others. These excess and early deaths are not primarily due to suicide, but to physical diseases that occur more frequently, are not prevented adequately, are not identified early enough and are not treated effectively. And this disparity is not confined to some regions and countries, but seems to be a global reality. This state of affairs is not in keeping with the spirit and letter of the Sustainable Development Goals. It should be unacceptable to any country or community.

What is needed? While interventions, guidelines and programmes have been developed to address the risk factors for excess mortality in persons with SMD, they will not really make a difference until a variety of challenges to their implementation are tackled, including problems with culture and attitudes of the various stakeholders involved, resources and expertise available, engagement of patients in the programmes, accessibility and feasibility of the interventions, their cost-effectiveness, and the fidelity of their application.

At the policy level, there is an obvious issue of prioritization. Reducing excess mortality in persons with SMD should become part of the broader health agenda. Top-level integration of various programmes (e.g., mental health and substance abuse, NCD, tobacco cessation, violence prevention, nutrition and physical exercise) should be set as a precedent for making strides in addressing complex, multifactorial health problems.

Health programme managers should promote awareness of the problem amongst health care providers and equip them with training, support and supervision to deliver comprehensive care. Health care providers should be especially attuned not to overlook somatic concerns and to pay attention to the lifestyle behaviours of persons with SMD. At the very minimum, persons with SMD should have access to the same care offered to people with other health conditions, including the same basic health screenings as the general population (e.g., for cardiovascular risk and cancer).

There are guidelines and tools available to assist general health care providers in the assessment and management of people with co-occurring physical and mental health conditions. An example of one such tool is the World Health Organization (WHO)'s mhGAP Intervention Guide for Mental and Neurological Disorders, the new version of which has been recently released[2]. The Guide presents algorithms for clinical decision-making including specific guidelines for assessment and management of co-occurring physical health conditions.

On the other hand, research challenges in this area should not be ignored. Among them are the problems of the representativeness of the study samples; of the availability and reliability of the information about the occurrence of mental disorders, the causes of death and the presence of the various risk and protective factors in the samples studied; and the difficulties in clarifying the relative impact of the various categories of risk and protective factors and the way these factors interact with each other. Furthermore, the evidence concerning protective factors is in general much more limited than that regarding risk factors, and high-quality research from low-income countries is still very scarce. The role of new communication technologies and of peer support in this field is also understudied. A major further challenge is the assessment of the impact of policy and health system interventions, which may emerge only after many years. Most importantly, the effectiveness and cost-effectiveness of evidence-based interventions and programmes will have to be evaluated systematically in different settings. Barriers to their implementation at various levels will have to be identified, and ways to address them appropriately tested.

Also, the current focus on cardiometabolic risk in people with SMD living in the community should not distract our attention from the scandal of premature mortality among the mentally ill who live in large asylums, and the millions of people with SMD who are currently detained in prisons worldwide (see also McKenna et al[3] in this issue of the journal), who are particularly exposed to chronic diseases (including, especially in low-income countries, infectious diseases), poor nutrition, victimization, neglect, suicide and substance abuse.

In the Forum of this issue of the journal, the available evidence on risk factors and effective interventions has been collated to present a multilevel risk model and associated intervention framework for excess mortality in people with SMD[4]. An important feature of the proposed framework is that it integrates individual-focused, health system-focused and policy-focused interventions. A group of commentators has been carefully selected to reflect the views of various categories of stakeholders: policy makers, researchers, health care providers and service users. We hope that this Forum will contribute to catalyze actions for implementing what we already know and also research to know more.

To fulfill our commitment towards sustainable global development *for all*, urgent and concerted efforts are needed to reduce preventable premature mortality in this population.

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S. Saxena is a staff member of the WHO. All opinions expressed in this editorial rest with the authors and do not necessarily represent the decisions, policy or views of the WHO.

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Mental health care and treatment in prisons: a new paradigm to support best practice

Stone walls do not a prison make,
Nor iron bars a cage;
Minds innocent and quiet take
That for an hermitage.

R. Lovelace's 17th century poem *To Althea, from Prison* alludes to the ability of a "quiet" mind to transcend the imposition implied by institutions which deprive people of their liberty. But our prisons are not full of "minds innocent and quiet"; rather they are overloaded by minds troubled by the experience of mental illness[1]. There is a need to reach into prisons to address mental health needs, but "stone walls" and "iron bars" constitute barriers to this intent. Systems designed to care for and treat mental illness struggle in institutions designed to punish, deter and incapacitate.

Yet people are sent to prison *as* punishment, not *for* punishment, which requires us to understand how humane treatment can be delivered in such environments. The existence of various international human rights instruments (such as the International Covenant on Civil and Political Rights, and the Convention against Torture and other Cruel, Inhuman or Degrading Treatment or Punishment) are necessary, but not sufficient by themselves, to ensure appropriate and humane care for some of the most vulnerable members of our citizenry[2].

Worldwide more than 10 million people are held in penal institutions at any given time and more than 30 million people pass through prisons each year, with some regions experiencing prison growth well above population growth. There is an elevated risk of all-cause mortality, including suicide, for prisoners in custody[3] and for ex-prisoners soon after release[4]. We therefore have a collective interest in ensuring that health related need is identified and effective care is delivered during incarceration and the critical period of transition to community life.

Research in this area has yielded increasing clarity about the central issues that need to be addressed to provide a comprehensive model of care for mentally unwell prisoners. First, the prison must screen for mental illness, at reception and at other critical times. At least five such screening instruments have been developed[5]. However, additional triage and case-finding measures are needed to ensure comprehensive case identification.

Once need is identified, hospital transfer may be required for the most unwell. Mental health legislation needs to accommodate such transfers. For others, prison-based care is often delivered through mental health in-reach teams, which have become increasingly systematic in creating care and treatment pathways for prisoners with serious mental illness, including contribution to release processes to enable sustained clinical involvement on release[6].

Systems of prison mental health care are not bereft of innovation. Multi-disciplinary teams can address complex mental health and social care needs and include cultural expertise in jurisdictions where indigenous populations or ethnic minorities are over-represented in prisoner populations[6]. Release planning constitutes an opportunity for "critical time intervention", focusing on ensuring continuity of care across a range of providers as the prisoner transitions through the gate[7]. The evidence for the success of such endeavours is gaining momentum, with indications of the positive impact of systematic prison in-reach models of care on detecting those requiring assistance[8] and improving post-release engagement with mental health services[4].

Modern prison outcomes are increasingly focused on reducing reoffending post release, and to this end we share a common purpose in the ultimate release of a rehabilitated prisoner whose mental health and addictions needs have been met. Yet, the pathway to this collective goal is far too often reliant on the goodwill of individual custodial staff or the ability of prison mental health in-reach teams to navigate the institutional barriers imposed when "safety and security" are prioritized over human suffering. Our social institutions are being challenged to re-think this siloed mentality. Whether change ultimately comes from legal challenges to human rights violations, or a pragmatic neoliberal emphasis on fiscal constraint, the shift is toward interagency collaboration. This is coupled with a person-centred approach with institutions re-focusing on the people they serve, rather than the self-perpetuating demands of the institution itself.

In courts, such transformation is spear-headed by the principles of "therapeutic jurisprudence", which invite legal systems to view their processes through a therapeutic lens. It is recognized that addictions, mental illness and social care needs (such as family support, housing and employment) are inextricably linked to rates of crime, to the extent that traditional adversarial courts have become revolving doors for offenders whose criminal behaviour arises from psychosocial challenges. The advent has been the proliferation of "solutions-focused" courts, which use the leverage of the legal process to encourage people to address the causes of offending and actively involve social agencies that can assist[9].

A paradigm shift is especially evident in youth justice custodial services. Research shows that justice-involved youth are exposed to high rates of trauma. Childhood physical, sexual and psychological abuse has negative consequences on subsequent life trajectories, leading to an increased likelihood of mental illness and ongoing involvement in the justice system[10]. Under a trauma-informed model of care, young people are held accountable for their offending behaviour, but all parties involved recognize and respond to the impact of trauma on

development, behaviour and identity. A trauma-informed model of care is one in which custodial services act in collaboration with families and wider social networks to facilitate and support the recovery and resilience of young people.

There are signs of change also in the adult corrections sector. Psychologically informed planned environments (PIPEs)[11] and therapeutic communities that target specific behaviours, such as drug and alcohol abuse and violent behaviour, are attempting to bridge gaps between therapy and custody. Rehabilitation has become a stronger emphasis in many prisons, with some approaches using the therapeutic alliance and recognition of strengths to bring about "recovery" to offenders. Yet, what is lacking is a penal paradigm that articulates the integration of therapy and custody. If a punishment paradigm is allowed to prevail, more damage is inevitable – to individual prisoners, to their family and loved ones, and to the communities from which they have come and to which they return on release.

The collective challenge for all stakeholders is to help transform toxic penal environments into true recovery opportunities. In this endeavour, there may be much to borrow from the way in which some secure forensic hospitals have blended care and custodial drivers to promote the recovery of this most vulnerable part of our community.

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A network theory of mental disorders

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In recent years, the network approach to psychopathology has been advanced as an alternative way of conceptualizing mental disorders. In this approach, mental disorders arise from direct interactions between symptoms. Although the network approach has led to many novel methodologies and substantive applications, it has not yet been fully articulated as a scientific theory of mental disorders. The present paper aims to develop such a theory, by postulating a limited set of theoretical principles regarding the structure and dynamics of symptom networks. At the heart of the theory lies the notion that symptoms of psychopathology are causally connected through myriads of biological, psychological and societal mechanisms. If these causal relations are sufficiently strong, symptoms can generate a level of feedback that renders them self-sustaining. In this case, the network can get stuck in a disorder state. The network theory holds that this is a general feature of mental disorders, which can therefore be understood as alternative stable states of strongly connected symptom networks. This idea naturally leads to a comprehensive model of psychopathology, encompassing a common explanatory model for mental disorders, as well as novel definitions of associated concepts such as mental health, resilience, vulnerability and liability. In addition, the network theory has direct implications for how to understand diagnosis and treatment, and suggests a clear agenda for future research in psychiatry and associated disciplines.

Key words: Psychopathology, network approach, mental disorders, symptom networks, mental health, resilience, vulnerability, diagnosis, treatment

(World Psychiatry 2017;16:5–13)

Like all medical branches, psychiatry is a problem-oriented discipline that is motivated by and rooted in the practice of clinical work. That practice revolves around certain sets of problems that people present themselves with. For instance, a person may be referred to a psychiatrist because he is afraid that other people can read his mind, causing anxiety and social isolation. Or, a person may approach a doctor because his drinking behavior starts interfering with his work, and he is unable to quit or cut back. Another person may have developed a fear of social situations that has started to interfere with his social life, leading to feelings of loneliness and sadness. An important task of psychiatry (and associated disciplines, such as clinical psychology) is to find out where these problems come from and how they can be solved. The present paper proposes a theoretical framework that addresses this issue.

Given the heterogeneity of the problems that psychiatry and clinical psychology deal with, it would perhaps be best to categorize them broadly as "problems of living". In the past century, however, scientific terminology took a very different turn, and as a result it has become commonplace to talk about people who struggle with such problems as "suffering from mental disorders". Accordingly, the problems found in clinical practice have been categorized as *symptoms*, as exemplified in diagnostic manuals like the DSM-5 and ICD-10. Via the analogy with medical work, this use of the word "symptom" suggests the presence of a "disease", and this provides a suggestive answer to the question of why some people suffer from certain sets of symptoms, while others do not; namely, because they have particular kinds of diseases, to wit, mental disorders[1,2].

However, there is an important difference between mental disorders and diseases. The use of the term "disease" implies a worked out etiology, by which symptoms arise from a common pathogenic pathway, while the term "mental disorder" refers to a syndromic constellation of symptoms that hang together empirically, often for unknown reasons. Unfortunately, for all but a few constellations of the symptoms that arise in mental disorders, common pathogenic pathways have proven elusive[1,3,4]. This frustrates the application of one of the most important explanatory schemes in general medicine: the search for *common causes* that give rise to overt symptomatology[1,2]. For instance, if a person coughs up blood, has pain in the chest, and is short of breath, a physician may hypothesize the presence of a tumor in the lungs. Such a tumor is a localized, physically identifiable abnormality in the body, that acts as a common cause with respect to the symptomatology[1]. As a result, even though the symptoms are phenomenologically distinct, they are causally homogeneous, because they are *causal effects of the same disease*. In this case, removing the disease entity (e.g., killing the cancer cells through chemotherapy) removes the common cause of the symptoms, which wane as a result. This type of strategy has not been very effective in psychiatry, precisely because no central disease mechanisms or pathogenic pathways have been identified for mental disorders. The question is why.

Recent work has put forward the hypothesis that we cannot find central disease mechanisms for mental disorders because no such mechanisms exist. In particular, instead of being *effects of a common cause*, psychiatric symptoms have been argued to *cause each other*[5,6]. For instance, if one thinks that other people can read one's mind (delusion), this may generate extreme suspicion (paranoia); this paranoia can lead one to avoid other people (social isolation), which, because one is no longer exposed to corrective actions of the social environment, may serve to sustain and exacerbate the relevant delusions. In this way, symptoms may form feedback loops that lead the

person to spiral down into the state of prolonged symptom activation that we phenomenologically recognize as a mental disorder[6,7].

Because the interactions between symptoms can be understood as a network, in which symptoms are *nodes* and causal interactions between symptoms are *connections between nodes*, this conceptualization has become known as *the network approach to psychopathology*. Methodological research within this approach has focused on developing statistical techniques designed to identify network structures among psychiatric symptoms from empirical data[7-12]. These techniques have now been applied to a range of constructs, such as depression[13-20], anxiety disorders[21,22], post-traumatic stress[23], complex bereavement[24], autism[25,26], psychotic disorders[27-29], substance abuse[30], the general structure of psychiatric symptomatology[31-34], diagnostic manuals themselves[34,35], health-related quality of life[36], and personality traits[37].

In general, findings from these studies are encouraging, in the sense that results accord with clinical intuition and standing theory. However, although the network approach has generated an important new way of thinking about the problems in psychopathology research, it has not yet been developed as an overarching theory of mental disorders. The goal of this paper is to present a set of explanatory mechanisms that may be combined into a general framework which specifies: a) what mental disorders are, b) how they arise, and c) how they may be optimally treated.

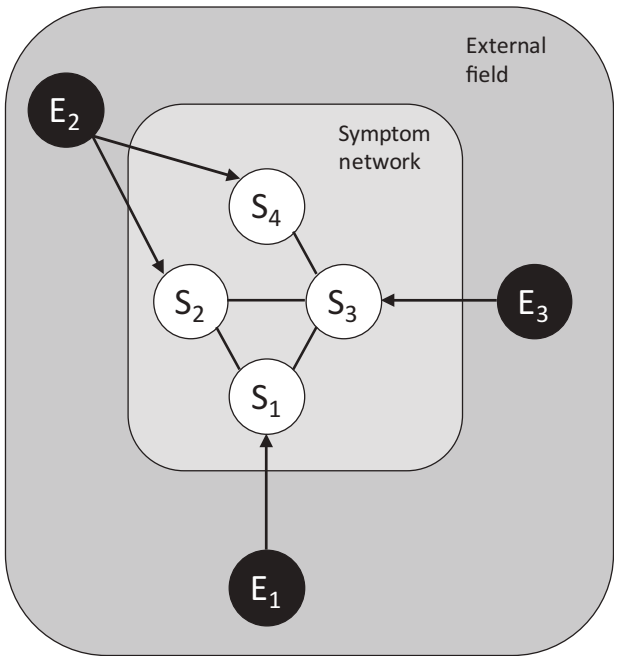

Figure 1 A symptom network of four symptoms (S_1-S_4). If two symptoms have the tendency to activate each other, they are connected by a line (e.g., S_1-S_2). Symptoms that are not directly connected to each other (e.g., S_1-S_4) can still synchronize if they share a common neighbor in the network (e.g., S_3). External factors that affect the network (e.g., adverse life events) are represented in the external field. These may be symptom-specific (E_1, E_3) or shared across symptoms (E_2).

SYMPTOM NETWORKS

The central tenet of the network approach is that mental disorders arise from the causal interaction between symptoms in a network[1,6]. Such causal interaction between symptoms can be interpreted using interventionist theories of causation[38]. In this interpretation, the presence of a causal connection means that, if an (experimental or natural) intervention changed the state of one symptom, this would change the probability distribution of the other symptom[38,39]. Importantly, network theory is agnostic with regard to how these causal relations are instantiated. Direct causal connections between symptoms may be grounded in basic biological (e.g., insomnia → fatigue) or psychological (e.g., loss of interest → feelings of guilt) processes, in homeostatic couplings (e.g., appetite and sleep both interact with the biological clock, so that when one is disturbed, the other is likely to be disturbed as well), in societal norms (e.g., dependence on heroin increases the probability of contact with law enforcement agencies in countries where it is prohibited by law), or in still other processes.

Patterns of symptom-symptom interaction can be encoded in a *network structure*. In such a structure, symptoms are represented as *nodes*. Nodes corresponding to symptoms that directly activate each other are connected, while nodes corresponding to symptoms that do not directly activate each other are not. An example of a network structure is given in Figure 1.

Conditions that can influence symptoms from outside the network (e.g., adverse life events) form the *external field* of the symptoms. Changes in the external field (e.g., losing one's partner) may activate symptoms in the network (e.g., depressed mood). In turn, this may cause the symptom's neighbors (e.g., insomnia, reproach, anxiety) to align their states with the depression symptom. Note that factors in the external field are outside of the network, but need not be outside of the person[7]. Inflammation[40], for instance, is a process inside the person, but its effects on symptoms like fatigue, mood and anxiety nevertheless come from outside of the symptom network, because there is no node in the network that corresponds to inflammation. Thus, the external field is external relative to the psychopathology network, but not relative to the physical boundaries of the person. Importantly (and, in some cases, plausibly), the external field may include abnormal brain functioning, commonly thought to be associated with mental disorders[41]; for instance, delusions or hallucinations may arise in this way.

If all symptoms in a network interact with each other, and these interactions also have the same strength, symptoms are exchangeable, except for their dependence on the external field. In this case, if the connections are strong, the symptoms in the network will show highly synchronized behavior: if one symptom is active, it is more likely than not that the other symptoms are also active. However, if not all symptoms directly

interact or if certain interactions are much stronger than others, certain symptoms in the network can be active, while others are not. In this case, the network structure will feature *clustering*: within the archipelago of psychopathology symptoms, we will find particular island groups that are very closely related and thus influence each other to a greater degree[34].

For instance, insomnia is likely to have a strong direct effect on fatigue, but a much weaker effect on feelings of guilt; if insomnia does influence feelings of guilt, that effect is likely to be mediated by, for instance, loss of interest or concentration problems. Similarly, excessive alcohol use will first impact one's ability to fulfill daily duties, a symptom that will probably mediate the origination of further problems (e.g., losing one's job). If such symptom groups form more tightly connected sub-networks in the larger psychopathology network, this will produce reliable patterns of co-activation among symptoms.

NETWORK THEORY

The ideas presented above can be generalized to a comprehensive theoretical model of psychopathology. In particular, I propose the following four principles to encode the backbone of the network theory of mental disorders:

Principle 1. *Complexity*: Mental disorders are best characterized in terms of the interaction between different components in a psychopathology network.

Principle 2. *Symptom-component correspondence*: The components in the psychopathology network correspond to the problems that have been codified as symptoms in the past century and appear as such in current diagnostic manuals.

Principle 3. *Direct causal connections*: The network structure is generated by a pattern of direct causal connections between symptoms.

Principle 4. *Mental disorders follow network structure*: The psychopathology network has a non-trivial topology, in which certain symptoms are more tightly connected than others. These symptom groupings give rise to the phenomenological manifestation of mental disorders as groups of symptoms that often arise together.

These principles imply that the etiology of mental disorders can be thought of in terms of a process of spreading activation in a symptom network[34,42-44]. If a symptom arises (which may occur for different reasons depending on person, time and context), this will influence the probability that a connected symptom arises as well. Thus, coupled sets of symptoms, which are close in the network structure, will tend to synchronize. Mental disorders then arise when groups of tightly coupled symptoms actively maintain each other, leading to a cluster of psychopathology symptoms that becomes self-sustaining.

Some remarks on these principles are in order. Principle 1, *Complexity*, appears the least problematic. With the exception of a few illustrative cases[3], no theoretically singular causes of mental disorders have so far been identified; therefore, accounts of mental disorders in terms of interacting components of a complex system are not only plausible, but in a sense the only game in town. Thus, this principle encodes the consensus that mental disorders are multifactorial in constitution, etiology, and causal background, which appears overwhelmingly plausible given the current scientific record[3,45].

Principle 2, *Symptom-component correspondence*, is less straightforward. The assumption implies that psychopathology symptoms are defined at the right level of granularity, and successfully identify the important components in the psychopathology network. Insofar as factors not encoded in common diagnostic systems play a role (e.g., psychological processes not included in the symptomatology, neural conditions, genetic antecedents), they must do so by: a) constituting the symptom in question (e.g., the symptom of anxiety involves a neural realization in the brain, which partly constitutes that symptom), b) constituting a symptom-symptom connection (e.g., the biological clock is part of the system that generates the insomnia → fatigue relation), or c) acting as a variable in the external field (e.g., chronic pain is likely to be an external factor that causes fatigue).

Principle 3, *Direct causal connections*, appears plausible on several grounds. First, diagnostic systems often explicitly require the presence of symptom-symptom connections for diagnosis. Second, clinicians spontaneously generate causal networks when asked how symptoms hang together[1,46], and people in general seem to experience little trouble listing the causal relations between their symptoms[47,48]. Third, momentary mood states that are closely related to symptomatology, as measured through experience sampling[49], indeed appear to interact[15,50-53]. Finally, network analyses of, for instance, DSM-5 symptoms show that many symptom pairs remain statistically associated, while controlling for all other symptoms[31]; this provides evidence, although indirect, for the hypothesis that the relevant symptoms are causally connected.

Principle 4, *Mental disorders follow network structure*, holds that the stable phenomenological grouping of symptoms, which forms the basis of the current syndromic definitions of mental disorders, as for instance presented in the DSM-5, results from the causal architecture of the symptom network at large: symptoms that belong to the same disorder are more strongly causally related than symptoms that belong to different disorders, as is illustrated in Figure 2. As a result, in factor analyses of the covariance among symptoms or total scores defined on them[54,55], tightly coupled groups of symptoms will tend to load on the same factor. If this is correct, existing factor-analytic work on the covariance structure of symptoms can be interpreted as yielding a first approximation to the network architecture of psychopathology.

An important consequence of the above principles is that *comorbidity* is an intrinsic feature of mental disorders[6]. That is, even though processes of symptom-symptom interaction may be most active within symptom sets that are associated with a given mental disorder, they will not stop at the border of a DSM diag-

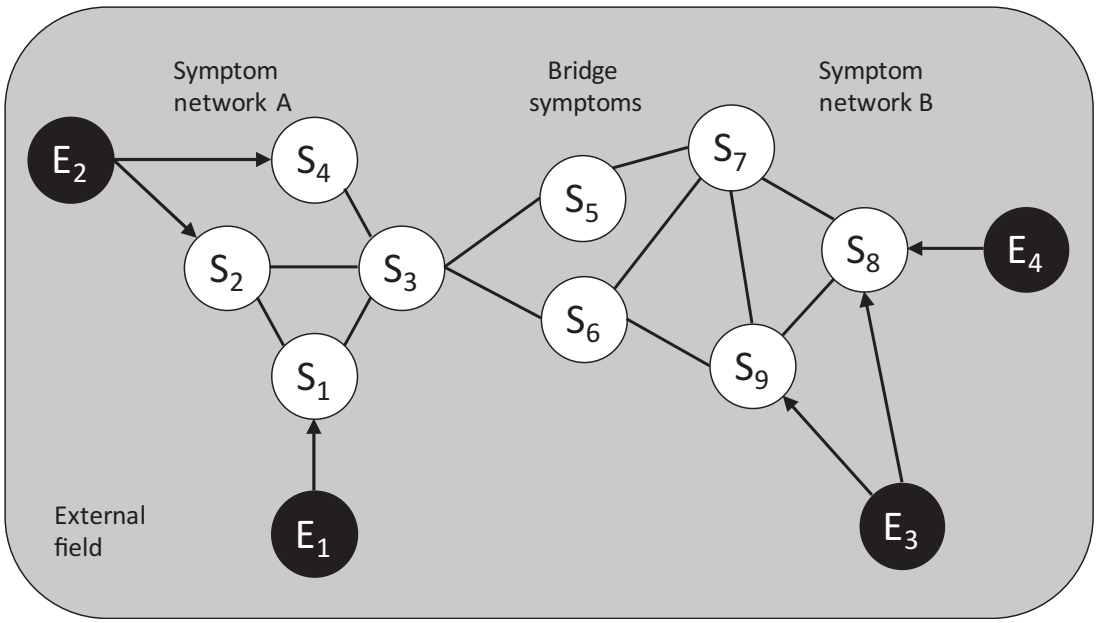

Figure 2 Two disorders (A and B) that are connected through bridge symptoms (S_5 and S_6) which play a role in both networks. Although the association of symptoms will be strongest within each network, structural overlap between the disorders is unavoidable, and as a result comorbidity will arise.

nosis. For instance, if a person develops insomnia in the context of post-traumatic stress disorder, that may cause fatigue and concentration problems – *bridge symptoms* that also belong to networks associated with major depressive episode and generalized anxiety disorder – and as a result comorbid patterns of symptom interactions will arise in the major depressive episode/generalized anxiety disorder network. Thus, instead of a nuisance that will go away once we have better measurement equipment, more insight in the biology of the brain, or more knowledge of the genetic structure of disorders, comorbidity should be seen as part of the flesh and bones of psychopathology[6].

THE DYNAMICS OF SYMPTOM NETWORKS

The implications of network thinking for the structure and comorbidity of mental disorders are straightforward, and as a result they were quickly identified once the network approach surfaced[5,6]. It took longer to realize that the network theory also has implications for the *dynamics* of mental disorders. Especially Cramer's work[56] was instrumental in this regard, because it proved the existence of a phenomenon called *hysteresis* in realistically parameterized symptom networks[57]. This is a major discovery which may hold the key to connecting the structure of symptom networks to their dynamics.

To illustrate the importance of hysteresis, we need to specify how the etiology of mental disorders pans out in a network. Figure 3 gives a representation of that process. Assume that we start from a fully asymptomatic Phase 1. In this phase, no symptoms are present, and the properties that underlie the causal interactions between symptoms in later phases are *dormant* (i.e., dispositional, in that they describe what *would* happen upon symptom activation, but not what *does* happen at that moment). In Phase 2, trigger events in the external field (e.g., adverse life events) produce *network activation*. In Phase 3, symptom activation will spread through the network via connections between symptoms. In a strongly connected symptom network, symptoms can enter Phase 4, in which they keep each other activated due to feedback relations. As a result, the network can become *self-sustaining*, and may stay active long after the events in the external field that triggered its activation have waned.

Strongly connected networks thus feature an asymmetry in their dynamics: although the *presence* of a given trigger event can *activate* a strongly connected network, the subsequent *absence* of that event needs not *de-activate* it. This is the phenomenon of hysteresis, a hallmark of phase transitions[58] that is present in many complex systems. Hysteresis is, in my view, a very plausible feature of psychopathology networks, because – in many cases of psychopathology – triggering events can cause pervasive problems long after the triggers themselves have disappeared. An important example would be the etiology of post-traumatic stress disorder, which develops and endures after the traumatic event itself has subsided[23], but we see similar examples in the development of major depression after the loss of a spouse[16] and in the effects of childhood abuse, which persist long after the abuse has ended[27]. The network theory thus offers an explanatory mechanism for these phenomena in the form of self-sustaining feedback between symptoms, as coded in its final principle:

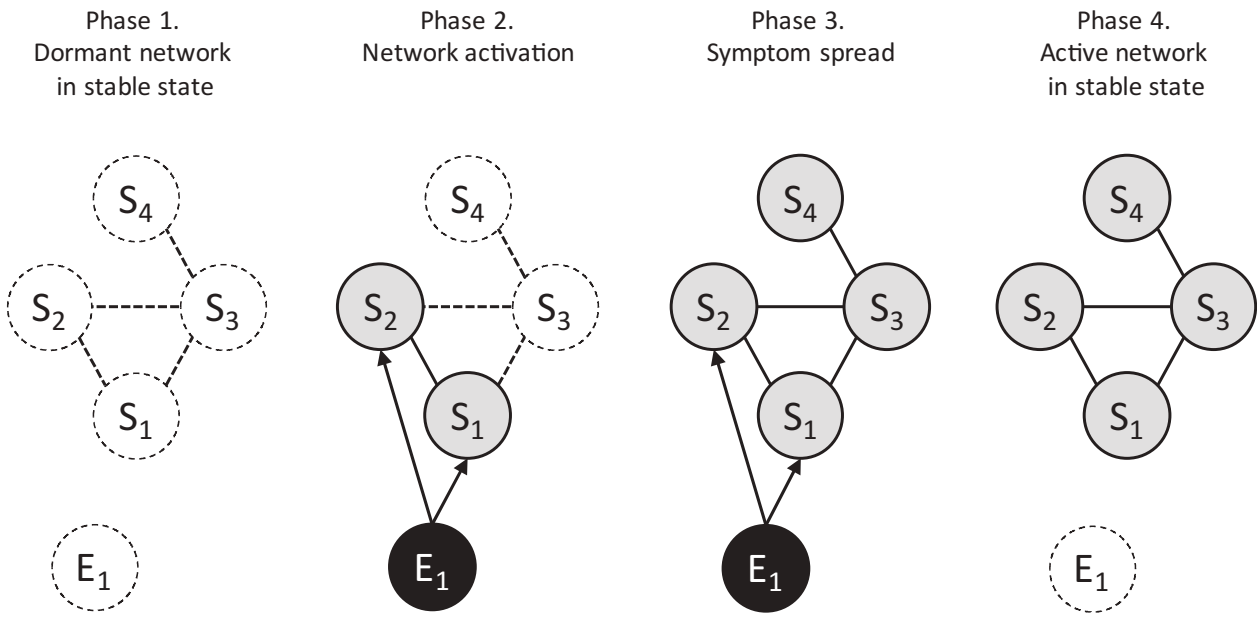

Figure 3 Phases in the development of mental disorders according to the network theory. After an asymptomatic phase, in which the network is dormant (Phase 1), an external event (E_1) activates some of the symptoms (Phase 2), which in turn activate connected symptoms (Phase 3). If the network is strongly connected, removal of the external event does not lead to recovery: the network is self-sustaining and is stuck in its active state (Phase 4).

Principle 5. *Hysteresis*: Mental disorders arise due to the presence of hysteresis in strongly connected symptom networks, which implies that symptoms continue to activate each other, even after the triggering cause of the disorder has disappeared.

Note that these dynamics only occur in strongly connected networks, because only these networks display hysteresis[56,57]. In weakly connected networks, more serious triggers can evoke strong reactions but, because the connections between the symptoms are not strong enough to render them self-sustaining, the network will gradually recover and return to its asymptomatic state. A process that may instantiate this phenomenon in networks of depression symptoms is normal grief. Normal grief can cause a symptom pattern that is indistinguishable from major depression but, because the symptoms do not engage in feedback, the symptom pattern is not self-sustaining, so that in time the system returns to its healthy stable state. This difference is represented in Figure 4.

The different dynamics of symptom networks under various parameterizations suggest novel definitions of well-known concepts in psychopathology research. First, the notion of *mental health* may be defined as *the stable state of a weakly connected network*. Note that this definition does not coincide with a definition of mental health as "absence of symptoms"; instead, it defines mental health as an equilibrium state, to which a healthy system returns if perturbed. Weakly connected networks can, however, feature symptomatology given stressors in the external field (e.g., normal grief); conversely, strongly connected networks can have temporarily absent symptomatology due to local suppression of that symptomatology (for instance, a person with a vulnerable network involving psychotic symptoms may be temporarily asymptomatic due to medication).

In parallel, the notion of a *mental disorder* itself assumes a new definition as *the (alternative) stable state of a strongly connected network*, i.e., the state of disorder that is separated from the healthy state by hysteresis. The concept of *resilience* can be defined as the disposition of weakly connected networks to quickly return to their stable state of mental health, and the concept of *vulnerability* as the disposition of strongly connected networks to transition into a state of disorder upon a perturbation in the external field. Individual differences in *liability* to develop different kinds of disorders (e.g., internalizing versus externalizing disorders) are due to differences in the network parameters of the corresponding symptoms[7]. This system of definitions is represented in Table 1.

DIAGNOSIS AND TREATMENT

In the network theory, diagnosis should be understood as a process by which a clinician identifies: a) which symptoms are present, and b) which network interactions sustain them. Arguably, this is quite close to how clinicians naturally conceptualize and diagnose disorders. For example, diagnostic manuals routinely require one to code not only the presence of symptoms, but also the interactions between them. The DSM-5 diagnosis of obsessive-compulsive disorder, for instance, not only requires the presence of obsessions and compulsions, but of their causal coupling (e.g., a person is driven to compulsive cleaning *in response to* an obsession with cleanliness); the

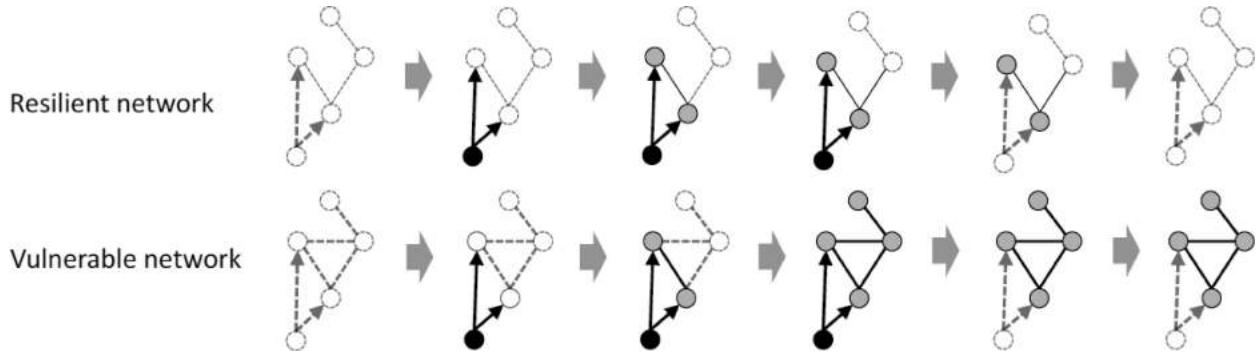

Figure 4 A weakly connected network (top panel) is resilient. Symptoms may be activated by events in the external field, but the symptom-symptom interactions are not strong enough to lead to self-sustaining symptom activity. A strongly connected network (bottom panel), instead, can sustain its own activity and thus develop into a disorder state.

diagnosis of substance use disorder requires giving up important activities *because of* substance use.

In addition, the DSM-5 contains many specifications of the context in which symptoms should arise (e.g., the presence of *insomnia* only counts as a symptom of major depressive episode in the context of a prolonged period of depressed mood and/or loss of interest). Finally, the DSM-5 contains a great many negative causal specifications, which require certain causes to be *absent* (e.g., substance use as a cause of symptoms in schizophrenia). Thus, although the DSM-5 may be "theoretically neutral" with respect to other theories of psychopathology[59], it is not neutral with respect to the network theory; rather, it specifies causal network structures throughout its definitional apparatus.

Naturally, there are also important aspects of the network theory that the DSM-5 does not articulate, such as the importance of feedback between symptoms in sustaining mental disorders. In addition, findings of network analysis may generate novel insights into the functional role and importance of specific symptoms in maintaining disorders (e.g., the centrality of symptoms in the network). Thus, while the network theory accords well with current diagnostic practice, it can also be expected to enhance that practice with novel concepts and methodology[12-14].

If diagnosis involves identifying a symptom network, then treatment must involve changing or manipulating that network. Due to the simplicity of networks, such manipulations can be organized in just three categories: a) *symptom interventions*, which directly change the state of one or more symptoms, b) *interventions in the external field*, which remove one or more triggering causes, and c) *network interventions*, which change the network structure itself by modifying symptom-symptom connections. As an example, consider a drug-using psychotic person who is convinced that other people can hear his thoughts, as a result does not go out, and becomes socially isolated, which in turn serves to sustain the delusion in question. In this case, an example of a symptom intervention may involve prescribing antipsychotic medication in order to suppress the delusion directly. A change in the external field may involve an intervention that suppresses one or more triggering events (e.g., get the person to quit precipitating drug use). Finally, a network intervention may involve cognitive behavioral therapy, which aims to teach the person how to deal with the delusion in question so that, even if it does arise sometimes, it no longer has the effect of causing social isolation.

If mental disorders can indeed be understood as symptom networks, and treatment can be categorized as suggested above, then one could couple a "library" of treatment interventions to a set of network structures, in order to optimally select and plan interventions. That is, if we could detect the network structure that governs a specific individual's pattern of symptom-symptom interaction – e.g., through the analysis of perceived causal relations[47] or the experience sampling method[49-53] – then we could search for the combination of treatment strategies that would most effectively lead the network to transition into a healthy state. It would seem likely that successful treatment will generally require a combination of network interventions (in order to make the healthy state accessible) and symptom interventions (to knock the system into that healthy state).

Table 1 Network connectivity and the external field

		Network connectivity	
		Weak	***Strong***
Stressors in external field	***Weak***	Mental health with high resilience	Elevated vulnerability (possibly remission state)
	Strong	Elevated symptomatology	Mental disorder

A weakly connected network will, under low external stress levels, occupy a stable state of mental health (top left cell). The network is resilient because – even if it may feature symptomatology if put under stress from the external field (bottom left cell) – it will return to its stable state when that stress level diminishes. In contrast, a highly connected network may be asymptomatic (top right cell), but is vulnerable because – as soon as a stressor arises in the external field – it can transition to an alternative stable state of mental disorder (bottom right cell).

CONCLUSIONS

The network theory of mental disorders, as advanced here, offers a consistent and transparent theoretical framework for thinking about psychopathology. The first empirical steps along the lines of this theory have already been taken, in the form of explorative studies that chart the network architecture of symptomatology[13-37]. Assuming that, in time, the structure of symptom networks becomes increasingly clear, the second empirical step would be to connect (individual differences in) the architecture of these networks to (individual differences in) relevant biological, psychological and socio-cultural factors. Finally, a better understanding of the processes that instantiate symptom thresholds and network connectivity parameters should allow us to optimally organize existing treatment interventions, and develop new ones. This presents a new kind of roadmap for progress in psychopathology research, which hopefully will be more successful than past attempts to understand and combat mental disorders.

A question that arises is how far the theory generalizes and what kind of theory it is. Because the network model is not tied to a particular level of explanation (e.g., biological, psychological or environmental), and does not single out particular mechanisms that generate the network structure, it is perhaps best interpreted as an organizing framework – an explanatory scheme with broad use across sub-domains of psychopathology. In this respect, the theory is reminiscent of Darwin's theory of evolution, which also yields a set of explanatory mechanisms (e.g., mutation, natural selection, adaptation) that may play out in different ways in different species. Like the theory of evolution, the network theory of psychopathology yields broad explanatory principles (e.g., hyperconnectivity in symptom networks yields alternative stable states that correspond to disorders), without specifying, in advance, the realization or implementation of these principles. This is an advantage, because it means that the network theory offers a framework for the integration of different levels of explanation (i.e., biological, psychological, sociological) that, in my view, is a necessary feature of any successful theory of mental disorders. At the same time, the model is not merely metaphorical or verbal: granted some simplifying assumptions, the network theory can be represented in mathematical form[60,61] and thus allows for simulating both the course of disorders and the effects of various treatment interventions.

However, to what extent the network theory may serve as an exhaustive explanatory model remains to be seen; clearly there are some disorders that fit the framework better than others. The match with episodic disorders and chronic disorders with a relatively well-delineated onset (e.g., major depression, post-traumatic stress disorder, obsessive-compulsive disorder, substance use disorder, panic disorder, generalized anxiety disorder, phobias, eating disorders) appears reasonable. Disorders with a cyclic pattern (e.g., bipolar disorder) may be accommodated in models for which the stable state is a cycle rather than a fixed point. It is less obvious that the theory could accommodate the genesis of slowly developing disorders (e.g., autism spectrum disorders, personality disorders, some aspects of schizophrenia). These disorders are likely to feature an interaction between different symptoms as well, but this must partly involve developmental processes that play out on very different time scales. For example, in autism, it is likely that a symptom such as avoiding eye contact, in the long run, will limit the ability of a child to learn the ways of social interaction, leading to a symptom like problems in maintaining relationships. However, this process itself likely includes fast feedback processes involving the reward structure of social interaction, leading to a Russian doll of networks within networks. Whether such disorders are amenable to a network theory, and what such a theory would look like, is therefore an important question for future research.

It is worth noting that the theory proposed in this paper is very simple. Especially principle 2, *symptom-component correspondence*, appears quite strict, but there are various other properties of the theory that, as research progresses, may well turn out to be strong idealizations and abstractions. This is a deliberate choice. Networks are quite complex by nature, and I think that, given our current state of ignorance, it is better to have at least a relatively tractable network theory, which may need to be altered as research data come in, than to start out with an overly complicated model, involving an indefinite set of variables, that places no restrictions on the data and bears unclear relations to the evidence. My hope is that, through successive iterations of the network model, we will ultimately converge on a reasonable model of mental disorders that, while probably more complex than the current formulation, will still be sufficiently tractable as to be scientifically workable.

Finally, as may be clear from the examples given in this paper, connections between symptoms are often prosaic. If you do not sleep, you get tired; if you see things that are not there, you get anxious; if you use too much drugs, you get into legal trouble, etc.. It is, in my view, likely that these symptom-symptom connections are rooted in very ordinary biological, psychological and societal processes (and thus may involve harmful dysfunctions in these processes[59]). This is surprising, because it means that disorders are not ill-understood ephemeral entities, the nature of which will have to be uncovered by future psychological, neuroscientific or genetic research (which appears a widespread conviction, if not the received view, among researchers). Rather, the fact that we have the set of basic symptoms, and also understand many of the relations between them, means that we already have a quite reasonable working model of what disorders are and how they work.

If so, our current lack of understanding of mental disorders may not have resulted from limited observational capacities, noisy measurement instruments, or inadequate data, as is typically supposed. Instead, we may have simply lacked a theoretical framework to organize the available empirical facts.

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The current conceptualization of negative symptoms in schizophrenia

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Negative symptoms have long been conceptualized as a core aspect of schizophrenia. They play a key role in the functional outcome of the disorder, and their management represents a significant unmet need. Improvements in definition, characterization, assessment instruments and experimental models are needed in order to foster research aimed at developing effective interventions. A consensus has recently been reached on the following aspects: a) five constructs should be considered as negative symptoms, i.e. blunted affect, alogia, anhedonia, asociality and avolition; b) for each construct, symptoms due to identifiable factors, such as medication effects, psychotic symptoms or depression, should be distinguished from those regarded as primary; c) the five constructs cluster in two factors, one including blunted affect and alogia and the other consisting of anhedonia, avolition and asociality. In this paper, for each construct, we report the current definition; highlight differences among the main assessment instruments; illustrate quantitative measures, if available, and their relationship with the evaluations based on rating scales; and describe correlates as well as experimental models. We conclude that: a) the assessment of the negative symptom dimension has recently improved, but even current expert consensus-based instruments diverge on several aspects; b) the use of objective measures might contribute to overcome uncertainties about the reliability of rating scales, but these measures require further investigation and validation; c) the boundaries with other illness components, in particular neurocognition and social cognition, are not well defined; and d) without further reducing the heterogeneity within the negative symptom dimension, attempts to develop successful interventions are likely to lead to great efforts paid back by small rewards.

Key words: Negative symptoms, schizophrenia, blunted affect, alogia, anhedonia, asociality, avolition, expression factor, experiential factor, assessment instruments, objective measures, treatment

(World Psychiatry 2017;16:14–24)

The first conceptualizations of negative symptoms of schizophrenia date back to the early 19th century, when J. Haslam described in young people a mental illness characterized by blunted sensitivity and affective indifference[1]. J. Hughlings Jackson[2] regarded negative symptoms as reductions in aspects of higher cognitive and emotional functioning, while considering positive symptoms as "release phenomena", episodic distortions or exaggerations in normal function. E. Kraepelin[3] described negative symptoms of dementia praecox as a "weakening of those emotional activities which permanently form the mainsprings of volition, emotional dullness, failure of mental activities, loss of mastery over volition, of endeavor and of ability for independent action", and E. Bleuler regarded affective blunting and emotional withdrawal as "fundamental" to schizophrenia, while defining hallucinations, delusions and catatonia as aspects of acute exacerbations[4].

In spite of the considerable attention received in those years, negative symptoms have long been neglected in the diagnosis and treatment of schizophrenia. During the 1970s, a renewed interest in these symptoms was elicited by Strauss et al[5], who re-asserted the primary and chronic nature of negative symptoms, while considering positive symptoms as a non-specific transient reaction to stress or biological causes.

During the 1980s, a dichotomic approach to schizophrenia classification was proposed by T. Crow[6], who described two subtypes: type I, characterized by positive symptoms (hallucinations and delusions), favourable response to antipsychotic medications, good cognitive abilities and an increase in dopaminergic D2 receptors, and type II, marked by negative symptoms (blunted affect, poverty of speech and loss of drive), poor response to antipsychotics, cognitive impairment and neuroanatomic abnormalities. N. Andreasen[7] also described a positive, a negative and a mixed subtype of schizophrenia. This dichotomic approach, however, showed several limitations, including the lack of diagnostic stability over time[8,9], limited prognostic implications[10,11], and an inconsistency with factor analyses of the psychopathology of schizophrenia, which systematically yielded more than two factors[12,13].

Carpenter et al[14] introduced the concept of deficit schizophrenia to identify a relatively homogeneous subgroup of patients characterized by the presence of primary and persistent negative symptoms since first presentation, cognitive deficits, insidious onset, poor premorbid adjustment and poor overall outcome[15,16]. Subsequent research provided some support to the hypothesis that deficit schizophrenia is a separate disease entity rather than the worst end of a severity continuum in schizophrenia[15,17-21].

Notwithstanding the role of negative symptoms in its characterization and outcome, schizophrenia can be diagnosed in the absence of these symptoms, although the dimensional approach proposed by the DSM-5 will hopefully result in a greater focus on this key aspect of the disorder.

More recently, the accumulating evidence concerning the impact of negative symptoms on real-life functioning of people with schizophrenia[22-30], as well as the development of new molecules[31-33], stimulation treatments and psychological programs targeting these symptoms[34,35], have generated a renewed interest in negative symptom conceptualizations.

It has been increasingly acknowledged that instruments often used to assess negative symptoms include some aspects

not relevant to that concept[36-38]. For instance, the Scale for the Assessment of Negative Symptoms (SANS)[39] includes aspects such as inattentiveness, poverty of content of speech, increased latency of response, blocking, inappropriate affect, poor grooming and hygiene, which are not related to the negative dimension of schizophrenia. The negative subscale of the Positive and Negative Syndrome Scale (PANSS)[40] includes difficulty in abstract and stereotyped thinking, whose relationship with the negative dimension is highly questionable[41]. Factor 2 of the Brief Psychiatric Rating Scale (BPRS)[42], often used as a proxy measure for negative symptoms, includes emotional withdrawal (i.e., deficiency in relating to the interviewer and interview situation), which can be due to paranoid delusions or disorganization, and motor retardation (i.e., reduction in energy level), which might be due to depression or catatonia.

During the past decade, a broad consensus has been reached on the inclusion of five constructs in the negative symptom dimension: blunted affect, alogia, anhedonia, asociality and avolition[43-46]. Hereafter, we review for each construct the current definition; the differences among the main assessment instruments; the available quantitative measures and their relationship with the evaluations based on rating scales; as well as the correlates and the experimental models. The evidence that the five constructs are reflected by a two-factor structure is discussed, and future implications for research highlighted.

BLUNTED AFFECT

Blunted affect is a decrease in the observed expression of emotion, i.e. facial and vocal expression, and expressive gestures[47-49]. The term is nowadays preferred to and distinguished from flat affect, which represents the extreme end of the spectrum of blunting.

Blunted affect is included in commonly used negative symptom rating scales, such as the PANSS, the SANS, the Clinical Assessment Interview for Negative Symptoms (CAINS)[45,46], and the Brief Negative Symptom Scale (BNSS)[50]. Its evaluation is based on the observed spontaneous expression of emotion during the clinical interview, or emotion expressions in response to prompts provided by the interviewer, rather than on the subjective experience of decreased emotional range.

In the PANSS, the focus of the assessment is on facial expression and communicative gestures. In the SANS, more features are taken into account: facial expression, expressive gestures, eye contact, affective responsivity and vocal inflections. On the other hand, some of the features included in the SANS assessment of blunted affect do not appear in more recently developed instruments for the evaluation of negative symptoms: in particular, inappropriate affect is currently regarded as an aspect of disorganization, while decreased spontaneous movements are regarded as unspecific and more relevant to the assessment of depression. In both the CAINS and the BNSS, facial expression, vocal expression and expressive gestures are rated as features of blunted affect.

Facial expression has been measured using observational coding systems, such as the Facial Action Coding System and its emotion variant[51,52], the Facial Expression Coding System[53]. The majority of studies reported that both medicated and unmedicated patients with schizophrenia, compared to healthy controls, show a reduction in facial expressions for all emotions, involving both frequency and intensity, up to the total lack of changes throughout a conversation and in response to different stimuli aimed to elicit an emotional response[54]. A significant correlation with blunted affect has generally been reported[54].

Studies based on electromyography have provided objective measures of facial expressions. Most of them reported that, in response to emotional stimuli, individuals with schizophrenia have comparable or less zygomatic activity (typically associated with positive emotion) and comparable or greater corrugator activity (typically associated with negative emotion)[55-58]. The increased activity of the corrugators does not necessarily index a greater emotion expression in subjects with schizophrenia, as the activity of this muscle also reflects effort, concentration or puzzlement. In addition, even if individuals with schizophrenia were not impaired in these subtle microexpressions of emotions, their failure to show observable expressions clearly detectable by people they interact with would still have an impact on their social interactions. Healey et al[59] investigated how well the general public, i.e. not clinicians and research examiners, recognizes facial emotion expressions of persons with schizophrenia compared to expressions of healthy individuals, and found that facial expressions of persons with schizophrenia were more poorly recognized and more easily misidentified as neutral.

The majority of studies comparing vocal expression in individuals with schizophrenia vs. healthy subjects reported less accurate spontaneous and voluntary vocal emotion expressions in the former. The impairment involves all speech parameters, suggesting a global deficit of prosody[60].

Studies aimed to provide an objective assessment of vocal expression in individuals with schizophrenia used methods of computerized acoustic analysis of speech. These studies confirmed the deficit of vocal expression in schizophrenia subjects as compared to healthy individuals; however, the magnitude of the deficit suggested a lower degree of impairment with respect to symptom rating scales[61]. The reasons for this discrepancy are not entirely clear. Vocal expression is a complex and likely multidimensional construct, and research is needed to clarify which aspects of this construct are most pertinent to schizophrenia pathology.

Expressive gestures include those made with the hands, head (e.g., nodding), shoulders (shrugging), and trunk (e.g., leaning forward). In social interactions, they help to define who is talking to whom, who will speak next, the reciprocal level of understanding, interest and attention to the ongoing conversation. An overall reduction in patients' nonverbal behaviour, including head and body movement, eye gaze and gestures, has been reported by a number of studies observing

patient's behaviour during two-way interactions with a psychiatrist[62-64].

Blunted affect is observed among individuals with schizophrenia both on and off medication, thus excluding the possibility that the symptom is always caused by antipsychotic agents[65-67].

The possibility that decreased emotion expression is due to a reduction of subject's internal emotion experience is not supported by available evidence, especially for negative emotions[54,60]. Findings on positive emotions are more controversial, and will be discussed in the section on anhedonia.

The main hypothesis on the pathogenesis of blunted affect and its components (diminished facial and vocal expression and expressive gestures) include abnormalities in emotion identification and discrimination and, more in general, perception of nonverbal social cues (facial affect, prosody, and body gestures), or deficits in motor activity. As to the first hypothesis, deficits in perception of nonverbal social cues have been reported in several studies[68,69]. However, an association between deficit in nonverbal social cue perception and diminished emotion expression or negative symptoms has not been found consistently[70].

As to the alternative hypothesis, i.e. a deficit of motor expression[54,71], it is worth mentioning that patients with motor abnormalities are prone to impairments in nonverbal communication. Underlying mechanisms may vary (e.g., abnormalities of the basal ganglia or frontal lobe dysfunctions), and may differ for the various components included in the assessment of blunted affect. An abnormal functioning of the mirror neuron system has also recently been hypothesized[72]. This hypothesis might link the deficit of social perception to the motor abnormalities by assuming that a dysfunction in mirror mechanism of gesture behaviour may underlie the patients' difficulties in producing gesture following demonstration by the examiner (imitation) or on verbal command (pantomime). However, we cannot assume that mechanisms underlying imitation or pantomime also apply to spontaneous expressive behaviour.

ALOGIA

Alogia is defined as a reduction in the quantity of speech and in its spontaneous elaboration. It is rated in commonly used negative symptom rating scales, such as the PANSS, SANS, CAINS and BNSS. Its evaluation is based on subject's language production during the clinical interview. The clinician rates the tendency to answer questions shortly, if not in monosyllables, throughout the interview. In the current conceptualization, alogia does not refer to impoverished content of speech.

In the PANSS, the symptom is named "lack of spontaneity and flow of conversation" and described as a decrease in the normal flow of communication associated with apathy, avolition, defensiveness or cognitive impairment. The relevant item evaluates both the amount of speech and the subject's attitude to avoid communication, while the latter is not regarded as relevant in other assessment instruments (actually, a reduction in the amount of speech aimed at avoiding communication may reflect psychotic features, e.g. persecutory delusions).

In the SANS, in addition to the reduction in quantity of speech (poverty of speech), alogia includes several items excluded in recently developed assessment instruments for negative symptoms, i.e. poverty of content of speech, blocking and increased latency of response. In fact, the poverty of speech content may be due to formal thought disorder (e.g., circumstantiality or derailment), anxiety or perseveration.

The BNSS provides separate items for quantity of speech and spontaneous elaboration (i.e., the amount of information given beyond what is strictly necessary in order to respond to the interviewer's questions, regardless of its relevance or importance), while the CAINS contains a single item for quantity of speech and does not assess spontaneous elaboration.

Cohen et al[73] conducted a meta-analysis of studies using an objective analysis of natural speech in patients with schizophrenia compared with non-psychiatric controls. They found that the reduction in speech production (reflecting alogia) had a large effect size ($d=-.80$; $k=13$), mainly driven by measures of pause behaviour as opposed to other aspects of speech, such as the number of words/utterances, that were reduced as well, but with a moderate effect size. Whether clinicians' judgment of alogia severity is mainly driven by the number and length of pauses deserves further investigation.

Several studies suggest an association between alogia and poor performance on verbal fluency tasks[74-77]. According to Fervaha et al[78], the relationship with verbal fluency is specific to alogia, i.e. not generalizable to other negative symptoms, suggesting that the two constructs tap into a common underlying mechanism. This mechanism could be a deficit of the ability to retrieve information from memory[79], since previous research showed that a deficit of controlled retrieval specifically affects the latency between words produced on category fluency tasks[80,81].

Controlled retrieval is likely to involve at least two components, i.e. the controlled activation of information in memory and the selection of specific information from the retrieved one[82]. The two aspects are associated with the activity of different brain regions: the left anterior ventrolateral prefrontal cortex and the left mid-ventrolateral prefrontal cortex, respectively. It might be of interest for future research on alogia in schizophrenia to disentangle the different cognitive components of controlled retrieval.

Cohen et al[61,63] have developed the cognitive resource limitation model, arguing that speech production in social situations places high demands on multiple cognitive processes. If cognitive resources are limited, patients will reduce their speech production. The association of alogia with cognitive deficits affecting controlled retrieval[79], semantic memory[84] and verbal fluency[75] would not contradict this hypothesis. The stronger negative correlations of general cognitive ability with alogia and blunted affect than with avolition/apathy and asociality[29,85] would also support the cognitive resource limitation model.

ANHEDONIA

Anhedonia, i.e. the diminished capacity to experience pleasant emotions, has traditionally been regarded as a core feature of both depression and schizophrenia[86]. However, this issue has turned out to be more complex than previously thought. In fact, although experiences of positive emotion during interview-based clinical assessments appeared to be reduced in people with schizophrenia, the use of emotion induction procedures under controlled laboratory conditions has shown that patients with schizophrenia do not differ from non-psychiatric controls in their subjective reactions to emotionally charged stimuli[54,87,88]. This discrepancy with previous findings of high rates of anhedonia in schizophrenia is attributed to limitations of self-report instruments, thought to be more cognitively demanding than laboratory based measures, often relying on complex cognitive processes, subject to systematic biases[89,90], or reflecting high rates of comorbid depression[91].

According to recent research, the anhedonia construct should be divided into at least two distinct aspects: a reduced experience of pleasure derived from ongoing enjoyable activities, also called consummatory anhedonia, which seems to be relatively intact in schizophrenia, and a reduced ability to anticipate future pleasure, also called anticipatory anhedonia, which seems to characterize people with schizophrenia[92-94]. However, some studies failed to confirm that anticipatory anhedonia is specific to schizophrenia, as it was found also in depressed patients[95]. Moreover, these aspects of the hedonic experience deficit in schizophrenia are more often regarded as part of the multifaceted construct of motivation, in which the ability to anticipate reward and pleasure is important to motivate behaviour aimed to achieve an expected, but not currently available, pleasant experience[96].

The assessment of anhedonia is not homogeneous across rating scales. This symptom is not included in the PANSS negative subscale. In the SANS, it is rated together with asociality, taking into account the subject's interest for recreational and sexual activities, as well as his/her ability to feel intimacy and closeness and to establish and maintain relationships with friends and peers; no distinction is made between consummatory and anticipatory anhedonia.

In the BNSS, anhedonia is rated by three separate items, measuring intensity and frequency of past (last week) pleasure, and intensity of future pleasure. Each item evaluates recreational, social, work/school, and physical pleasure. The frequency assessment does not require a precise count of activities over the past week, but rather a global consideration of behaviour relative to that person's demographic characteristics.

In the CAINS, anhedonia is rated by five items: two of them measure the frequency of past week recreational and social activities, while the other three measure the expected frequency of pleasurable work/school, social and recreational activities in the next week. No item for physical pleasure is included.

Strauss and Gold[97] found a low convergence between CAINS and BNSS items assessing anhedonia, and offered several possible explanations for the finding: a) the BNSS rates both intensity and frequency of past week pleasurable activities and only the expected intensity of future pleasurable activities, while the CAINS only considers the frequency; b) the BNSS evaluates four domains of pleasurable activity (work/school, recreational, physical, and social activities), whereas the CAINS evaluates two domains (social and recreational activities); c) the BNSS encourages the use of probe questions to help the subject to identify past and future pleasant activities, while the CAINS highlights the importance of avoiding probe questions relevant to expected pleasure, because the clinical goal is to assess the capacity to generate these expected events and activities.

In addition to rating scales, several self-assessment instruments, not developed and validated for schizophrenia specifically, are available for measuring anhedonia, such as the revised Social Anhedonia Scale (SAS)[98], evaluating pleasure in social activities; the revised Physical Anhedonia Scale (PAS)[99], measuring pleasure for physical stimuli; the Temporal Experience of Pleasure Scale (TEPS)[100], assessing trait anticipatory pleasure and consummatory pleasure; and the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS)[101], that rates both consummatory and anticipatory social pleasure.

So far, few studies have explored correlations between self-assessed and observer-rated anhedonia. Overall, the measures appear to be poorly correlated[97,102,103]. Whether this is due to the different assessment modality or to the different facets of anhedonia explored by the various instruments should be addressed in future research.

Abnormalities of pleasure experience in schizophrenia have also been conceptualized as difficulties in reporting past or future experiences[54], and the proposal has been made to avoid the term "anhedonia" and replace it with "reduced pleasure-seeking behaviour" or "beliefs of low pleasure"[54,104]. Recent evidence from cognitive neuroscience seems to lend support to this conceptualization, as it shows that anticipating future events relies upon the same neural processes involved in episodic memory[105,106].

In summary, the prevailing view today is that people with schizophrenia have a preserved ability to experience consummatory pleasure, but show a deficit in the anticipation of pleasure and the ability to engage in pleasure-seeking behaviours. The mechanisms underlying these deficits may be relevant to some aspects of motivation (e.g., reward anticipation or effort valuation) or of cognitive functioning (impaired episodic memory interfering with subject's ability to recall previous pleasant experiences).

ASOCIALITY

Asociality often predates the onset of schizophrenia[107], and also occurs in schizoid personality disorder and autism[108,109]. Commonalities and differences in phenomenology and pathophysiology across these disorders are still to be elucidated.

In people with schizophrenia, asociality is currently defined as a reduction in social initiative due to decreased interest in forming close relationships with others. It should not be defined in purely behavioural terms (i.e., whether the subject has or not social interactions and close relationships), but mainly as a reduction in motivation for social contacts (i.e., whether the subject values and desires social interactions and close social bonds)[46,50].

A reduction in social activities and contacts can be secondary to factors such as delusions and hallucinations, which can deteriorate relationships and other social ties; suspiciousness or depressed mood, that may induce withdrawal from social life; or lack of opportunities to establish and maintain social relationships. This distinction might have important clinical and research implications: adequate information on identifiable and treatable underlying causes of secondary negative symptoms might translate into better care for people with schizophrenia, although more systematic research is needed in this respect[38,110].

In the assessment of asociality, both the SANS and the PANSS mostly rely on subject's behaviour. In the SANS, asociality is rated by two items included in the same subscale as anhedonia: ability to feel intimacy and closeness, and relationships with friends and peers. Also in the PANSS asociality is rated by two items: poor rapport (rating based on the observed interpersonal behaviour during the course of interview) and passive, apathetic social withdrawal (rating based on the reports about patient's social behaviour provided by primary care workers or by relatives).

The CAINS and BNSS ratings are based on both internal motivation (interest and desire for close relationships and friendships) and behavioural aspects (actual engagement in social activities). In the BNSS, asociality inner-experience and behaviour are rated by separate items. In the CAINS, asociality items (motivation for close family/spouse/partner relationships and motivation for close friendships and romantic relationships) are subsumed under motivation for social relationships. Correlations between BNSS and CAINS items are moderate to high[97].

In spite of the pivotal role that asociality plays in schizophrenia course and outcome, few studies have explored its pathophysiological mechanisms. Currently, asociality is mostly regarded as social amotivation[111-113], and factor analyses showing that it loads on the same factor as avolition lend support to this view[43,49,112].

Felice Reddy et al[114] investigated asociality in schizophrenia using Gray's model of behavioural approach (i.e., behavioural activation system, BAS, relying on a reward system sensitive to appetitive stimuli and termination of punishment) and behavioural avoidance (i.e., behavioural inhibition system, BIS, sensitive to aversive stimuli, activated by anxiety, novelty, and fear stimuli, and responsible for inhibiting behaviour), and classified subjects according to the presence of negative symptoms and different levels of BIS and BAS scores. Among subjects with elevated negative symptoms, the authors identified two subgroups with different approach/avoidance profiles leading to asociality: one characterized by avoidance tendencies (high inhibition/moderate activation) and another characterized by lack of approach motivation (low inhibition/low activation). The former subgroup was interested in relationships, but avoided them because they were viewed as aversive and anxiety provoking; the latter did not value close friendship and showed diminished interest in people and reduced drive to develop close interpersonal bonds. Only the latter subgroup would meet the current definition of asociality.

Research addressing the relationship between asociality and social cognition also deserves attention. Social cognition refers to mental activities underlying social interactions, including perceiving, interpreting and generating responses to the intentions, dispositions and behaviours of others[115]. It is impaired in people with schizophrenia and contributes to their poor functional outcome[116-119]. The relationship between asociality and social cognition is likely to be complex: lowered motivation to participate in social activities might result in poor development of social cognition[120], or poor social cognition may result in a failure to experience reward signals during social interactions and translate into anhedonia, poor motivation and asociality.

Unfortunately, studies have generally looked at the association between negative symptoms in general (not focusing on asociality) and social cognition. Findings have been mixed, with some authors describing significant associations[121-124] and others reporting no association[125-127]. The reasons for these discrepancies may include the lack of focus on asociality as currently conceptualized and measured, but also the failure to control for confounding variables such as intellectual deficits, duration of illness or the use of assessment instruments for negative symptoms including cognitive measures or disorganization symptoms. Piskulic and Addington[128], for instance, reported that the PANSS negative scale item that emerged as the main predictor of social cognition variance was stereotyped thinking, i.e. an item that current conceptualizations would not place among negative symptoms. Thus, although a link between asociality and social cognition cannot be excluded, the extent and nature of this association is still to be clarified[129,130].

A relationship between dysfunctional beliefs and asociality has also been envisaged: negative expectancies about future rewards or success in social interactions would lead to a loss of motivation to engage in social activities[131].

Recently, several studies have suggested an involvement of oxytocin in asociality of patients with schizophrenia, as well as of people with autism spectrum disorders. In mammalian vertebrates, oxytocin is implicated in the central neuromodulation of social behaviour, and current research is trying to clarify its role in fine-tuning neuronal circuits underlying social interaction. An association between lower endogenous oxytocin levels and greater severity of negative symptoms, including asociality, has been found[132-134]. The relevance of these findings to the current conceptualization of asociality and their possible implications for treatment require further investigation.

AVOLITION

In the past decade, there has been a renewed interest in avolition, also due to the evidence that this symptom leads to severe impairments in real-life functioning[29,135] and predicts poor functional outcome[136,137] in people with schizophrenia.

Avolition is currently defined as reduced initiation and persistence of goal-directed activity. There is no agreement on the degree of overlap between the terms avolition, decreased drive, amotivation and apathy, and they are often considered interchangeable[138]. It is also highly debated whether the definition and assessment of avolition should rely upon the rater's or caregiver's observation of patient's behaviour, or patient's self-report of her/his engagement in different activities or self-declared interest in engaging in activities.

As for asociality, it is recommended not to base the ratings of avolition only on the observed behaviour. In fact, a failure to initiate and persist in goal-directed activities may be due to several factors that do not reflect negative symptoms (e.g., paranoid beliefs, depression or lack of opportunities). The assessment should always include the subject's desire and interest for goal-directed activities.

Clinical rating scales of avolition involve a retrospective assessment that often combines more than one source of information, whose correspondence has rarely been tested[139]. In the SANS, apathy/avolition is assessed by three items, all focusing on subject's behaviour: grooming and hygiene, impersistence at work/school, and physical anergia. In the PANSS, only one item actually refers to avolition, i.e. emotional withdrawal, which relies upon caregiver's report on patient's interest and emotional involvement in daily life. The BNSS includes separate items for avolition internal experience and avolition behaviour; both items cover motivation for work/school, recreational activity, self-care, and general time spent in inactivity. In the CAINS, avolition is assessed by two items of the scale "motivation and pleasure": motivation for work and school activities, and motivation for recreational activities. Inner experience and behaviour are rated within each single item; self-care is not rated. Correlations between BNSS and CAINS items are moderate to high, but lower than those observed for blunted affect and alogia[97].

According to current conceptualizations, motivation is a multifaceted construct, including hedonic experience, reward prediction and other elements, such as reward valuation, effort valuation, encoding of action-outcome contingency, and decision making processes[94]. This multifaceted framework closely resembles the conceptualization of motivation in the positive valence system within the Research Domain Criteria (RDoC) project[140], and in the last decade has become the object of several experimental models, that will be briefly reviewed hereafter.

The hypothesis that an impairment in reward functions undermines motivational aspects of the schizophrenia negative dimension has received great attention. It has been clarified that many subjects with schizophrenia experience pleasure as much as healthy subjects when engaging in pleasant activities during everyday life or when exposed to pleasant stimuli[92,141]; however, they less frequently engage in behaviours aimed at obtaining rewards and pleasurable outcomes[142], due to their failure to anticipate future rewards. Studies on reward anticipation in schizophrenia have mainly focused on the neurobiological underpinnings of this process, and consistently reported an impairment in reward prediction mechanisms mediated by striatal nuclei[93,143,144].

The ability to predict a reward requires a learning process. Therefore, several studies focused on reward learning processes in schizophrenia, and reported difficulties when rapid learning of reward cues is requested and changes in outcomes and feedbacks occur (e.g., a previously rewarded response is followed by punishment), while no differences are observed when subjects learn over many trials (habitual/procedural learning)[94,145,146].

The possibility has also been considered that the motivational deficit involves the ability to "represent value information", i.e. to link the hedonic properties of a stimulus with individual's internal state (e.g., food is more valuable to a hungry person), with the delay between the stimulus and the reward, as well as with the need to modify response contingencies (a previously rewarded stimulus that becomes associated with punishment). There is evidence that the ventromedial prefrontal cortex is involved in the representation of goal values[147].

Another approach to understanding the relationship between reward anticipation and avolition evaluates the amount of effort an individual is willing to exert for a certain amount of reward. Recent attention has focused on experimental paradigms that measure cognitive, perceptual and physical effort. Initial results from studies exploring the psychometric characteristics of different measures[148] appear promising. Tasks require an incrementally greater effort, either cognitive or physical, to obtain a monetary reward; the level of effort is increased from trial to trial to find the subject's "breakpoint", i.e. the point at which the subject is no longer willing to put effort to obtain the offered reward. Subjects with schizophrenia tend to have breakpoint scores lower than or equivalent to controls, and a lower breakpoint is significantly associated with greater severity of motivational deficit[149-154]. The brain areas that appear to be involved in computing the expected effort cost are the dorsomedial prefrontal cortex and the insular cortex[155].

The hypothesis that a deficit of executive functions contributes to subject's difficulty in engaging in goal-directed activity has also been supported by some research findings[156-158]. However, inconsistent results have been reported[46,85], and a more systematic assessment of both domains will help to identify reasons for discrepancies.

Notwithstanding the interest and progress brought about by the described experimental models, it is clear that the interaction of neural systems involved in motivation is a complex one, and we are probably just beginning to unravel this complexity. Besides the neural level, also the psychopathological level needs further refinement; in particular, the assessment should involve different instruments and sources of information,

and possible discrepancies should be highlighted. In addition, the possibility that personalizing reward (e.g., making monetary reward proportional to subject's income) could have an impact on patient-control differences should be addressed, and sources of secondary avolition carefully considered and possibly excluded.

FACTORS WITHIN NEGATIVE SYMPTOMS

Factor analyses of negative symptoms have demonstrated that the structure of these symptoms is not unidimensional. In studies focusing on the SANS, a number of factors ranging from two to five has emerged. However, the most replicated and stable structure (especially after excluding items unrelated to negative symptoms, such as inattentiveness or inappropriate affect) includes two factors, i.e. diminished expression and avolition[37,159,160]. Factor analyses on the Schedule for the Deficit Syndrome (SDS)[161], including six negative symptoms (restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive), have confirmed the two factor structure[28,162,163]. The same model has been confirmed by factor analyses of most recent assessment instruments, the CAINS and the BNSS[46,50,164]. In the relevant literature, the two factors are often referred to by different terms: diminished expression is also named as the expression factor, and avolition as apathy or motivation and pleasure or the experiential factor[165].

For the BNSS, six items (facial expression, expressive gestures, vocal expression, spontaneous elaboration, quantity of speech, and lack of normal distress) load on the expressive factor, and seven (intensity of expected pleasure from future activities, asociality behaviour, asociality inner experience, avolition behaviour, avolition inner experience, intensity of pleasure during activities, and frequency of pleasure during activities) load on the avolition/apathy factor. The factor structure seems to be independent of medication[37,160,162,166] and to hold up across time[28] and cross-culturally[28,162,163,167].

Few studies have attempted to identify external validators of the two negative symptom subdomains. The avolition factor seems to be associated with poorer premorbid social adjustment in childhood, more insidious onset of psychosis, executive functioning and abstraction-flexibility deficits, and a preponderance of male gender[70,157], while the diminished expression factor with an abrupt onset of psychosis, longer duration of hospitalization and impaired overall cognitive performance[70,85]. However, discrepant findings have also been reported, in particular concerning relationships with cognitive functioning[29,158].

Recent research has shown that the two factors have a different impact on psychosocial outcome. In fact, a strong relationship between avolition and poor social outcome has been consistently found[137,157,168], whereas findings relevant to the expressive subdomain have been mixed, and generally negative when the role of avolition is simultaneously accounted for[29,137,168]. The possibility that the strong impact of avolition on real-life functioning is due to the partial overlap between these two constructs cannot be ruled out. However, findings from studies using instruments developed to assess negative symptoms based on inner experience (e.g., lack of interest and motivation in different activities, impaired anticipation of rewarding outcome), instead of behavioural aspects (e.g., deficit in initiating and persisting in different activities, which are generally the focus of real-life functioning assessment), would argue against this possibility[24,29,169].

In summary, the two-factor structure appears highly replicable across instruments, medication status and phase of the illness. It is advisable that future research on negative symptoms avoids combining the two subdomains in order not to lose information relevant to pathophysiological mechanisms and to the ability of each factor to predict functional outcome.

CONCLUSIONS

From time to time, the conceptualization of negative symptoms has changed. Sometimes they have been considered as a key feature of schizophrenia, at other times neglected because they are difficult to be reliably assessed. Currently, negative symptoms are regarded as a core aspect of schizophrenia with a pivotal role in its functional outcome. However, the pathophysiology of primary and persistent negative symptoms is still unknown and they remain a major challenge in the treatment of those suffering from the disorder.

The assessment of the negative symptom dimension has certainly improved. A large body of research has clarified that some symptoms previously included in the negative symptom dimension – such as inattentiveness, poverty of content of speech, increased latency of response, blocking, inappropriate affect, poor grooming and hygiene – are not negative symptoms. The constructs currently considered as relevant to the negative dimension include blunted affect, alogia, anhedonia, asociality and avolition. This reconceptualization has, among the others, the advantage of reducing the overlap of negative symptoms with the cognitive, disorganization and depression dimensions of schizophrenia.

Whether this will represent an enduring consensus is hard to predict. In fact, while the need to exclude constructs unrelated to negative symptoms is undisputable, the choice and definition of current constructs should be regarded as work in progress.

As highlighted for each construct, largely used assessment instruments vary in terms of definitions and assessment modalities. The evaluation of alogia and blunted affect provided by the SANS and the PANSS, for instance, is based on different items, some of which are no longer regarded as relevant to the negative symptom domain (e.g., poverty of content of speech, inappropriate affect). The assessment of anhedonia, avolition and asociality also varies greatly: anhedonia is not rated in the PANSS; it is rated together with asociality in the

SANS; it is subdivided into consummatory and anticipatory in the BNSS and CAINS, but not in the SANS. In addition, the assessment includes physical anhedonia in some instruments but not in others, and some scales focus on behaviour, while others privilege subject's internal experience.

In addition to differences across instruments, methodological differences within the same instrument might also have important implications in terms of reliability of the observed findings. In fact, while the evaluation of some constructs (alogia and blunted affect) is mostly based on rater's observation during the interview, for other domains (anhedonia, avolition and asociality) the assessment relies upon subject's or other informant's recollection of the recent past.

The BNSS and the CAINS are considered by most experts in the field as state of the art for the assessment of the negative dimension constructs. They have been translated in several languages and are used in several clinical trials. Multinational, multicenter trials, aimed at adapting these instruments to different cultural contexts and validating them across illness stages and medication status, represent a possible step forward in the standardization of the assessment of negative symptoms. Hopefully this will translate in more consistent and clinically relevant research findings.

In the scientific community, there is also a rising interest for self-rated instruments that do not require a significant investment of time and effort by clinicians and are likely to reflect patient's internal experience. However, the reliability of these measures and the consistency with examiner-rated assessment instruments is still uncertain.

Future studies aimed at clarifying the neurobiological substrates of negative symptoms or investigating new compounds as potential treatments might benefit from experimental designs that take into account: a) the need to distinguish negative symptoms due to identifiable causes (e.g., extrapyramidal symptoms, depression or positive symptoms) from the primary ones, and b) the need to assess individual negative symptoms. It should be stressed that, for the time being, there is no evidence behind the assumption that a common pathophysiological mechanism underlies all negative symptom constructs; therefore the use of a total score for the negative dimension, although attractive from a statistical point of view (having more than one endpoint to deal with requires appropriate statistics and sample sizes), might prevent important conclusions relevant to individual constructs.

The search for objective measures represents a commendable effort. Their use might overcome the dismissive attitudes toward negative symptoms, justified by uncertainties concerning the reliability of rating scales. However, the discrepancy with data provided by rating scales deserves attention, since it has generated new hypotheses and insight in the complexity of the constructs, but in some cases might also lead to potentially misleading conclusions. For instance, quantitative measures of the activity of facial muscles involved in emotional expression might show no difference between patients with schizophrenia and healthy subjects, but the failure of these patients to show observable expressions clearly detectable by people they interact with would still have an impact on their social interactions.

The exclusion of some aspects which were previously part of the assessment of negative symptoms has contributed to reduce their overlap with other illness dimensions. However, the boundaries and relationships with neurocognition and social cognition are not yet well defined. Alogia, for instance, like poor verbal fluency, has been conceptualized as a deficit in the ability to retrieve information from memory; a similar deficit might underlie difficulties in gesture and facial expressions; anhedonia as difficulty in reporting past or future experiences might rely on the same neural processes underlying deficits in episodic memory; and asociality might be the origin as well as the result of poor social cognition. Further studies, either based on longitudinal designs or network models, might contribute to clarify these issues.

Heterogeneity among, and even within, the different negative dimension constructs cannot always be addressed by considering all of them as study outcome measures. The two-factor structure, highly replicable across instruments, medication status and phase of the illness, has been proposed as an alternative to either the use of a total score or of five different scores. However, the assumption that domains within the same factor share the same neurobiological mechanisms and that these mechanisms differ between the two factors has still to be substantiated by empirical data. So far, we cannot rule out the possibility that different constructs load on the same factor because of reasons different from shared underlying neurobiology, such as the focus on the behavioural aspects during the interview for blunted affect and alogia, versus the more introspective and retrospective approach for the anhedonia/avolition/asociality factor.

For the time being, both lumping and splitting approaches should be pursued, especially in studies investigating pathophysiological mechanisms of negative symptoms. The identification of different neural processes underlying different symptoms/constructs might imply the need for therapeutic interventions with different mechanisms of action. Without reducing the heterogeneity within the negative symptom dimension, attempts to identify successful treatments are likely to lead to great efforts paid back by small rewards.

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The limitations and future of violence risk assessment

Laws to protect the public from mentally ill people who have committed a violent offence date from the attempted assassination of King George III by a disturbed ex-soldier in 1800[1]. In the last 50 years, the assumption that mental illness is both a cause and a predictor of violence has led to changes in mental health laws that limit involuntary treatment to those considered to be dangerous[2] and to research into how to assess the risk of violence[3].

The most common form of violence risk assessment is still a judgment made by a clinician. However, this form of assessment lacks transparency, is vulnerable to cognitive biases and relies on the experience and expertise of the clinician. Actuarial assessments based on a score from of a list of identified risk factors have made violence risk assessment more objective, reliable and probably more accurate. More than 200 actuarial violence risk instruments have been described[4]. Despite their advantages over unaided clinical judgment, there are both scientific and ethical problems with the use of these instruments in clinical practice.

The scientific concerns are about the strength of the statistical separation of high-risk and lower-risk groups, the over-reliance on measures of discrimination (such as the area under the curve or odds ratios) rather than measures of prediction (such as the positive predictive value)[5], the applicability of instruments to different groups, and the extent to which aggregate risk data apply to individuals[6]. The ethical concerns include the potential for risk assessment to add to the stigma and discrimination experienced by the mentally ill, unfair restrictions after false positive predictions, and denial of care to those assessed to be lower-risk[7].

With these concerns in mind, any evaluation of the current state of violence risk assessment must answer two important questions: Does violence risk assessment produce valid information? And is this information clinically useful?

The first question has been answered by a recent meta-analysis of 92 studies that independently replicated the results of nine popular violence risk instruments[8]. The pooled estimate of the diagnostic odds of violence among high-risk patients was 3.08 (95% CI: 2.45-3.88), indicating that the rate of severe violence can be expected to be about three times higher in high-risk groups than lower-risk ones[8]. An odds ratio of three indicates that risk assessment produces valid information with a modestly strong effect size – a degree of separation between high-risk and lower-risk groups similar to the risk of suicide associated with male gender.

To answer the second question about the usefulness of the information generated by a violence risk assessment, we need to consider whether there are treatments or interventions that can be reasonably allocated to high-risk patients but denied to lower-risk patients, and whether the transfer of treatment resources from lower-risk to high-risk groups actually reduces the overall rate of violence.

Intervening on the basis of a score generated by a violence risk instrument can only be reasonable if the proportion of patients correctly predicted (true positives) is sufficiently high to justify the treatment of all those at high risk (true and false positives). Hence, risk guided interventions must be both effective and benign, because the low base rates for serious violence means that there will always be many false positives for every true positive prediction. Moreover, even if there is the opportunity to prevent some episodes of severe violence, interventions guided by the results of risk assessment can only be justified if there is a compelling reason for not intervening in lower-risk patients, who inevitably commit a proportion of all violent acts[9]. Few interventions meet this test, which might explain why, among the thousands of publications about risk assessment, there are as few as three controlled studies of risk guided interventions that have rates of violence as an outcome measure[10].

The time has come to shift the debate away from arguments about the numerical properties of violence risk instruments towards a consideration of whether being able to identify individuals with a greater risk can actually result in a reduction in the overall rate or severity of violence. A few controlled trials of the violence reducing properties of risk guided interventions would produce more useful information than any number of studies of the predictive properties of violence risk instruments.

What then is the future of violence risk assessment? Incremental improvements in predictive accuracy might follow the discovery of new risk factors or new ways of combining established risk factors using more sophisticated statistical techniques, or a reduced reliance on historical factors and a greater emphasis on the person's current situation.

In the future, violence risk assessment is likely to shift from cross-sectional prediction to ongoing clinical monitoring, using technology such as the analysis of social media and even telemetry reporting physiological markers of intoxication and abnormal mood states. We might tolerate some increased intrusion into the lives of our patients if new methods are shown to be effective in reducing violence.

However, any new methods should not only be assessed by their predictive ability, but also by reliable evidence that they can actually reduce violence and that any reduction is not at an unacceptable cost to an already disadvantaged section of society.

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Victimization of persons with severe mental illness: a pressing global health problem

A colleague likes to say that an alien visiting the US from outer space, after watching a few hours of television, would surely conclude that persons with severe mental illness (SMI) perpetually perch on the cusp of violence and mass mayhem. Media accounts in the US portray such persons as if their greatest risk of violence is towards others, and the risk of violent victimization of trivial concern. It is hard for the general public and even many clinicians to acknowledge that this simply is not so. Research to date has amply documented that acts of violence perpetrated by people with SMI are rare and committed by a small minority of individuals[1]. Indeed, if mental illness in the US was cured tomorrow, violence would only be reduced by roughly 4%, and 96% of violence would continue unabated[2]. In contrast, violent victimization is all too prevalent among persons with SMI[3].

What puts these persons at great risk of violent or criminal victimization? Such victims tend to be younger, socially active, and more symptomatic than those not victimized[4]. However, their impoverished social environments, risky interpersonal behaviors and often predatory peer networks likely put them at greater risk than their psychiatric symptoms. A longitudinal community study in four inner cities in England followed patients with recent psychosis for a year and observed that, compared to the general population, they were twice as likely to be victims of violence (16%), more likely to be homeless, abuse substances, have comorbid personality disorders and be more violent themselves[5]. These data suggests that victimization and risk of perpetrating violence may share a common social-environmental pathway.

A birth cohort in New Zealand, followed for 21 years, revealed that – compared to individuals with no mental illness and when controlling for socio-demographic characteristics, risk of violence and comorbid psychiatric conditions – those with anxiety disorders suffered more sexual assaults, those with psychotic illnesses experienced more threatened and completed assaults, those with alcohol abuse experienced more completed physical assaults, and those using marijuana encountered more attempted assaults[6]. A systematic review of nine studies reporting on criminal victimization of persons with mental illness found a large variation in risk of victimization, ranging from 2.3 to 140 times higher than reported in the general population. The wide range of risk is likely due to differences in measures of victimization, study populations and geographic region[7]. Association of victimization with substance use, homelessness, severe psychopathology and involvement in criminal activity was a common finding in most studies. Other factors that increased risk of victimization included poor social and occupational functioning, female gender, lack of daily activity, and childhood sexual and physical abuse.

Another systematic review, including 34 studies, similarly found that younger age, comorbid substance use, and being violent and homelessness are risk factors for victimization. Violent victimization also has long-term adverse consequences for the course of mental illness, and further erodes the quality of lives of patients with SMI and their families[8].

Studies focusing on victimization in women find a particularly adverse psychosocial impact on vulnerable homeless women with psychiatric illnesses[9]. Similarly, a UK based study observed that women with SMI were more likely to report psychological and social problems following violent victimization than the general population. These women experienced a four-fold increase in the odds of experiencing domestic and sexual violence, and a ten-fold increase in community violence[10].

Violence against persons with SMI is a pressing global health concern thwarting recovery and community integration. The preoccupation of the popular media with the violence risk of such vulnerable and disenfranchised individuals only serves to further exacerbate their community exclusion and, worse, to perpetuate cycles of victimization.

The prevention and management of victimization optimally starts with assertive engagement in mental health care, integrated with substance use prevention and treatment. But the social environment matters a great deal. In addition to a durable connection to mental health and substance use services, social and housing supports are vital to offer, as far as possible, non-criminogenic and non-substance abusing peer networks, meaningful engagement in vocational and leisure activities and safe living environments.

All this may sound aspirational, but treatment itself will only get us part of the way toward reducing victimization in this population.

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The long-term impact of bullying victimization on mental health

There is little doubt today that being bullied in childhood is an adverse experience that casts a shadow on children's and adolescents' mental health and wellbeing. After several decades of general skepticism about the true impact of bullying victimization, accumulating evidence now demonstrates a detrimental effect on youth's mental health and reveals other poor outcomes including low self-esteem, self-harm and academic failure. Recently, emerging findings have pointed toward a possible long-lasting effect of bullying beyond the childhood and adolescent periods. The impact of bullying on the young victims may therefore persist once the bullying has long stopped. This conclusion would imply a profound shift for prevention and intervention strategies, which commonly focus on the perpetrators of bullying, in the direction of greater attention to the victims, with the aim of reducing the burden of bullying victimization on individual lives and societal costs.

To date, three longitudinal cohorts have documented the adult outcomes of bullying victimization in childhood: the Epidemiologic Multicenter Child Psychiatric Study in Finland, the Great Smoky Mountains Study in the US, and the National Child Development Study in the UK. Studies indicated that young victims of bullying have higher rates of agoraphobia, depression, anxiety, panic disorder and suicidality in their early to mid-20s, compared to those who have not been bullied in childhood[1-3]. Child victims of bullying also have an increased risk of receiving psychiatric hospital treatment and using psychiatric medications in young adulthood[4]. Another study found that victims of bullying in childhood report high levels of psychological distress at age 23 but, most importantly, also at age 50[5]. Adults who were victims of frequent bullying in childhood had an increased prevalence of poor psychiatric outcomes at midlife, including depression and anxiety disorders, and suicidality. The effects were small, but similar to those of other adverse childhood exposures measured in that cohort study, such as placement in public or substitute care, or exposure to multiple adversities within the family.

These findings are based on observational data and thus do not allow causal inferences. The consistency of the results across three separate cohorts is, however, compelling. The three cohorts: a) used prospective measures of bullying victimization in childhood and later outcomes in adulthood; b) controlled for mental health problems in childhood, indicating that bullying victimization contributes either to new or to additional mental health problems in later years; c) accounted for a range of potential confounders, including childhood IQ, parental socio-economic status and gender; d) are representative of the population of three different countries. Conclusions from these studies cannot be ignored.

The developmental processes that translate childhood bullying victimization into health problems later in the life course are poorly understood. To identify targets for intervention programs aimed at reducing the harmful outcomes of being bullied in childhood, we need a better understanding of these processes. One such possible process relates to theories of the biological embedding of stress. Studies of monozygotic twins discordant for bullying exposure indicate that bullying victimization in childhood is associated with a blunted cortisol response[6], which in turn is associated with problems in social interaction and aggressive behavior[7]. A further study showed that the bullied twins had higher methylation levels on the serotonin transporter gene compared to their non-bullied co-twins[8]. These higher levels of methylation were associated with lower levels of cortisol response. Effects of this kind may serve as an interface between childhood bullying victimization and later vulnerability to stress and psychopathology.

Other studies have indicated that those who were victimized by bullies also showed problems with social relationships, poor physical health and financial difficulties in adulthood[5]. This suggests that other processes could involve a detrimental effect of being bullied on life opportunities for building the human and social capital that young children need to overcome adversity and have successful and fulfilling lives. Another process refers to the fact that poor health outcomes are a function of symptoms that developed at the time of the bullying exposure. For example, mental health problems like depression and anxiety are likely to persist, especially when they manifest early in life. Untreated signs of psychological distress that appear early in life, or markers of physical illnesses, may be the precursors to a life of poor health, both mental and physical. The possibility of poly- and re-victimization should also be considered, whereby being bullied in childhood may generate further abuse from peers or adults, forming the first stage in a cycle of victimization that perpetuates over time and across situations[9].

Although described separately, these processes are likely to operate together in contributing to adverse outcomes. Multidisciplinary research across different levels, from biological embedding of stress to poly-victimization and genetic influences, will be essential to understand the underpinnings of men-

tal health difficulties among victims of bullying. Animal models may provide useful insights, because they allow for a better control of the bullying experience and offer an opportunity to explore biological mechanisms in more depth. For example, an experiment on mice demonstrated the role of brain-derived neurotrophic factor in the mesolimbic dopamine pathway to explain social aversion among mice exposed to repeated aggression[10].

Tackling bullying behaviors could not only reduce children's and adolescents' mental health symptoms but also prevent psychiatric and socio-economic difficulties in adulthood. Anti-bullying programs show promise in controlling bullying behaviors[11]. However, the chances of eradicating bullying completely are minimal and we need to acknowledge that, despite such programs, a considerable proportion of young people will not escape this form of abuse. Intervention efforts should therefore also focus on limiting distress among young victims and possibly, by the same token, preventing long-lasting difficulties in later life. A new innovative strategy could aim at preventing children from becoming the targets of bullying in the first place. Such a public health approach might be a more effective way to reduce the bullying-related burden.

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Suicide risk assessment: tools and challenges

The World Health Organization estimates that over 800,000 people die by suicide each year, and for each suicide as many as 20 more individuals have attempted suicide[1]. The assessment and management of suicide risk is considered a core competency for psychiatrists, yet guidelines diverge in their recommendations and there is no universally accepted model. Risk assessment and management is best conceptualized as a process – not a single event – that includes structured evaluation, intervention, and re-assessment. Here, we comment on benefits of risk assessment, tool selection, risk assessment in self-injurious patients, and the unique challenge of working with patients who harbor thoughts of suicide that they do not disclose.

Some psychiatrists are reluctant to use risk assessment suicide tools, worrying that risk stratification is too inaccurate to be useful; that suicide-specific treatments, including medications and psychotherapies, are unavailable or do not improve outcomes; or that an over-emphasis on risk management might lead to defensive medicine. Although tools are imperfect, most experts agree that a structured assessment, meaning a consistent way of assessing and integrating risk and protective factors, is more likely to elicit relevant patient information and produce consistent risk formulations. Additionally, several evidence-based suicide-specific treatments exist, including commonly available medications, increasingly available psychotherapies, and relatively simple multidisciplinary interventions[2]. While uncertainty about a patient's suicide risk might lead to conservative recommendations, using and documenting a risk assessment process that educates patients about their risk, while prioritizing autonomy and outpatient treatment, should result in the most appropriate individualized care, effective communication with other providers, and medico-legal protection.

A growing literature supports this assertion. The Collaborative Assessment and Management of Suicidality (CAMS) model is a prototype clinical framework organized around the cooperative completion of the quantitative and qualitative Suicide Status Form (SSF). This model, which encourages problem-solving to reduce the suicide "drivers" and boost coping, is designed to enhance the patient-clinician alliance, build motivation, and avoid inpatient hospitalization. Completion of the initial SSF identifies suicide drivers, and the abbreviated follow-up form tracks improvement[3]. Drawing on CAMS, military-sponsored researchers developed a more complete and flexible approach, the Therapeutic Risk Management (TRM) framework. In this framework, clinicians augment evaluation with a risk assessment tool of their choosing, to stratify risk in terms of severity (low, medium, or high) and temporality (acute or chronic), and to collaboratively develop a safety plan based on a six step template[4]. The CAMS and TRM models share a clinically-motivated emphasis on avoiding involuntary hospitalization, arguing that it can damage the alliance and result in psychosocial setbacks that might exacerbate long-term suicide risk.

For psychiatrists not trained in CAMS, we recommend the TRM framework, including use of an assessment tool. When selecting a tool, consider whether it has been validated, has a quantitative component, can be repeated, is not diagnosis-specific, is available in a variety of formats, and is available in relevant languages. In our view, the Beck Scale for Suicide

Ideation (SSI)[5] and the Columbia-Suicide Severity Rating Scale (C-SSRS)[6] are good options.

The SSI is a 19 item clinician-administered scale querying, among other things, the patient's wish to die, wish to live, and the duration and intensity of thoughts of suicide. Each item is rated on a 3-point scale from 0 to 2, with a total score ranging from 0 to 38. Cutoffs and odds ratios for suicidal behaviors have been established for various populations[5], and the scale has been validated in multiple languages. The SSI can be administered at initial evaluation and subsequently repeated to assess improvement.

Similarly, the C-SSRS characterizes current thoughts of suicide and past suicidal behaviors. It features a clinician-administered initial evaluation form, a "since last visit" version, and a self-report form. Studies have shown the C-SSRS to be sensitive, specific, and reflective of changes in patients' conditions[6]. The C-SSRS has also been translated into and validated in several languages.

Many patients, particularly adolescents and those with borderline personality disorder, suffer from non-suicidal self-injury and/or low-lethality suicidal behavior. Historically, clinicians have viewed non-suicidal self-injury as distinct from suicidal behavior and/or dismissed low-lethality suicide attempts as "suicidal gestures". Some are concerned that repeated safety assessments reinforce these behaviors or are disproportionate to the patients' suicide risk. However, self-injuring patients are, in fact, at high risk of death by suicide, and the risk is even higher among patients who experience multiple episodes of self-injury and among patients who report suicidal intent, regardless of lethality[7]. Additionally, consistent attention to and an agreed-upon strategy for managing suicidal crises has been identified as a common factor among five evidence-based treatments for borderline personality disorder[8]. Thus, we recommend taking both self-injury and low-lethality suicidal behavior seriously, by educating these patients about their elevated risk, diagnosing personality disorders when present, and offering a safety-focused treatment.

Some suicidal patients deny having suicidal thoughts. This might be a conscious attempt to avoid hospitalization or speed discharge, or an unconscious defense against suicidal impulses. Some patients suffer transient but intense suicidal thoughts, which are not captured at the time of assessment. In any case, the obligation to engage and treat patients who feel they do not need or want help is a special challenge in psychiatric medicine. New research suggests that objective measures of patients' cognitive processes might provide insight into their suicide risk. Specifically, the "death/suicide implicit association test", which asks patients to categorize words associated with life and suicide as fast as they can, has been shown in a prospective study to predict suicidal behavior among veterans over and above other known risk factors[9]. Researchers are also beginning to subtype suicidal behavior and to explore the potentially distinct mechanism of impulsive suicide attempts[10].

Although more research is needed to improve assessment and prevention of suicidal behavior, there have been undeniable advances in our ability to manage suicidal patients. By combining foundational ethical and clinical concepts – such as respect for autonomy and the importance of a strong patient-clinician alliance – with a process-oriented framework and evidence-based tools and interventions, psychiatrists can reduce patient risk without excessive use of restrictive and expensive treatment settings.

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Excess mortality in persons with severe mental disorders: a multilevel intervention framework and priorities for clinical practice, policy and research agendas

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Excess mortality in persons with severe mental disorders (SMD) is a major public health challenge that warrants action. The number and scope of truly tested interventions in this area remain limited, and strategies for implementation and scaling up of programmes with a strong evidence base are scarce. Furthermore, the majority of available interventions focus on a single or an otherwise limited number of risk factors. Here we present a multilevel model highlighting risk factors for excess mortality in persons with SMD at the individual, health system and socio-environmental levels. Informed by that model, we describe a comprehensive framework that may be useful for designing, implementing and evaluating interventions and programmes to reduce excess mortality in persons with SMD. This framework includes individual-focused, health system-focused, and community level and policy-focused interventions. Incorporating lessons learned from the multilevel model of risk and the comprehensive intervention framework, we identify priorities for clinical practice, policy and research agendas.

Key words: Excess mortality, physical health, severe mental disorders, schizophrenia, bipolar disorder, depression, risk factors, individual-focused interventions, health system-focused interventions, community level and policy-focused interventions

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Persons with severe mental disorders (SMD) – i.e., schizophrenia and other psychotic disorders, bipolar disorder, and moderate-to-severe depression – die 10 to 20 years earlier than the general population. This premature mortality has been well documented in meta-analyses and systematic reviews[1-7]. Additionally, recent studies, commentaries and editorials have brought heightened awareness and attention to the topic[8-12]. Despite this, little to no progress has been made – in fact, evidence suggests that the gap may be increasing over time[4], and recently published studies show standardized mortality ratios that are higher than those previously reported[13].

The majority of deaths in persons with SMD are due to preventable physical diseases, especially cardiovascular disease, respiratory disease, and infections[14-16]. These persons have a 2 to 3 times higher risk of dying from cardiovascular diseases than the general population[17,18]. Up to 75% of persons with schizophrenia (compared to 33% of the general population) die of coronary heart disease[19]. Persons with SMD die of respiratory diseases at 2 to 6 times the rate of the general population[5,15,20], even after controlling for tobacco smoking and substance abuse, and die of infectious diseases at about 2 to 4 times the rate of the general population[4]. These persons are also more likely to die of diabetes mellitus[15] and cancers[21]. In low- and middle-income countries (LMICs), available studies suggest that excess mortality is similar, if not worse – with the large majority dying of physical diseases, especially infectious diseases[16].

The remaining deaths in persons with SMD are due to unnatural causes, including suicide, homicide and accidents. Suicide continues to be an important cause of death, especially in the first year following discharge from an inpatient unit[22]. Compared with the general population, persons with SMD are about 2-3 times more likely to die by accidental death, which appears more common than suicide in this population[18,23]. Furthermore, persons with SMD appear to be overrepresented among homicide victims and are 2-4 times more likely to die by homicide or violent deaths than the general population[7,24].

Overall patterns of mortality appear similar across countries, but there are likely differences in which solutions are needed. In the following sections, we present: a) a multilevel model of risk for excess mortality; b) a comprehensive framework, informed by the multilevel model of risk, to guide the development and implementation of effective interventions that offer the promise of reducing excess mortality in persons with SMD[25,26]; c) a set of priorities for clinical practice, policy and research agendas in this area. The aims of this paper are in line with the vision statement of the World Health Organization (WHO) Comprehensive Mental

Table 1 Multilevel model of risk for excess mortality in persons with severe mental disorders (SMD)

Individual factors	Health systems	Social determinants of health
Disorder-specific	***Leadership***	***Public policies***
• Severity of disorder	• Absence of relevant policies and guidelines	• Discriminating policies
• Family history	***Financing***	• Low financial protection and limited coverage in health packages
• Symptoms/pathophysiology	• Low investment in quality care	***Socio-economic position***
• Early age of onset	***Information***	• Unemployment
• Recency of diagnosis	• Limited health information systems	• Homelessness
Behaviour-specific	***Service delivery***	• Low health literacy
• Tobacco use	• Verticalization and fragmentation of health services	***Culture and societal values***
• Poor diet	• Lack of care coordination and management	• Stigma and discrimination in society
• Inadequate physical activity	• Limited access to services	• Negative perceptions about persons with SMD
• Sexual and other risk behaviours	***Human resources***	***Environmental vulnerabilities***
• Substance use (alcohol and drugs)	• Poor quality service provision	• Infections, malnutrition
• Low motivation (e.g., treatment seeking, adherence)	• Negative beliefs/attitudes of workforce	• Access to means of suicide
	• Poor communication	• Impoverished or unsafe neighbourhoods
	Medications	***Social support***
	• Antipsychotic medications (no treatment, polypharmacy, higher than recommended dosages)	• Limited family, social and community resources

Health Action Plan 2013-2020[27], which underscores the importance of persons with mental disorders to be able to enjoy the full range of human rights and to access high-quality, culturally-appropriate health and social care in a timely way to promote recovery.

MULTILEVEL MODEL OF RISK FOR EXCESS MORTALITY

The multilevel model of risk (Table 1) highlights risk factors for excess mortality in persons with SMD at the individual, health system and socio-environmental levels.

Risk factors at the individual level include characteristics inherent to SMD or an individual's health-related behaviours. These can be related to the severity of the SMD (e.g., symptoms, hospitalizations, impulsivity, physiological and emotional dysregulation); affect the engagement or interaction of the person with the health care system (e.g., cognitive deficits, social skills deficits, low motivation or mistrust of providers); or include behaviours that lead to or exacerbate health problems. Importantly, about 50-60% of persons with SMD smoke, one of the leading preventable causes of death[28]. Moreover, persons with SMD tend to have poorer diets[29] and more sedentary lifestyles[30] than the general population.

Health system factors include treatments, delivery of services, and organizational characteristics such as the workforce or information systems infrastructure. These often vary across different settings. As an example, a mainstay of treatment for many persons with SMD is antipsychotic medications, which are associated with well-known side effects that can contribute to obesity, glucose intolerance and dyslipidemia[31,32]. Depending on the setting, both a lack of antipsychotic medication[16] and excess dosing of this medication[33,34] appear to be risk factors for elevated mortality. Once antipsychotic medications are prescribed, monitoring for potential side effects is important and requires knowledge and communication between providers[10].

Persons with SMD often receive poor quality of physical health care, spanning from health promotion and disease prevention to intervention. Although they have two times as many health care contacts, they receive less physical check-ups and screenings, less prescriptions and procedures[35,36], and less cardiovascular and cancer diagnoses, even though they have a higher risk of dying from these conditions[15,35,37]. For example, in a study from Western Australia, although persons with SMD had the same cancer incidence as the general population, they were more likely to die from cancer[22]. Even under universal health care, persons with SMD do not receive adequate treatment for cardiovascular problems, such as a coronary artery by-pass, prescriptions of beta-blockers and statins, admissions for stroke, and revascularization procedures[36,37].

When hospitalized for medical care, persons with SMD often have poor outcomes, including more adverse events, more days in an intensive care unit and more complications than those without

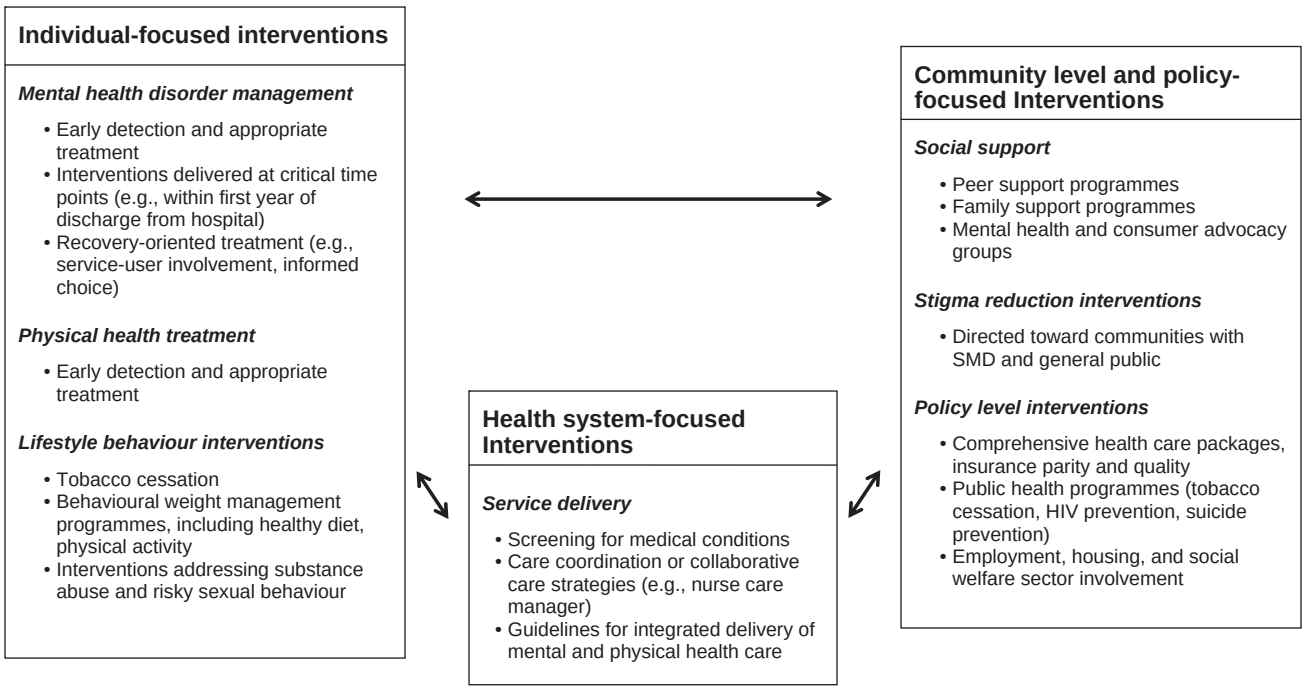

Figure 1 Multilevel model of interventions to reduce excess mortality in persons with severe mental disorders (SMD)

SMD[38,39]. There is also evidence for a time dimension to appropriate care: many studies highlight a peak in excess mortality for both natural and unnatural causes during the first year after discharge from hospital[16,18], suggesting a systematic failure of the health care system to prevent, identify and treat physical diseases during hospitalization for a mental disorder.

Some authors suggest that the poorer health outcomes could be related to providers' negative beliefs and attitudes towards persons with SMD, including beliefs about the causes of illnesses, ability of persons with SMD to maintain an active and healthy lifestyle, or other beliefs about functioning[40]. Mental health and primary care providers' attitudes towards patients with SMD appear related to treatment intentions, including their likelihood of referring patients to a specialist or refilling their prescription[41]. There is evidence of variation in the quality of care depending on the provider, insurer and type of health care system[42].

Fragmented health care systems (e.g., dichotomized physical and mental health care) present a challenge to meeting the complex physical health needs of persons with SMD[43]. A component cause may be the limited expertise of mental health providers to recognize and address physical health care needs, and of physical health providers to address the full range of health concerns of those with SMD[10].

Social determinants of health include, but are not limited to[26], public policies, an individual's socio-economic position, cultural and societal values, environmental vulnerabilities and social support. Persons with SMD often have limited access to health care either due to cost or denial of insurance coverage[44]. They are also more likely to be poor and at risk for homelessness. In high-income countries, homelessness and a low socio-economic status confer additional mortality risk to those with SMD[45,46]. Disability associated with the disorder may contribute towards unemployment, which is a strong independent risk factor for increased mortality[15,47].

Persons with SMD also tend to live in less safe neighbourhoods, have less access to healthy foods, and have less opportunities to be involved in healthy activities, which may contribute to poor lifestyle behaviours. They may be perceived as dangerous by others, which may drive the high rates of homicide victimization. A large majority has limited social support, including never being married (e.g., nearly 75%[15]) or limited family involvement. When family members are involved, they may already be under a heavy caregiver burden, and additional physical health problems may overstretch family support[16].

It is important to emphasize that these factors are intertwined, and interrelationships at multiple levels likely contribute towards excess mortality. No single factor alone causes excess mortality: persons with SMD have high rates of adverse health behaviours, including tobacco smoking, substance use, physical inactivity and poor diet; yet, studies clearly demonstrate the role of factors beyond disorder-specific and lifestyle behaviours in excess mortality. For example, although a large majority of persons with SMD die of cardiovascular diseases, only 25% of them receive a diagnosis for this – after controlling for whether a person had received a diagnosis, the risk due to ischemic heart disease approximates that of the general population[15].

Parceling out the effects of clinical factors, health system factors and socio-economic factors continues to show that factors at each level are involved[48]. In general, the more factors included in the model, the more variance is accounted for in excess mortality[5].

MULTILEVEL INTERVENTION FRAMEWORK TO REDUCE EXCESS MORTALITY

A number of interventions, guidelines and programmes have been developed to address correlates of excess mortality in persons with SMD. These primarily target mental health, lifestyle behavioural risk factors, and screening for and management of physical health conditions. Some interventions have proven to be effective but are not widely disseminated; others have not been rigorously tested; for some the evidence is mixed or inconclusive. For example, care programmes with an emphasis on monitoring and managing the adverse metabolic effects of antipsychotics are being implemented in several contexts, but many have not been well evaluated. Overall, the number and scope of truly tested interventions remain limited, and strategies for implementation and scaling up of programmes with a strong evidence base are scarce. Moreover, the majority of available interventions focus on a single or an otherwise limited number of risk factors.

Informed by the multilevel risk factor model, we describe here a comprehensive framework that may be useful for designing, implementing and evaluating interventions and programmes to reduce excess mortality in persons with SMD (Figure 1).

Our first level of interventions is individual-focused, while the second focuses on health systems. We then incorporate socio-environmental interventions emphasizing broader social determinants of health, including social support and stigma reduction. Some programmes address components at multiple levels (e.g., simultaneously targeting individual behaviours and health systems through behavioural weight management plus care coordination); we have categorized them based on the main emphasis of the programme. The assumption of our framework is that an effective approach must comprehensively target individual behaviours, health systems and social determinants of health. However, the effective and scalable combinations of these different interventions have yet to be fully evaluated.

Individual-focused interventions

Interventions at this level include strategies delivered to the individuals with SMD to target their mental health condition, physical health and lifestyle behaviours. Although individual-focused interventions are described separately, the implementation and impact of these interventions are likely affected by the functioning of the larger health care system.

Mental health disorder management

Persons with SMD first of all require an early detection and appropriate treatment of their mental health condition. Especially in LMICs, no access to treatment or a long interval before mental health treatment is started can increase the risk for mortality[16,49]. A comprehensive tool to address most major mental health conditions, the Mental Health Gap Action Programme (mhGAP) intervention guide[50], incorporates evidence-based recommendations for a range of disorders, including SMD. The guide's innovation is in facilitating the delivery of evidence-based mental health interventions in LMICs through primary health care services, using specific assessments and decision points to reach a comprehensive management plan for each person. Although research on the implementation and impact of the guide is still ongoing, it offers a promising approach to effective and efficient delivery of mental health services.

Appropriate administration of medications can reduce excess mortality in persons with SMD. Recent studies and evidence summaries highlight the beneficial impact on mortality of continuous medication treatment[30,51], proper dosing ranges[33] and current and long-term use compared with no medication, particularly in schizophrenia[52]. Adherence to medication guidelines – such as the American Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations[53] – appear to have an effect on reducing mortality in schizophrenia. Recovery-oriented programmes, with a focus on psychoeducation and increased awareness of symptoms, coping with stress and problem-solving skills, are also beneficial[54], as well as strategies supporting people with SMD and their families around treatment engagement[55].

The risk for suicide is highest within a year following discharge from a psychiatric hospitalization[56], with at least one quarter of cases occurring within 30 days of discharge[57]. Thus, suicide prevention interventions[58] need to be an important component in mental health treatment plans for those with SMD, especially early in the course of illness. In addition, persons with SMD are commonly victims of interpersonal violence, with a recent meta-analysis estimating the prevalence of recent violence at 24%[59]. Few interventions have addressed victimization in persons with SMD, and more studies are needed in this area.

Physical health treatment

Medical treatment for hypertension, diabetes mellitus and dyslipidemia should be similar for those with SMD as they are for the general population. However, self-management components (e.g., for diabetes) may require tailoring which accounts for cognitive, functional or motivational deficits.

Available evidence suggests that interventions to improve screening for obesity, hyperlipidemia and hypertension have been effective at improving the detection of these conditions among persons with SMD[42], although much more work is needed in this area.

Interventions addressing lifestyle behaviours

Tobacco cessation interventions have proven beneficial in adults with schizophrenia and are recommended at the earliest possible phases of treatment[42,53]. Combination treatment with counseling and bupropion with or without nicotine replacement therapy or varenicline is efficacious and has benefits on both point abstinence and continuous abstinence

from tobacco, though relapse is common[60]. Longer-term studies are needed to better understand optimal treatment duration, and importantly more work is needed to incorporate evidence-based tobacco cessation treatment into regular health care management for persons with SMD who smoke.

Behavioural weight loss programmes tailored for persons with SMD have been shown in randomized clinical trials to be successful in achieving clinically significant weight loss[61-63]. Effective interventions are often built on those shown to be successful for improving diet and increasing exercise in the general population, but with adaptations for cognitive needs of those with SMD, such as tailoring content and delivery to address memory and executive function deficits, and emphasizing environmental supports[64-66].

Some questions remain unanswered for optimal implementation and dissemination of these programmes, especially in LMICs. These include: a) what will be the true needed duration and intensity for long-term effectiveness of healthy weight interventions, as they are likely relatively labor intense (e.g., more frequent contacts) in persons with SMD; b) who should deliver these interventions in different types of environments; c) how can lay providers be trained to deliver effective weight management and other healthy lifestyle behaviour change interventions to this population.

There is a limited evidence base on effectiveness of interventions addressing substance abuse and risky sexual behaviour. The literature on interventions for reducing substance abuse in persons with SMD is large but inconsistent[67]. Outcomes for these interventions remain limited, especially due to problems with engagement and retention in programmes[68]. The impact of interventions for reducing risky sexual behaviours is also limited, even though they might be able to increase other health promoting behaviours, such as immunizations. For example, one comprehensive intervention programme delivered in mental health care settings addressed screening, testing, immunization, reducing risky behaviours and medical referrals for HIV and hepatitis, using a health promotion empowerment model; however, although participants had a higher prevalence of hepatitis B and C testing, higher immunization for hepatitis A and B, increased hepatitis knowledge and decreased substance use than the control group, risky sexual behaviour did not decrease[69].

Health system-focused interventions

The next level in the framework encompasses interventions and programmes within health systems targeting health care providers and service delivery components. These will vary across different settings depending upon many parameters, such as the number of specialists versus primary care providers, the different distribution of health risk factors, the presence or absence of universal health care, and the availability of health technologies and medications. Strengthening of the six building blocks of the health systems – service delivery; health workforce; information; medical products, vaccines and technologies; financing; and leadership and governance (stewardship) – would improve outcomes for persons with SMD[70].

Care coordination, collaborative care or integrated care programmes include support to better equip health systems, usually through the provision of additional supportive members who can serve as a liaison between mental health and physical health care systems or through linking of delivery of physical and mental health services. Few randomized trials have tested care coordination programmes for physical health conditions and cardiovascular risk factors in adults with SMD.

One intervention used a nurse care manager at a community mental health center to help participants become more involved in their own health care, communicate with physical and mental health providers, and assist in minimizing system-level barriers for health care[71]. At 12 months, nearly 60% of those in the intervention group received recommended preventive services compared to just over 20% in the control group. In addition, the former were more likely to have a primary care provider (71.2% vs. 51.9%) and, among the subset with laboratory data, they had lower (better) Framingham cardiovascular risk scores[71].

A recent trial examined a one-year intervention of care coordination alone, lifestyle coaching plus care coordination, or treatment as usual in adults with schizophrenia-spectrum disorders and increased waist circumference, with a primary outcome of cardiovascular risk reduction[72]. A nurse delivered care coordination, including contacting primary care providers and communicating test results and need for physical health care to participants. Lifestyle coaching provided weekly home visits with cardiovascular risk factor counseling based on individual participant preferences. The study did not find differences in outcomes, which may be due in part to the preexisting high quality of health care delivery. Also, while incorporating participant preferences is an important component of behaviour change, the resultant lifestyle coaching may not have been efficacious enough for change in risk behaviours. As suggested by the authors, environmental change may be a next step to investigate for lifestyle modification in that setting[72].

Guidelines that incorporate combinations of screening for physical health conditions, care coordination among mental health and primary care providers, metabolic monitoring, and delivery of medical services in mental health settings have been implemented in several countries, including the US, the UK and Australia[73-78].

In the US, the Substance Abuse and Mental Health Services Administration funded 187 grants since 2009 for community-based agencies to create or increase the capacity to provide primary care services to persons with SMD at settings where they already receive mental health care[79]. An evaluation of the first years of the program reported that sites provided a range of integrated behavioural health and primary care services to persons with need for care[80]. Challenges included lower than estimated consumer engagement, financial sustainment, and organizational culture issues. In addition,

implementation of lifestyle behavioural interventions for weight management and tobacco smoking was challenging. Several suggestions were put forth for current and future agencies receiving funding, such as incorporating strategies to improve consumer access to services and addressing fidelity to evidence-based wellness interventions.

In Australia, the Western Australia Department of Health Mental Health Division developed a package of Clinical Guidelines for the Physical Health Screening of Mental Health Consumers and a set of Health Nurse Practitioner protocols[81]. The package was built up as a preventive, evidence-based framework for mental health services, to facilitate coordination of care between health providers and with mental health consumers, relevant for hospital, clinic or community care settings. A 2010 report[76] showed three key areas of concern: standardization across services, fidelity and frequency of use, and sustainability of the guidelines. Recommendations included management plans modified for each setting and coordination between health professionals to prevent failure to screen or redundant screening.

The set of protocols focuses on nurse practitioners in mental health, and highlights their role as both coordinators and providers, including for: comprehensive physical health evaluation; management and referral; education and support to consumers; enhancing continuity of care for patients; facilitating communication, appropriate access and utilization of hospital services for persons with SMD; collaboration between mental health professionals and primary care, including dieticians and other lifestyle consultants; provision of health promotion; assisting the patient in making appointments or involving the case manager in ensuring the patient is able to attend appointments.

In New South Wales, Australia, a metabolic monitoring programme[82] is used to guide public mental health workers to monitor and manage metabolic syndrome and provide education to clinicians and patients. A study showed that this was implemented with about 60% coverage of monitoring of blood glucose and lipids and 54% of weight measurement. The compliance with measurement of waist circumference was lower (7%)[83].

In the UK, the National Institute for Health and Care Excellence (NICE) guidelines on psychosis and schizophrenia[74] include direction about providers' assessment and treatment of physical health conditions, and routine monitoring of the physical health side effects of medication, offering behavioural counseling and linking to other guidelines (e.g., obesity or diabetes) when appropriate. Since 2009, NICE has recommended that mental health care providers routinely monitor weight and cardiovascular and metabolic indicators of morbidity in people with SMD and offer interventions for obesity, lipid modification or preventing type 2 diabetes, as appropriate. In 2014, NICE provided updated guidelines about physical health in persons with SMD, specifically new tobacco cessation recommendations. In addition, the guidelines specifically called for data collection on the prevalence of those with schizophrenia who received combined healthy eating and physical activity interventions and tobacco cessation interventions.

Most recently, a multi-country effort has encouraged the use of the Lester UK Adaptation of the Australian Positive Cardiometabolic Health Resource, which summarizes safe interventions to help frontline staff make assessments of cardiac and metabolic health in persons with SMD[78]. Several dissemination efforts include a downloadable poster and forms for clinicians and clinics, service user cards for persons with SMD to approach their general practitioner or mental health provider in order to get additional help, and an action planning toolkit to help with the health care delivery system implementation of the resource.

This level of the intervention framework also includes health care leaders implementing national and international guidelines for care of persons with SMD in their organization, and aligning financing policy and information systems for the missions of improving and monitoring quality of care[63]. An important question for organizational leaders is who will deliver an evidence-based preventive health or care coordination intervention to decrease premature mortality in SMD. For example, dieticians and exercise leaders may be cost prohibitive, and sustainability may be more likely if mental health employees could deliver a physical health intervention. However, if mental health providers are to implement the intervention, they will likely need specific training and supervision. This is an important area for future research.

While many components of these health system-focused interventions are evidence based, implementation of these programmes and guidelines on the whole have not been formally evaluated for their success in achieving their intended outcomes. Several doubts remain about sustainability and the most effective and cost-efficient model of care. Furthermore, these programmes are largely based on high-income countries; the degree to which they are feasible in LMICs will be an important area of further study. Meanwhile, as the provision of mental health care grows in LMICs in primary care settings[49], these settings may provide opportunities to further test and refine effective models of mental health care that can reduce excess mortality.

Interventions focused on socio-environmental determinants

The broadest level of the framework incorporates socio-environmental factors and the social determinants of health. This part of the model acknowledges the range of potential interventions originating from the community to address contributors to premature mortality.

Peer support programmes, family support programmes and mental health consumer groups[84] are important potential resources that can implement or assist with health interventions, whether focused on health behaviours, chronic disease self-management, or recovery-based programmes.

Evidence for peer-led interventions for chronic disease self-management appears promising: a 6-week programme tailors chronic disease self-management interventions for those in the general population to those with SMD, delivered by

peers with SMD[85], and addresses tasks common across chronic health conditions such as action planning and feedback, modeling of behaviours and problem-solving, reinterpretation of symptoms and training in specific disease management techniques. The programme has been shown to improve health status and efficiency of health care utilization. The available evidence shows improvements in quality of life, medication adherence, and a primary care visit[86]. In a small randomized trial of a different adaptation of the same programme, also using peers with SMD and consisting of 13 weekly group sessions, participants showed improvement in self-management and better use of health care compared to controls[85]. Both of these studies had relatively short follow-up and used self-report measures for outcomes; however, they support recovery-oriented illness self-management interventions for persons with SMD and a chronic medical condition as well as roles for peers with SMD to deliver these interventions. More work is needed to develop the evidence base for peer-led and peer-supported interventions to improve physical health in persons with SMD.

Stigma reduction programmes[87,88] also appear important for improving the lives of persons with SMD, within and beyond the health care community. A recent review of effective interventions to reduce mental health related stigma and discrimination reported that, for the general population, interventions can improve short-term attitudes, and of these, social-contact based interventions seem to be the most effective. For those with mental disorders, group-level interventions appear helpful. However, across studies for those with and without SMD, further research is needed with strong designs, longer term follow-up and a focus on mental health consumers' perceptions of stigma. In addition, studies should examine behavioural and not only attitudinal change as a result of interventions to decrease stigma and discrimination[88], as well as effective stigma reduction strategies in LMICs[87].

On a wider scale, policies that have a beneficial effect on all individuals may also be beneficial for those with SMD, or policies may need to be shaped specifically to influence health for persons with SMD. For example, public health policies providing mental health parity could greatly improve lives of those with SMD. Employment programs[89] and policies to provide stable housing may impact the ability of persons with SMD to fully integrate into society, which should lead to improved physical health. Policy-level interventions that affect screening or management of suicide, HIV or tobacco smoking are especially relevant to those with SMD and may have even greater effects on the health and well-being of this high-risk population. Knowing how policy-level interventions need modifications to best improve and lengthen the lives of persons with SMD will be important for future impact. For example, protection legislation may be in force, but individuals may not seek this protection due to not wanting to be identified as having a mental disorder.

In the UK, the Health and Social Care Act 2012 established new legal responsibility for the national health system to deliver parity between mental and physical health, i.e., ensuring that there is as much focus on improving mental health as physical health and that persons with mental health problems receive an equal standard of care. Furthermore, the Commissioning for Quality and Innovation Scheme provides additional income for national health system trusts that meet specific indicators for people with mental health problems under that care, including recording relevant data on patient health, completing yearly physical health checks, and encouraging smoking cessation. Critically, the scheme mandates communication with the patient's general practitioner on discharge from hospital or after review by a community team. Sustainability of such policies will be important in the future.

In the US, a proposed option is the designation of persons with SMD as a health disparity group by the federal government, which would also require the tracking of vital health statistics separately for this population and make them eligible for more technical assistance opportunities[63].

Importantly, the factors in this part of the model link across to both health system and individual-focused interventions. Public health policies affect health systems, and specific environmental or social support programmes are often implemented through health systems (e.g., peer support programmes). Public health policies such as mental health parity or insurance coverage affect the services that the individual mental health consumer can access and will be critical to their sustainability. However, an evidence base for policies that effectively reduce excess mortality in persons with SMD is still needed.

PRIORITIES FOR CLINICAL PRACTICE, POLICY AND RESEARCH AGENDAS

Incorporating lessons learned from the multilevel model of risk for excess mortality and the comprehensive intervention framework, we prioritize the following key action points for clinical practice, policy and research agendas to decrease excess mortality in persons with SMD.

Clinical practice

Evidence from current literature combined with principles of health equity provide sufficient rationale to advance certain practice concepts. Individual practitioners can take steps now to provide guideline-consistent care. At minimum, the same guidelines for physical health care as the general population can be offered to persons with SMD. Practitioners should be especially attuned not to overlook somatic concerns and to pay attention to the lifestyle behaviours and physical health of persons with SMD.

The evidence base and considerations for health equity support the following practices:

- Coordination of outpatient support efforts is recommended in the first year after discharge from psychiatric hospitalization (e.g., following-up with health care providers, continuity of care) to

help with reducing suicides[57]. This may be especially needed among certain age groups of those with SMD who are at a high risk of suicide[22].

- Patients with SMD should have providers responsible for their mental health and physical health. If these are different providers (e.g., psychiatrist and primary care physician), there should be communication and coordination between them, so that screening, preventive services, and monitoring for antipsychotic side effects (if applicable) are ensured[10,76,78].
- Patients with SMD should be offered the same basic health screenings[90] as the general population (e.g., cardiovascular risk and cancer).
- Providers should address tobacco cessation with every patient with SMD. Persons with SMD can quit and many want to quit smoking; however, practitioners often do not address tobacco cessation[91-93].
- Lifestyle interventions with an evidence base in SMD to address health behaviours, such as diet and physical activity, should be implemented. Behavioural interventions, if not already tailored, will likely need to be modified to account for motivational and cognitive challenges in this population. These may include social support strategies and environmental supports[42].

Persons with SMD should be viewed as a vulnerable population characterized by significant health care disparities. For example, for interventions including smoking cessation, provider training and materials specific to those with SMD may be recommended. Adding environmental supports (i.e., resources or cues in the environment that facilitate functioning, such as smartphone reminders), strategies to adapt for cognitive and motivational deficits (e.g., breaking large tasks or pieces of information into smaller components, repetition, multimodal delivery of information), increased frequency of contact, and social support may help health provider interactions be most effective.

These clinical practice action points are made with an understanding that implementation will vary based on the distribution of specialists, primary care providers and lay health providers in different countries.

Policy

At the international level, reducing excess mortality in persons with SMD should be part of the broader health agenda. The WHO Mental Health Action Plan 2013-2020 established mental health as a fundamental component of WHO's definition of health, with objectives that include comprehensive and integrated mental health care services[27]. Mental health is now included as a priority in the United Nations Sustainable Development Goals. Reducing the life expectancy gap in those with SMD would also be a major step towards the goals of achieving universal health care coverage, effective treatment of non-communicable diseases, tobacco cessation, and suicide reduction[58]. These policies further promote the rights of persons with SMD to attain the highest level of health possible and full participation in society and at work.

Internationally, top-level integration in the plans and programmes among various efforts (e.g., mental health and substance abuse, non-communicable diseases, tobacco cessation, violence prevention, nutrition and physical exercise) would set a precedent for combining efforts and making strides in addressing complex, multifactorial health problems. This might lead to special considerations specifically for those with SMD across health domains that can help with closing the health equity gap in this vulnerable population. For example, the Package of Essential Non-communicable (PEN) disease interventions for primary health care in low-resource settings recommends counseling for all health behaviours in the general population[94]. Persons with SMD may need more resources and more targeted approaches to implement any given guideline than the general population, and special considerations for this population (such as supportive assistance, longer duration and intensity of interventions, and cognitive tailoring) might be included in these documents. Such policies further converge with WHO Mental Health Action Plan's six cross-cutting principles of universal health care coverage, human rights, evidence-based practice, a life course approach, a multisectoral approach, and the empowerment of persons with SMD.

At the national level, policies should be geared at strengthening existing health care platforms. These will facilitate the delivery and integration of effective interventions into the health system and the community to improve mental health[95].

In addition to specific programmes targeting services for individuals and populations, national policies should enable and provide sufficient resources for routine data collection of key indicators of excess mortality in persons with SMD at local facilities, national and regional databases. Health information and surveillance systems will be needed to monitor mortality records and cite trends. Country-level data need to be specific to the needs of their populations, examining the impact of excess mortality in persons with SMD on disabilities and deaths, including prevalence of cardiovascular risks, infectious diseases and other relevant conditions. This will be especially important for LMICs, where trends and needs may be different from high-income countries. Ultimately, this will allow for both intra-country and international comparisons and provide data to inform efforts to close the mortality gap.

Research

Scientists working to understand causes of excess mortality and design and test interventions and programmes to decrease contributors to premature death in persons with SMD have made progress in recent years, and this is reflected in the evidence supporting the multilevel model of risk presented in this paper. At the same time, there is a need to delineate specific risk factors more clearly, identify which ones are modifiable, and how these may be different across settings, particularly in LMICs.

While evidence for mental health treatments is strong, the evidence for effectiveness of interventions in ordinary

settings to prevent and treat physical conditions in those with SMD is limited. Also missing in the literature is the role of resilience and other factors that may be protective, and a parsing out of the roles of factors that are intrinsic to SMD versus those related to socio-economic and health system variables. This includes the need for a better understanding of attributable risk for excess mortality in those with SMD.

While evidence exists for the effectiveness of specific behavioural and pharmacological interventions for unhealthy dietary habits, sedentary life style and tobacco smoking cessation, behavioural intervention trials for other risk behaviours are needed, especially for comorbid substance abuse. For current evidence-based interventions, research is needed on optimal length and dose needed to positively affect health, which will also be important for resource allocation. Timing of these behavioural and pharmacological interventions may also instigate health benefits.

Interventions developed for the general population geared at non-communicable diseases, infectious diseases or other health problems are likely less effective for persons with SMD, given cognitive deficits and special needs of this population. Thus, interventions for SMD require tailoring. However, more work is needed on the degree of tailoring required. Multimodal approaches, which can include behavioural plus pharmacological interventions and include components such as peer support or technology are promising, but have yet to be studied systematically to clarify whether or which multicomponent programs are effective, and which components of the intervention are most beneficial. Recent results suggest that some combined approaches may not be effective or may be dependent on existing health care systems[72]. We need to consider how structural interventions can facilitate these efforts. Many people with SMD have multiple cardiovascular and other risk behaviours which may be modifiable, and future research studies should test interventions addressing multiple risk factors, as well as those which are directly linked to mortality.

Research is needed to identify and manage barriers to and facilitators of implementing evidence-based guidance and policy recommendations at all levels (individual, health systems and social determinants) of the intervention framework. We need to understand how to deliver evidence-based interventions successfully in the real world, taking into account training and workforce issues and often-limited resources in local community settings. We need to understand to what extent interventions and programmes could or should be disseminated across countries.

Another important area of research will be to assess the effects of health system and policy interventions on excess mortality in SMD. We need to understand why those with SMD have not benefitted from trends in the general population towards reduced mortality in some diseases and smoking cessation. Researchers should take advantage of natural experiments and also design studies in health systems and at the population level to evaluate the impact of these programmes.

Although several guidelines for screening, monitoring and management of mental health and physical conditions have been developed from evidence-based best practices, the implementation of these guidelines has not been studied systematically in order to support their widespread application and impact on risk factors for excess mortality in persons with SMD. Similarly, integrated care programmes will need to be evaluated for their actual effectiveness on risk factors for excess mortality. Care coordination approaches are often elements of these integrated care programmes and have utilized providers, nurses, peers and others to play key roles in facilitating the adequate provision and connection of mental health and physical health care. Questions remain regarding the appropriate elements of care coordination, including tasks, roles and responsibilities of involved persons. Finally, as these are resource-intensive programmes, cost-effectiveness models of different approaches[96] in persons with SMD will be important, especially in low-resource settings. This will be particularly needed as we seek to prioritize understanding risk factors for premature mortality of persons with SMD in LMICs.

CONCLUSIONS

Excess mortality in persons and populations with SMD remains an important global public health problem. Persons with SMD represent a vulnerable group with many and large health care needs. Despite known risk factors for premature mortality, evidence for effective interventions in persons with SMD is limited.

In this paper we proposed and described models to better understand the complex relationships among risk factors and correlates of mortality, and to conceptualize interventions at the individual, health system and socio-environmental levels. These models guided us to outline key action points for clinical practice, policy and research agendas to move towards health equity for those with SMD.

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Reversing the downward spiral for people with severe mental illness through educational innovations

In two earlier papers on physical diseases in people with severe mental illness (SMI) which appeared in this journal[1,2], we indicated that the screening, assessment and management of physical health aspects in these patients were poor, even in developed countries. Although (young and adult) people with SMI are entitled to the same standards of care as the rest of the population[3], Liu et al[4] report now, half a decade later, that little to no progress has been made. Moreover, it seems that the mortality gap between these people and the general population is only increasing over time[3,5]. Thus, despite numerous calls to take their physical health seriously, people with SMI still suffer excess morbidity and mortality from physical causes and receive inferior physical health care.

It is a fact that the integration of physical and mental health care systems is still a long way from becoming a reality and that poor or absent liaison links limit the ability of most psychiatrists to focus beyond their own specialty. Moreover, in several countries, reforms in mental health, emphasizing on community care and ambulant therapies, have led to shorter and infrequent hospital admissions with less time available to deal with physical health problems.

In their paper, Liu et al[4] propose a multilevel model of interventions to reduce the excess mortality in people with SMI. This model assumes that an effective approach must comprehensively implement interventions or strategies that focus on the individual, the health system, and the community. Although we believe that the adoption of this model would contribute to a significant improvement in the physical and related mental health of people with SMI (despite that actions are not easy to realize at a system level, especially for developing countries)[2], there is more than meets the eye. The physical health of people with SMI is an issue that should concern both primary and secondary care services. However, it seems that most psychiatrists and primary care providers or general practitioners are wandering on the road of the Cheshire cat. Like the conversation between Alice and the Cheshire cat in the famous novel *Alice's Adventures in Wonderland*, there still seems to be a lot of confusion and uncertainty. Before interventions or strategies can result in improved outcomes for people with SMI, it is important that both know which way they have to go.

According to a 2014 report of the UK National Audit of Schizophrenia[6], the monitoring of people with SMI for physical health problems falls well below agreed standards. Only about one fifth of people with schizophrenia had had their physical health properly monitored – following the clinical guidelines on schizophrenia of the UK National Institute for Health and Care Excellence (NICE) – by their general practitioner and, of those with documented evidence of risk factors, many were not receiving appropriate treatment. Recently, the NICE published a new set of quality standards which specifically address the problem of poor physical health in young and adult people with schizophrenia. This guideline requires for primary care providers to carry out monitoring of physical health risk factors for all service users with schizophrenia[7,8]. To avoid a lack of clarity and consensus as to where the responsibility of primary caregivers and psychiatrists lies, it is specified that specialist mental health teams should assume lead responsibility for the first 12 months or until the service user's condition has stabilized, and that thereafter primary care providers should assume that responsibility, unless there are particular reasons for this remaining with secondary care. For example, people with SMI may be seen with greater frequency by mental health care providers than by their primary care providers, and may prefer to be monitored by the former. In any case, taking care of the physical health of people with SMI also requires supporting the rapid sharing of the results of routine physical health monitoring between primary and secondary care.

However, more is needed than new recommendations and structural changes to reverse the negative, downward spiral for people with SMI. First, we think there is an urgent need to change the culture of both psychiatrists and primary care providers, who see the mental and physical health of their patients still as mutually exclusive responsibilities. Second, we have to provide them with more information on physical health problems commonly associated with SMI. Both can be accomplished through educational innovations[3,7,8]. On the one side, we should teach psychiatrists during their training that they have to ensure that persons with SMI receive appropriate treatment for physical health problems and that the monitoring of simple and modifiable health risk factors, such as weight and blood pressure, should be part of routine psychiatric care. Thus, they should learn not to overemphasize on mental health to the exclusion of physical health. Furthermore, they should improve their communication skills, avoid erroneous beliefs about the patients' capability to change their lifestyle, and adhere to treatment guidelines. The latter is particularly important. Besides mental illness-related factors, disparities in health care access and utilization, stigma and lifestyle factors, psychotropic medications can contribute to the emergence or aggravation of physical diseases[3,8-10]. Higher dosages and polypharmacy seem to be associated with a greater effect on most physical diseases[10].

This is not as straightforward as it seems. An editorial in *The Lancet* drew attention to a "worrying" lack of training in physical health needs amongst psychiatrists and psychiatric nurses[11]. Therefore, doctors who pursue a career in psychiatry should be educated and trained to recognize physical illness and perform

basic medical tasks. Moreover, knowledge about specific medication effects and greater attention to the possible impact of psychotropic medications on the physical health of people with SMI can aid psychiatrists in selecting appropriate treatment[3,10].

The same is true for primary care providers. Some primary care professionals hold negative attitudes toward this vulnerable group, or wrongly attribute physical illness signs and symptoms to concurrent mental disorders, leading to underdiagnosis and mistreatment of the physical conditions. It seems that there still is a lack of awareness among these providers that people with SMI face a greater risk of developing physical illnesses, such as heart disease, obesity and diabetes[3]. Primary care providers may also not be knowledgeable about the health risks associated with psychotropic medications and the resulting health monitoring that is indicated for persons with SMI. They therefore should specifically be trained to identify and treat physical health problems in people with SMI[3].

It is clear that deficiencies in the care of those with SMI, due to cultural and educational factors and unclear roles and responsibilities of their providers, continue to leave many service users with SMI vulnerable to serious physical health issues, which may limit their recovery. We can change these aspects through educational innovations. Only then we can leave the road of Cheshire cat and will multilevel interventions or strategies, as those proposed by Liu et al[4], result in improved outcomes for people with SMI.

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Perspectives from resource poor settings

Over the last decade, concern has been mounting over the excess mortality in persons and populations with mental, neurological and substance use disorders, and the health and economic burden they represent[1,2]. It has been stated that excess mortality in persons with severe mental disorders (SMD) is a "right to health" issue and that the lack of access to effective physical health care is a form of "structural discrimination"[3]. Liu et al[4] propose and describe a multilevel model for understanding the relationships among risk factors and correlates of excess mortality in persons with SMD, and a framework for interventions at the individual, health system and socio-environmental levels. They also outline priorities for clinical practice, policy and research to enable a move towards health equity for those with SMD. I will critique the otherwise robust paper from the perspective of its relevance for resource poor settings.

Liu et al quote sophisticated evidence which shows that persons with SMD – i.e., schizophrenia and other psychotic disorders, bipolar disorder, and moderate-to-severe depression – die 10 to 20 years earlier than the general population; and that the majority of deaths in persons with SMD are due to preventable physical diseases, especially cardiovascular disease, respiratory disease, infections, diabetes mellitus and cancers. However, they overstate the case when they claim that this is also true regarding low- and middle-income countries (LMICs). Systematic reviews of population-based epidemiological studies conducted to inform the Global Burden of Disease estimates showed that nationally representative data for mortality in persons with SMD were virtually non-existent across LMICs. Such data were available from just five LMICs for schizophrenia and one LMIC for major depression[5].

Quantifying mortality presents several challenges in LMICs, because many deaths are not medically certified, and different data sources and diagnostic approaches are used to derive cause-of-death estimates[6]. The need to improve and expand sources of national mortality estimates should be emphasized. It is hoped that documents presenting evidence of relevance to LMICs carefully parcel out the actual evidence from those countries themselves rather than making generalizations mostly based on high-income country estimates.

Infections may be a particularly important factor related to premature mortality among persons with SMD in LMICs, accounting for half or more of the excess mortality in these settings[7,8]. This should be covered in greater detail in a framework for interventions, beyond the HIV risk management implied under "sexual and other behavioural risks", because tuberculosis and other infections relevant to "local settings" account for at least as much mortality as HIV in people with SMD.

Based largely on data derived from management of schizophrenia, Liu et al state that appropriate administration of medications can reduce excess mortality in persons with SMD. This is a problematic statement in a situation where moderate-to-severe depression, a condition that explains a greater proportion of population attributable risk than schizophrenia

and bipolar disorder[1,2], is included in SMD, as guidelines on its management are less medication-centric[9]. An overemphasis on pharmacological solutions has been a regrettable trend in response to mental health problems in LMICs[10].

Almost missing in the discussion is the fact that health care delivery in LMICs is dominated by primary health centres, with the bulk being provided by general physicians, nurses and ancillary health workers. Many recommendations based around coordination between mental and physical health care divisions sit uneasily against the reality of primary health centre based care in LMICs, where coordination may be required more in terms of referral between sub-primary, primary and specialist care rather than between specialists of different disciplines.

The proposed framework is not configured to assess whether more holistic and sustainable culturally appropriate interventions for LMICs could be useful. Instead, it mostly focuses on health strategies successfully used in North America and Europe, with emphasis on active engagement in surveillance, education and care. These strategies may or may not translate well to LMIC settings. The authors describe facilitators and barriers to application of recommendations and provide advice on how the recommendations can be put into practice, but do not assess resource implications for application of recommendations and monitoring in under-resourced settings.

Another issue relates to the responsibility and capacity of the state to provide adequate care for its citizens[11]. Persons with SMD tend to live in less safe neighbourhoods, have less access to healthy foods, and have less opportunities to be involved in healthy activities, which may contribute to poor lifestyle behaviours. The proposed framework for intervention largely shies away from comments on structural economic, political and social determinants of mortality in SMD. Rates of inequality and inequity within countries affect the distribution of health and welfare resources, so advances in medical science and health and social welfare sector responses by themselves cannot reduce mortality and morbidity. Moreover, the emphasis on chronic disease self-management and parity in service access, in the absence of structural correctives, may facilitate the erosion of traditional state-centred mechanisms of care and the will to care[11].

Finally, the proposed framework for intervention assumes that improved care for comorbid physical disorders would strengthen the overall response to SMD. However, it is possible that the focus on mortality rather than disability, in the resource strapped settings of LMICs, may draw attention away from the mental disorders in general and towards risk factors that are supposed to underlie both physical and mental illnesses.

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A policy implementer's perspective

We live in a time when we have a fair knowledge about what works for mental health, how best to deliver it, where best to fit the intervention and who should be doing it. Yet we are still far from achieving what we are committing ourselves to in the World Health Organization's Mental Health Action Plan 2013-2020[1].

When it comes to the framework proposed by Liu et al[2] to address the excess mortality in persons with severe mental disorders, it is clear that the authors are tackling all relevant levels with the aim of building up a holistic evidence-based approach to address the issue. Let me list, however, some crucial points.

The first point is an operational one, that can be summarized by the following questions: How does this framework link with local health systems at country level? What would be the cost and what is the best order of implementation of the different proposed interventions? Are there any best buys for countries that cannot fully implement? How does the framework rank in terms of priority with respect to other mental health interventions at country and global levels? Should some proposed interventions – especially policy level ones – be a prerequisite for other clinical ones? For example, should we consider launching tobacco cessation programmes for persons with severe mental disorders even if a country does not have policy regulations in line with the Framework Convention on Tobacco Control? These are the kind of over-arching questions that arise when considering the implementation of this framework.

The second point focuses more on the content of the framework and more explicitly on the groupings used for severe mental disorders and the integration of mental health into primary care.

The inclusion of moderate-to-severe depression within the "severe mental disorders" grouping might be problematic, as the course of that condition, the help-seeking behavior of the person, and the stigma around it are different from those related to schizophrenia. The inclusion of moderate-to-severe depression within the same framework as schizophrenia might be counter-productive for both

disorders, as the implications for service design and delivery seem to be – at least in our experience – different, for example at the primary care level.

Furthermore, when talking about the integration of mental health into primary care, it might be beneficial to allocate some attention to the way it is being done. Although implementation research is still ongoing, the Mental Health Gap Action Programme (mhGAP) Intervention Guide has been useful in training and supervising the primary care staff. However, to ensure the effective and sustainable integration of mental health within health systems, tools for the implementation and incorporation of the mhGAP within existing health systems are much needed. Such tools would help in the allocation of tasks/roles among different professionals at the primary care level, in the care packages and pathways for different disorders, in the health information system, and in the links of the primary care with specialized services.

A lot of attention is also needed for human resources. The tipping point in positive attitude change towards persons with mental disorders for many primary health care staff is often seen after they disclose a personal experience with mental health concerning themselves or a member of their family to an mhGAP supervisor and feel that the supervisor is able to listen and support. Addressing the mental health of the staff is a key action for integrating mental health into primary care and as such deserves closer attention.

A further factor to consider in order to enhance the integration of mental health into primary care is the use of innovations in domains such as management and information technology that have the potential to decrease cost and increase efficiency.

The third point highlights the importance of the context where persons with severe mental disorders live. Two main examples are prisons and humanitarian crisis. It might be a good idea if the framework delineated by Liu et al could include an item to highlight persons with severe mental disorders living in prisons as a vulnerable group in need of specific interventions. The same applies to persons with severe mental disorders living in humanitarian settings, where they are often either locked in big institutions or very disadvantaged in reaching the needed services, which in both cases will put them at a higher risk for premature death.

In summary, details pertaining to the implementation of the framework and to how it links to other mental health priorities are needed. This being said, this framework adds to the available tools and usefully highlights the importance of addressing the excess mortality in persons with severe mental disorders. In low-resource contexts – where mental health systems are under development with competing priorities – mental health disorder management, physical health treatment, screening for medical conditions, and stigma reduction interventions seem to be the components of the framework that would be easier and most important to consider, especially when the health system as a whole is fragmented or facing big challenges.

Finally, as mental health professionals and policy makers, we can learn a lot if we look to other disciplines and to emerging research in related fields, such as the newly published report "Insights for impact"[3]. This can help us increase the coherence of any model we propose with the bigger socio-political and technological world in which we live. Leveraging the knowledge we can gather on management innovations as well as latest evidence in human psychology and in mental health at the workplace, we can develop tailored interventions for health systems management and for the health workforce that would increase the engagement, well-being and efficiency of every health worker and of the system, helping them to achieve their goal of improving the health of the persons served.

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A service user's perspective

To address the alarming rate of excess mortality in persons with severe mental disorders (SMD), a multidimensional approach is the way to go, provided that communication and collaboration with the overall health system is effected and that it further extends to community-based, peer support and advocacy organizations which are providing psychosocial rehabilitation and support services.

Successful treatment of SMD does not merely rely on pharmaceutical intervention, but requires a holistic approach, one that specifically honors the entitlement of the rights of persons with mental disorders – the right to have access to quality health care services, have a good quality of life, enjoy life opportunities on an equal basis, and do so with dignity.

It is important to acknowledge the role that stigma plays in accessing health services and the severe neglect of mental health within the general health system. It is imperative that stigma reduction initiatives form an integrated component in all the suggested interventions and that mental health receive equal recognition as physical health.

Mental health services must provide a human rights focused approach that is perceived by persons with SMD as a means of care and support. Unfortunately, these services may present themselves as "punishment" in the sense of exposure to abusive attitudes and denying persons with SMD the right to participate in their treat-

ment and recovery plans. A system that does not recognize the "voice" of persons with SMD or acknowledges their views and opinions becomes an enforcer of disempowerment. Persons with SMD must be acknowledged as the key partners in scaling up mental health care services and reducing stigma. They must be empowered to a level where they can be actively involved in policy development, implementation and monitoring of health systems.

The Rural Mental Health Campaign in South Africa engaged with service users to assess the implementation of South Africa's Mental Health Policy Framework and Strategic Plan, and published the outcome in a report[1]. A service user from one of the participating rural communities confirmed the gap in acknowledging service users as key partners in improving mental health services, by stating: "People tend to disregard a mad person's opinions on issues of discussions". Service user engagement exercises conducted by the South African Federation for Mental Health further confirmed the experiences of service users who feel that they are often being denied the right to fully participate in their own treatment and recovery plans, that they are not taken seriously and that their views and opinions are often automatically dismissed.

General health workers need to receive adequate training in mental health related disorders, especially SMD, as part of their curriculum and become sensitized to the needs of persons with SMD, to eliminate attitudinal barriers that result in persons with SMD avoiding to seek services or failing to remain treatment compliant for both mental and physical health conditions. Some research studies conducted on the attitudes of health care workers towards persons with mental disorders interestingly indicated that they had less positive attitudes than the general public[2,3]. Another study showed that mental health care workers (registered nursing staff and medical orderlies) had both positive and negative attitudes towards persons with mental disorders, and suggested that mental health specific training (replacing myth with fact) can influence attitudes[4]. It is important to understand how these attitudes are formed to allow for the development of a targeted approach to educational initiatives, for health care service delivery to improve.

Community-based health care facilities or clinics need to move away from being "dispensers of medication", but rather become a "one-stop" service that accepts persons with SMD as equally deserving of all services available, a comprehensive package that looks at the person as a whole, as proposed by Liu et al's[5] multilevel intervention framework.

It is imperative to acknowledge peer and family support initiatives and service user groups as essential elements to the social model that focuses on eliminating systemic barriers, negative attitudes and exclusion by society, as stigma causes ripple effects in creating barriers in accessing services and life opportunities, further leading to human rights violations.

Considering that unemployment is a strong independent risk factor for increased mortality, it must be a vital target of interventions focusing at addressing socio-environmental determinants. Unemployment of persons with SMD is an issue that receives very little attention, yet it has an enormous impact on the lives of these persons – leaving them with feelings of worthlessness, inability to be independent and financially self-sustainable, and becoming isolated. Occupational therapists would be ideal to lead specific interventions to facilitate access to employment or supported employment, and assist persons with SMD in optimizing cognitive functioning and achieving independence as far as possible where they are able to take charge of their lives and invest in their overall health and mental wellbeing.

Health systems must collaborate with community-based organizations to create an effective and holistic service delivery platform for persons with SMD. If there is a disconnect between the two, it can cause great frustration to persons with SMD, who are trying to consolidate a treatment and recovery plan that is centered around their individual needs.

The aspiration of the Sustainable Development Goals of "leaving no-one behind" must be honored in the name of persons with SMD, especially in low-resourced or rural communities. "Rural-proofing" of policies[6] must be conducted to ensure that those communities are not left behind as they are most marginalized when it comes to accessing social and economic opportunities, including health care.

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Reducing premature mortality from non-communicable diseases, including for people with severe mental disorders

The Sustainable Development Goals approved by the United Nations General Assembly in 2015 include a specific target in goal 3.4 for non-communicable diseases (NCDs): by 2030, reduce by one third premature mortality from NCDs through prevention and treatment and promote mental health and well-being[1]. This target aligns well with the paper

by Liu et al[2], which offers a multilevel intervention framework to reduce excess mortality in persons with severe mental disorders (SMDs). The World Health Organization (WHO)'s Global Action Plan for the Prevention and Control of NCDs (2013-2020)[3] shares this goal and provides a menu of options, including risk factor control, scaling up management in primary health care, surveillance and other cross cutting areas. A life course approach including human rights and equity and universal health coverage are overarching principles in implementing this global action plan.

A focus on prevention, especially on the four common shared risk factors of tobacco use, harmful use of alcohol, unhealthy diet and physical inactivity, is a cornerstone of NCD control. The impact of general population interventions, such as taxation or restriction to access, may not be the same in people with SMDs. People suffering from SMDs will need a tailored approach to risk reduction: cognitive capacity, enabling factors, information and skill building of care providers and family members are needed. Some of the risk factors, such as weight gain and eating patterns, are influenced by people with SMDs' condition and medications and will have to be factored in. A perception change in carers and health providers may be needed for them to see the relevance of risk factor control in people with SMDs.

NCDs, especially cardiovascular diseases (CVDs), diabetes, cancer and chronic respiratory diseases, are becoming more prevalent due to an epidemiological and demographic transition. In addition to prevention, early identification and prompt management can reduce premature mortality and morbidity and improve the quality of life. Treatment of NCDs in earlier stages is more feasible, less expensive and can be taken up at lower levels of health care.

The WHO has developed a Package of Essential NCD (PEN) interventions which are suitable for primary health care and can be applied in resource constrained settings. They include protocols for identifying people at high risk for CVDs, identification and management of asthma and chronic pulmonary diseases, along with a protocol for individual counselling. A short list of essential medicines and technology is provided to support the use of these protocols[4]. The proposed approach of Ask (for risk factors), Assess (examination and tests), Estimate (CVD risk), Refer (for high risk) and Counsel and treat is a feasible framework that can be appropriately integrated in the WHO Mental Health Gap Action Programme (mhGAP)[5].

Health care providers for SMDs, including mental health professionals, can be informed, and their capacity can be enhanced to undertake this simple assessment depending on the clinical condition. Individuals at high risk for CVDs based on the risk assessment can be offered additional support and checking of parameters along with the follow-up of their mental health condition. This integration will have to be taken up through active engagement of care providers of both streams (NCDs and mental health) and also through appropriate operational interventions in health care settings. Mental health services may have to be supported with NCD medicines and technology, and skill building of providers. Including NCDs as part of the medical records will also help to identify and focus on people who have SMDs and NCDs.

Diabetes is also an important consideration in SMDs. The WHO PEN offers a protocol for management of diabetes, and the special needs for people with SMDs will have to be reflected in developing care plans. Dietary restrictions and physical activity which are part of the management plan may have more challenges in people with SMDs than medication interventions. Self-care which is often proposed to people with NCDs may not be directly applicable to people with SMDs.

Respiratory diseases like asthma are overtly symptomatic and are more amenable to detection and management. Awareness of signs and symptoms of common cancers among mental health care providers can potentially lead to early diagnosis, for instance of breast cancer.

All major NCDs need prolonged treatment, including adherence to medicines. Periodic follow-up and checking for signs of complications can help to prevent or delay adverse events in NCDs. Including these tests in protocols and adhering to them as part of the care for SMDs will have to be part of the management plan.

People with NCDs may have mental health conditions such as depression and anxiety, and it is also important that NCD care providers have the skills and capacity to detect and manage or refer these comorbidities as needed.

Integration of NCD prevention and management for people with SMDs will happen only through a systematic and sustained process at different levels. National programmes for NCDs, mental health and primary care services can work together to develop operational guidance and resource allocation. National strategies and action plans in these areas and in overall health sector plans should reflect this adequately.

Appropriate system level interventions, including changes in protocols, health workforce capacity, medicines and technology, counselling support and financial protection measures, will have to be developed and implemented in a structured manner. Context specific approaches can be developed based on the general guidance, and sustained practice can benefit both people with SMDs and those with NCDs.

The WHO is planning to demonstrate this approach in settings which are implementing mhGAP to include PEN protocols and vice versa. The framework proposed in Liu et al's paper will help to accelerate this work.

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The views expressed in this commentary are solely the responsibility of the author and they do not necessarily reflect the views, decisions or policies of the institution with which he is affiliated.

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Mind and body: physical health needs of individuals with mental illness in the 21st century

It is well recognized that individuals with severe mental illness show high rates of suicide and also various physical illnesses which contribute to reduced longevity[1]. This is a major public health challenge in the 21st century. Drugs and alcohol consumption and tobacco use further add to the increased rates of morbidity and mortality. The delays in help-seeking, whether it is for physical illness or psychiatric illness, and the underdiagnosis due to stigma and other factors contribute further to this disparity. Liu et al[2] provide a model based on a multi-level approach at individual, health care systems and social determinant levels to cope with the excess mortality among mentally ill people. We believe that it is a relevant proposal in the framework of modern medicine.

At the individual level, although early recognition of physical comorbidity and early interventions are effective strategies to reduce mortality, it is also relevant to explore what people seek help for and where they seek it from. In fact, culture and explanatory models will guide people to the sources of help, especially those which are easily available and accessible[3]. Explanations of distress and symptoms (explanatory models) will vary across cultures and communities and also be related to educational and socio-economic status.

Health care systems need to be geographically and emotionally available and accessible for people affected by mental illness, so that they can seek help early. Some of the physical comorbidity may not be recognized by clinicians and on occasion the responsibility for managing physical illness may be left to primary care physicians or specialists who in turn may not recognize mental illness or due to stigma may not intervene early enough. This might be due, in the West at least, to a somewhat rigid division between mental health and physical health services. For centuries, the mind-body dualism attributable to Descartes' dogma has affected clinical practice and has increased the dichotomy between psychiatric and physical health care services. This dualism may well have contributed to stigma against mental illness, the mentally ill and the psychiatric services[4]. Furthermore, if physicians are not very good at identifying psychiatric disorders or carrying out mental state examinations, psychiatrists are often not very good at identifying and managing physical illnesses either. When interventions have taken place in partnerships between services, physical health of patients with severe mental illness has been shown to improve[1].

At a social level, explanatory models of disease do not only vary across cultures and communities. They may also differ between the patients, their families and their carers, who may interpret these experiences on the basis of physical or psychosocial factors. More industrialized societies are likely to have psychological, medical or social causative factors as explanations, whereas more traditional societies may hold supra-natural and natural explanations[3]. In many cultures, mind and body are seen as in connection with each other, and patients may link their symptoms to both body and mind, thus making sense of their experiences in a holistic manner. Among Punjabi women in India and Pakistan, for example, the distress may be expressed in different parts of the body feeling hot and cold at the same time[3]. So, when they seek help from physicians who are not aware of these cultural differences, the clinician may miss the distress and underlying psychiatric disorders completely.

In 2013, in a report for the UK Mental Health Foundation[5], we recommended an integration at multiple levels similar to Liu et al's model. One of the potential solutions might be to develop units based on medical liaison, such as consultation-liaison psychiatry, where physicians work with psychiatrists to help early diagnosis and management[6]. Also, we believe that the multi-level model proposed by Liu et al has major implications for training. Training health professionals is a critical first step to make them aware of various components of patient's health. Moreover, education on cultural factors that may influence physical and mental health is relevant. One option may well be teaching social sciences and medical humanities at early stages of training[7], so that clinicians are aware of the impact of cultures on presentation and the interaction between mind and body.

Psycho-educational programmes about physical health among mentally ill patients need to be widely explained and utilized, as they are known to be effective[1]. In addition to the general information about various risk factors, specific programmes must be developed for vulnerable groups and individuals. Also, screening at early stages of treatment may help to reduce physical complications, improving psychiatric outcomes[1,6]. Integration with social care may help individuals with chronic mental illness so that all their needs are met in a single port of call.

Integrated care across primary and secondary care, across physical and mental health, and across social and health care means that training, recruitment and re-

tention of workforce needs to be at the top of the political agenda, so that patients with severe mental illness get the best services they need, deserve and will utilize[8]. It is imperative that psychiatrists take the lead in identifying the physical health needs of persons with severe mental illness as well as in orienting the public mental health agenda to ensure that cultural norms and values are taken into account when developing and delivering integrated care at all levels. They must work with stakeholders, including service users and their families groups, to ensure that integrated care and services are sensitive to patients' needs.

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Excess mortality in severe mental disorder: the need for an integrated approach

Liu et al's paper[1] comes at a crucial and relevant time, because it coincides with a period of increased global efforts to raise interest and awareness in mental health issues so that appropriate treatments are made available to narrow the mental health gap. We need to ensure that up to date medical interventions are available to people with severe mental disorder in the same way that they are available to everybody else and, as a family doctor, I particularly welcome this.

Although we know that people with severe mental disorder such as schizophrenia and bipolar disorder die 10 to 20 years earlier than the general population, there has been little progress in addressing this health disparity over time and there is an urgent need to narrow this gap.

People often try to find linear answers to complex issues, but Liu et al's paper highlights that excess mortality is not due to a single factor. This means that we require novel approaches to this complex problem. Doing nothing is not an option. We can no longer continue to treat the statistics about poor outcomes in mental disorder as if it is all that can be expected. Every life matters and that of course includes lives affected by mental ill health.

There has always been controversy about which elements of mental health promotion and lifestyle choices contribute to an improvement in mental health outcomes, including excess mortality. The research evidence provided in Liu et al's paper lends support for some health promotion activities, including smoking cessation and weight management. Furthermore, it is traditionally believed that substance use disorder has a significant impact on long-term physical and mental health outcomes in people with a diagnosis of mental disorder. Many interventions to address this particular comorbidity have been put forward and the paper notes the limited evidence base about the effectiveness of our current strategies. This is consistent with a recent review[2], highlighting the need to direct resources at continuing research into the effective treatment of substance abuse in people with severe mental illness in order to reduce morbidity and mortality.

The proposed framework supports current thinking about the need to deliver interventions for such complex problems through an integrated care pathway, recognizing that each component of that pathway is a care package. Some care packages will need to be delivered by the individual affected by ill health, some through social care interventions, some through primary care, and some through secondary care.

Policy change is often seen as a tool to deliver care packages, but this should not be the case. Policies should be regarded as a care package in their own right. This new way of thinking needs to be recognized by those who purchase and commission services, so that they can change their own ways of working, especially as current commissioning practice has not made a significant impact on rates of excess mortality in people with severe mental disorder.

The proposed multilevel intervention also highlights the need to have combined mental and physical health guidelines to address both screening and treatment, because for too long there has been an over-reliance on specialism and so called "silo working", which has not delivered the desired health outcomes for people with severe mental disorder. It also reinforces the need for services to have an integrated approach to care which delivers health promotion and emphasizes the role of the individual and self-care, and the need for research that is aligned with practice so that we can continue to apply those interventions that we know will work.

Innovative working and task shifting such as developing workforce roles for the management of long-term physical and mental health conditions is needed, because mental and physical health comorbidity significantly increases costs of care and use of health care resources[3,4].

As a family doctor, mental health advocate and somebody who has previously been involved in commissioning health and mental health services, I find Liu et al's paper useful because it brings together much of the relevant evidence

about what works into a single construct and provides a framework that makes the task of intervention less daunting. However, I would have liked to see more about the role that family interventions can play in addressing the excess mortality in people with severe mental disorder, especially as there is already strong evidence for the role of families in the prevention of relapse and re-hospitalization[5].

There has been a systematic failure of the health care system in preventing, identifying and treating physical diseases in mental health conditions, partly through a failure of recognition that a policy is a care package, not just a tool. Liu et al's paper represents a call for action to do something that is possible, and provides a comprehensive framework to make this happen.

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Public attitudes towards psychiatry and psychiatric treatment at the beginning of the 21st century: a systematic review and meta-analysis of population surveys

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Public attitudes towards psychiatry are crucial determinants of help-seeking for mental illness. It has been argued that psychiatry as a discipline enjoys low esteem among the public, and a "crisis" of psychiatry has been noted. We conducted a systematic review and meta-analysis of population studies examining public attitudes towards various aspects of psychiatric care. Our search in PubMed, Web of Science, PsychINFO and bibliographies yielded 162 papers based on population surveys conducted since 2000 and published no later than 2015. We found that professional help for mental disorders generally enjoys high esteem. While general practitioners are the preferred source of help for depression, mental health professionals are the most trusted helpers for schizophrenia. If respondents have to rank sources of help, they tend to favor mental health professionals, while open questions yield results more favorable to general practitioners. Psychiatrists and psychologists/psychotherapists are equally recommended for the treatment of schizophrenia, while for depression psychologists/psychotherapists are more recommended, at least in Europe and America. Psychotherapy is consistently preferred over medication. Attitudes towards seeking help from psychiatrists or psychologists/psychotherapists as well as towards medication and psychotherapy have markedly improved over the last twenty-five years. Biological concepts of mental illness are associated with stronger approval of psychiatric help, particularly medication. Self-stigma and negative attitudes towards persons with mental illness decrease the likelihood of personally considering psychiatric help. In conclusion, the public readily recommends psychiatric help for the treatment of mental disorders. Psychotherapy is the most popular method of psychiatric treatment. A useful strategy to further improve the public image of psychiatry could be to stress that listening and understanding are at the core of psychiatric care.

Key words: Public attitudes, psychiatry, psychotherapy, psychotropic medication, depression, schizophrenia, systematic review, meta-analysis

(World Psychiatry 2017;16:50–61)

In recent years, the notion of a crisis of psychiatry has spread in professional circles. In scientific journals, the question has been asked whether psychiatry is "on the ropes"[1] and "psychiatrists are an endangered species"[2]. Numerous internal threats to psychiatry (e.g., feeling of loss of autonomy, competing views which highlight biological or social factors, or tension between generalists and specialists) as well as external threats (e.g., changes related to health care and medical education policies, intrusion of other health professional groups into the territory which psychiatry claims for itself) have been identified[1,2].

There is also growing concern about the poor image of the discipline in the eyes of the general public as well as of medical students, health professionals and the media[3,4]. Psychiatrists increasingly feel underestimated as well as stigmatized and discriminated against[5]. In a recent online survey across twelve countries around the globe, psychiatrists reported significantly higher perceived stigma and discrimination experiences than general practitioners. About 17% of the psychiatrists perceived stigma as a serious problem, with a higher rate among younger participants[6]. In response to this problem, the World Psychiatric Association established a task force and entrusted it with the development of a "guidance on how to combat stigmatization of psychiatry and psychiatrists"[7]. A few years later, the European Psychiatric Association followed with the publication of a "guidance on improving the image of psychiatry and of the psychiatrist"[5].

The question arises as to whether this negative image perceived by the profession actually reflects attitudes towards psychiatry that are prevalent among the general public. Therefore we decided to investigate, based on a systematic review and meta-analysis of pertinent studies, to what extent psychiatric care is accepted (or rejected) by the public. More specifically, we wanted to explore to what extent the public sees seeking help from a psychiatrist (in comparison to the help provided by a psychologist/psychotherapist or a general practitioner) as useful and does recommend it, or instead considers it as harmful and advices against it. We were also interested in attitudes towards various psychiatric treatments, with special focus on psychotropic medication and psychotherapy. In addition, we wanted to examine how attitudes towards psychiatric treatments are influenced by mental health literacy and stigmatizing attitudes. Since attitudes do not necessarily remain stable over time, we focused on the current situation, including only studies conducted since the turn of the century, but also considered time-trend studies exploring how attitudes have developed over the last decades.

METHODS

Systematic review

We first systematically reviewed all papers reporting results of representative population-based studies on beliefs and attitudes about mental disorders published in peer-reviewed journals between January 2000 and December 2015. To search for

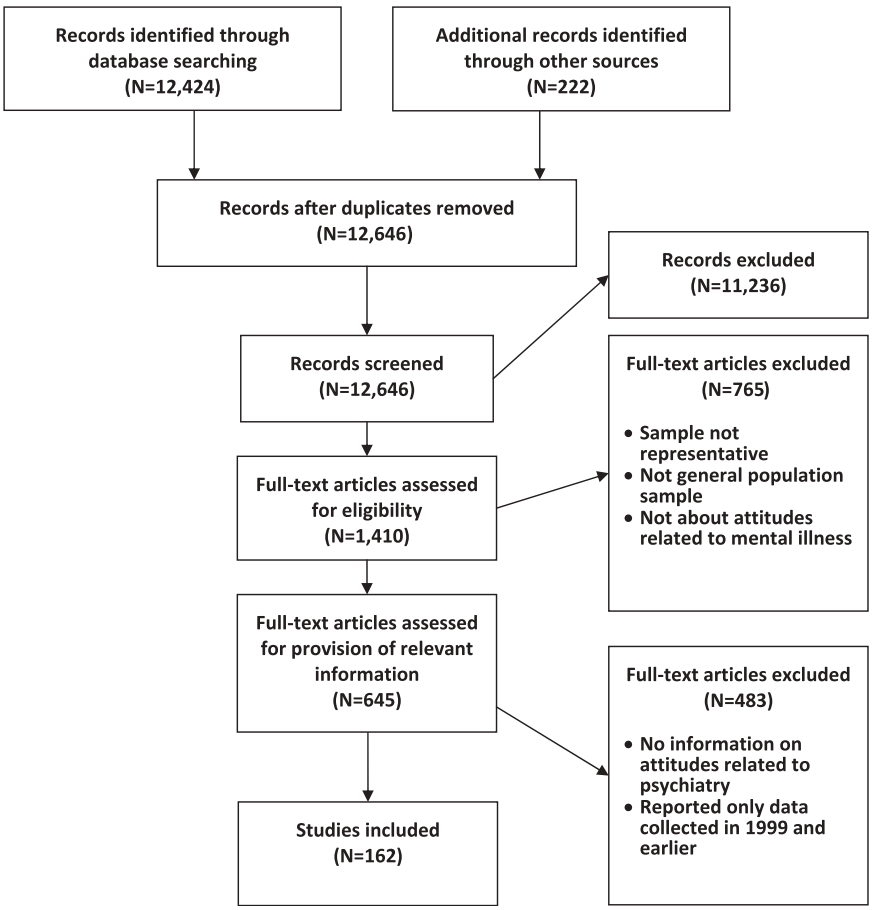

Figure 1 PRISMA diagram of the literature search

relevant papers, we took a stepwise approach according to the systematic literature review guidelines of the Centre for Reviews and Dissemination[8] and the Cochrane Collaboration[9]. As a starting point, we conducted a literature search in PubMed, Web of Science and PsychINFO using the terms: (population OR representative) AND (depression OR schizophrenia OR "mental disorder" OR alcohol OR "substance abuse" OR "bipolar disorder" OR "obsessive compulsive disorder" OR suicide OR "anxiety disorder" OR "dementia" OR "eating disorder" OR "attention deficit hyperactive disorder" OR "post-traumatic stress disorder") AND (knowledge OR attitude OR stigma OR stereotype OR discrimination OR "mental health literacy"). We used MeSH terms and truncations according to the properties of each database. We included all papers written in any of the European languages.

Our search on May 25, 2016 resulted in 4,399 articles from PubMed, 8,912 articles from PsycINFO, and 14,033 articles from Web of Science. After manually removing all duplicates, this resulted in 12,424 references. Two independent researchers screened titles, abstracts and (where appropriate) the full text of all identified papers. All reports on studies meeting the following inclusion criteria were retained: a) the focus of the study was on the general public (studies investigating beliefs and attitudes of particular subgroups such as consumers, health professionals or students were excluded); b) samples were obtained by either random or quota sampling methods; c) while we included studies focusing on attitudes about substance-related disorders, those merely dealing with attitudes toward substance use and not referring to any disorder were excluded.

After exclusion of papers not meeting those criteria, we ended up with 423 papers. We then hand-searched the identified literature for relevant citations and searched electronically for other relevant publications by authors of papers thus far identified. By this method we identified 222 further papers that met our inclusion criteria. Our search strategy then yielded in total 645 papers (see Figure 1), 65 of which (10.1%) were written in languages other than English.

A full-text analysis of all these papers was carried out independently by two researchers. Only papers reporting results from population surveys conducted since the turn of the century were included in the review. We excluded studies investigating attitudes prevalent among youth or attitudes towards mentally ill youth. Studies on help-seeking from mental health professionals in general without specification of psychiatrists were also excluded. The following data were extracted from each paper: a) attitudes towards seeking help from a psychiatrist (as compared to a psychologist/psychotherapist or a gen-

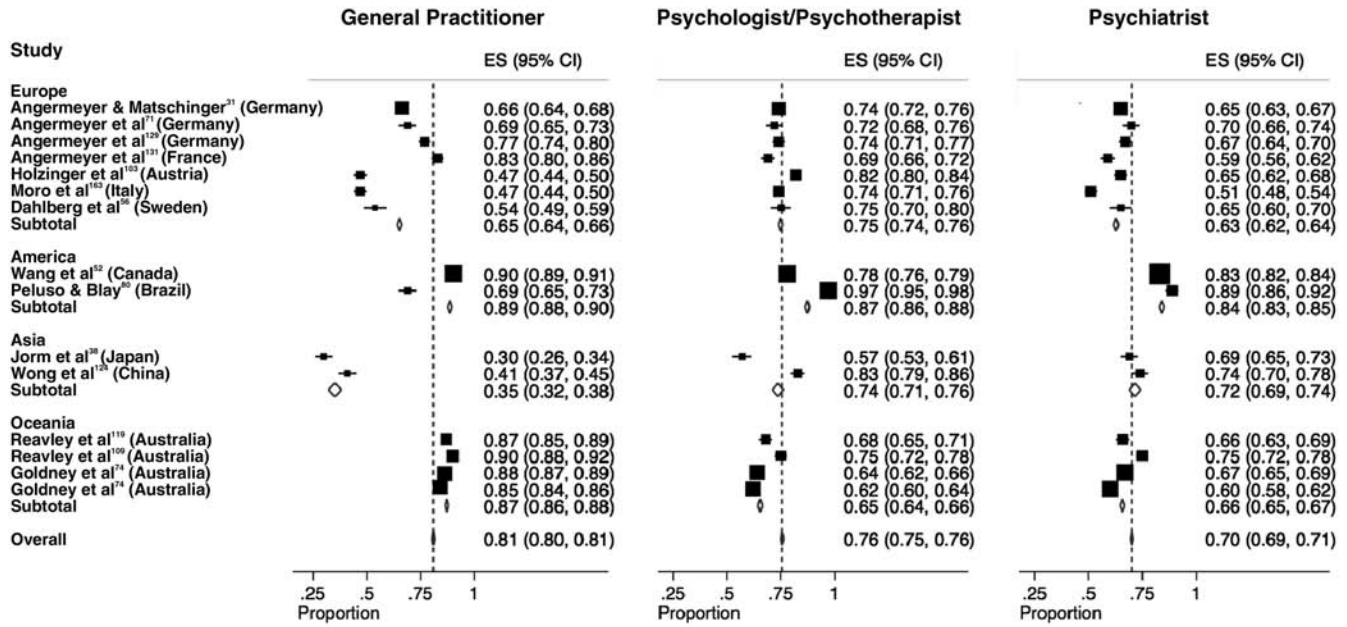

Figure 2 Forest plots for recommendations of different sources of help for depression (proportion of respondents recommending a particular source of help). Studies 31,71,103,129 and 131 examined the recommendation of a psychotherapist; the other studies of a psychologist. ES – estimated proportion

eral practitioner); b) attitudes towards psychiatric treatments, particularly psychotropic medication and psychotherapy; c) evolution of attitudes over time; d) association of these attitudes with mental health literacy and stigma.

In total, 162 papers containing relevant information could be identified[10-171]. If necessary, native speakers were contacted to provide translations. Disagreement about inclusion of individual papers into the review or about the allocation to the various analytic categories was resolved by discussion.

Meta-analysis

Three main methodological approaches can be distinguished when evaluating attitudes towards psychiatric treatment: a) rating of different sources of help (respondents are usually presented with a case vignette or an illness label, and offered a list of possible help-seeking strategies; they are then asked to indicate for each source of help how likely they would recommend it for the problem described); b) ranking of these sources of help (first choice, second choice, etc.); c) open-ended questions (asking for unprompted recommendation or help-seeking intentions). We chose the largest group of methodologically similar papers: those eliciting help-seeking attitudes via rating of different sources or methods of treatment for either depression or schizophrenia.

We distinguished three sources of professional help: general practitioners, psychiatrists and psychologists/psychotherapists. The term "psychotherapist" has slightly different meanings in the various countries of the world, being applied to people with different professional training and affiliation. In this review, the term is used in the sense of "provider of psychotherapy". We grouped psychotherapists and psychologists together as the latter also offer primarily psychotherapy, and contrast them with psychiatrists, who offer pharmacotherapy and, to a varying degree, psychotherapy.

To account for cultural differences, we performed separate meta-analyses for different geographical regions, and then combined these into an overall meta-analysis. Because we were interested not only in the absolute proportion of respondents recommending different treatment modalities, but also in their relative importance compared to other sources of help, we included only those studies that simultaneously examined recommendations of either psychiatrist, psychologist/psychotherapist and general practitioner as sources of help, or medication and psychotherapy as treatment methods for depression or schizophrenia.

All statistical analyses were performed using Stata/MP software, release 13.1[172]. Meta-analyses of treatment recommendations were performed using the *metaprop* package[173]. An inverse variance weighted fixed-effects meta-analysis was performed using score test-based confidence intervals on the proportions of recommendation for general practitioner, psychiatrist, psychologist/psychotherapist, medication and psychotherapy in schizophrenia and depression respectively. In all meta-analyses, the I^2 statistic indicated no significant heterogeneity between studies ($I^2=0.0\%$).

In contrast to common meta-analysis, a meta-regression focuses on the annual change of the treatment and help-seeking recommendation (rather than on the overall recommendation). Therefore, only studies reporting results for at least two time

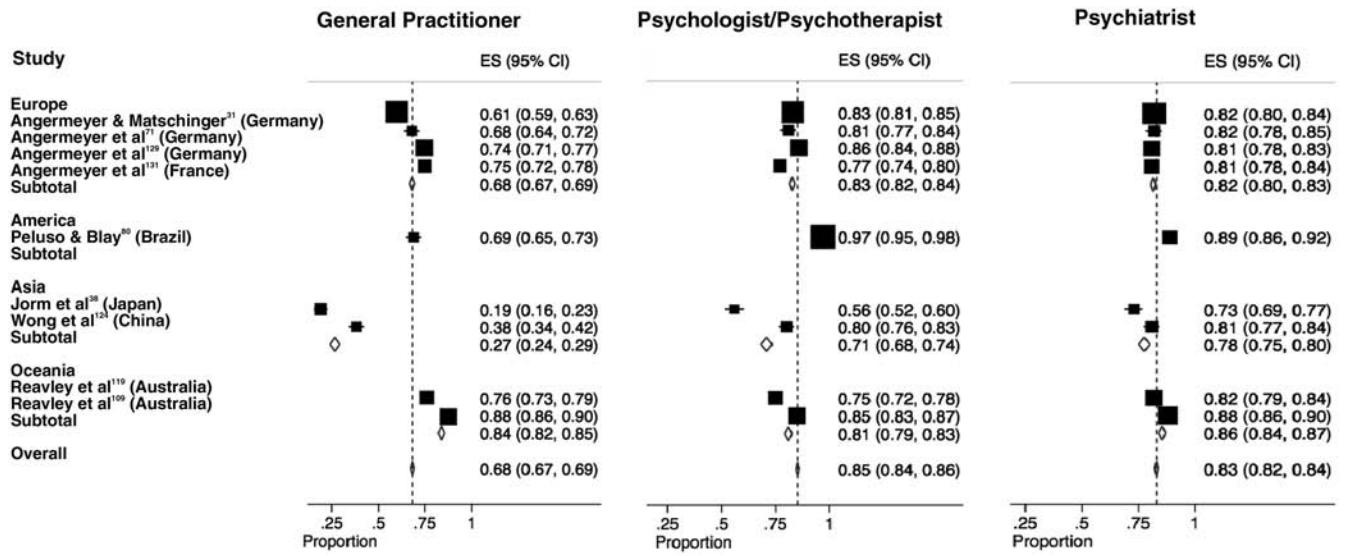

Figure 3 Forest plots for recommendations of different sources of help for schizophrenia (proportion of respondents recommending a particular source of help). Studies 31,71,129 and 131 examined the recommendation of a psychotherapist; the other studies of a psychologist. ES – estimated proportion

points were chosen. Each time point of each study was taken as one observation with its independent proportion of respondents endorsing a specific recommendation in one survey. To estimate the overall recommendation change per year, we used the revised version of the *metareg* command[174], which performs a random effect meta-regression analysis using aggregated-level data. For each recommendation (general practitioner, psychiatrist, psychologist/psychotherapist, medication and psychotherapy for schizophrenia and depression, respectively), change was adjusted for country, allowing for differing country-specific baselines for any recommendation change.

All reported p values are two sided. For our figures and tables, proportions (values between 0 and 1) were transformed into percent (0-100) to reflect the reported percentages in the single studies.

RESULTS

Attitudes towards seeking help from a psychiatrist or psychologist/psychotherapist

Figures 2 and 3 show the results of meta-analyses of studies eliciting recommendations of different health professionals for depression and schizophrenia. Overall, the proportion of respondents recommending professional help was high (68 to 85%). For depression, general practitioners were recommended by 81%, followed by psychologists/psychotherapists (76%) and psychiatrists (70%). For schizophrenia, psychologists/psychotherapists were recommended by 85% and psychiatrists by 83%, followed by general practitioners with 68%.

In all regions, specialist mental health care was more frequently recommended for schizophrenia than for depression. Looking at differences between continents, it appears that general practitioners are less popular in Asia (being recommended by a subtotal of 27% and 35% for treating schizophrenia and depression).

A number of studies enquired recommendation of a general practitioner, psychiatrist and "other mental health worker", most notably the Stigma in Global Context – Mental Health Study[142], which itself comprised surveys in 16 countries, and the Mental Health Module of the US General Social Survey[65]. These studies used four-point Likert scales to elicit recommendations without a neutral midpoint, resulting in generally higher rates of recommendations. We performed a separate meta-analysis of these studies. Here, psychiatrists were recommended more often than "other mental health workers" for treating both schizophrenia (95% vs. 93%) and depression (91% vs. 87%). For both disorders, general practitioners were recommended by 92%, which again positioned them above mental health specialists for depression, and below them for treating schizophrenia.

When asked to rank different sources of help, respondents tended to prefer specialist care over general medical care. For schizophrenia, psychiatrists and psychologists/psychotherapists were consistently named more frequently as first choice than general practitioners[40,80,148]. For depression, studies from Germany[40], Australia[18], Hong Kong[111], Jordan[125], Pakistan[41] and China[148] found psychiatrists and psychologists/psychotherapists as popular or even more popular for treating this disorder compared to general practitioners. When comparing the ranking of psychologists/psychotherapists and psychiatrists, 6 out of 9 studies found the former being preferred over the latter[41,80,103,139,148,163], only one study found the opposite[125], and two studies found no difference[18,40].

When using open ended questions, general medical care was mentioned more often than specialist care. Studies from Germany,

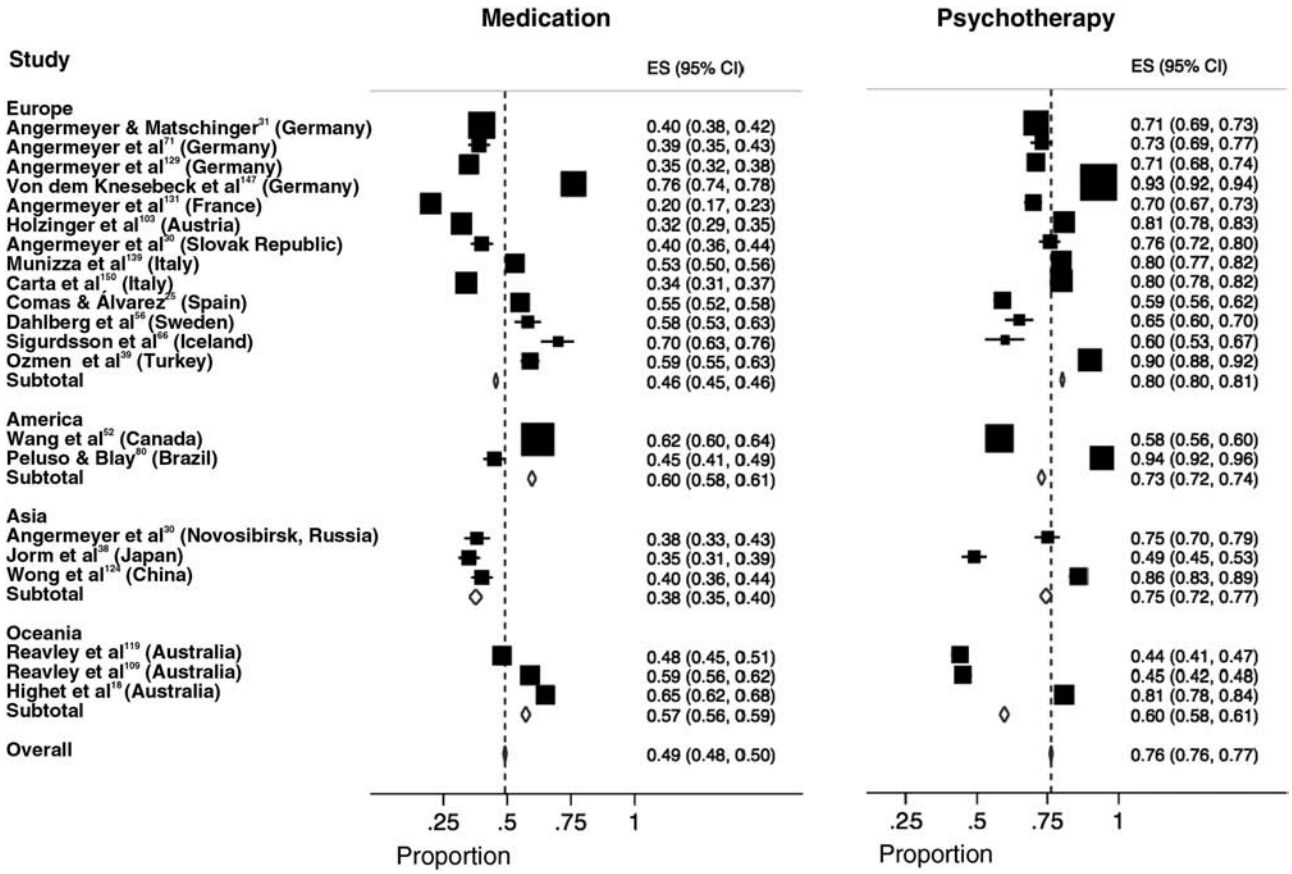

Figure 4 Recommendation of psychotropic medication and psychotherapy for depression (proportion of respondents recommending a particular treatment method). ES – Estimated proportion

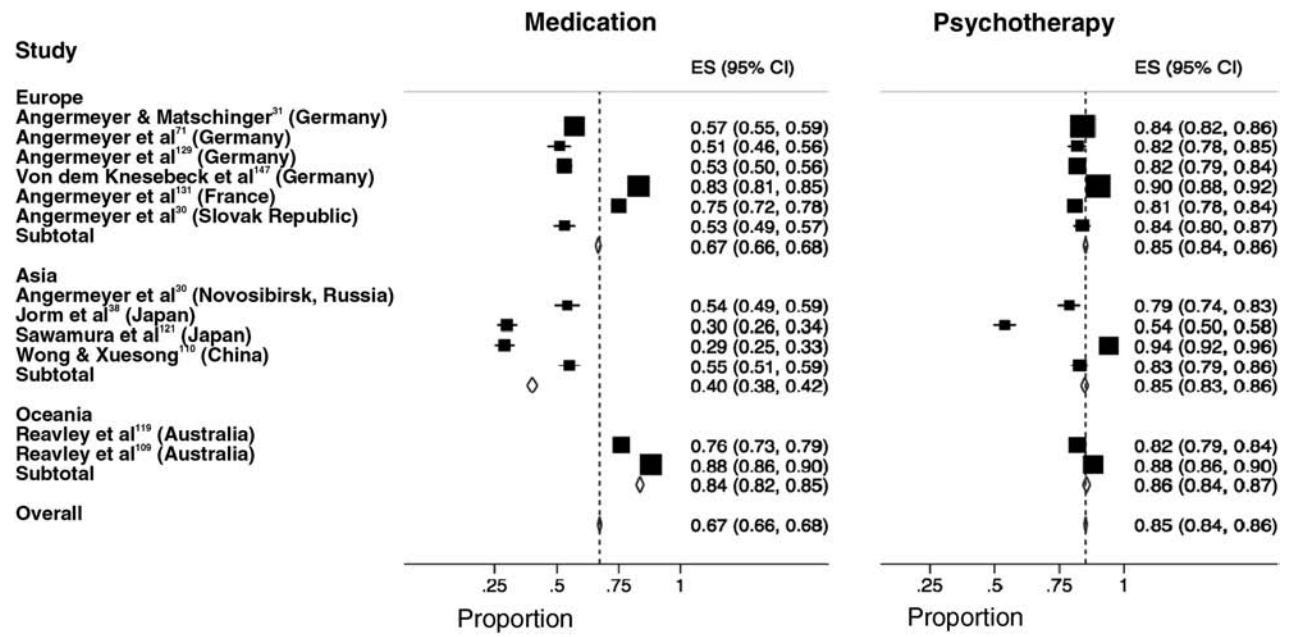

Figure 5 Recommendation of psychotropic medication and psychotherapy for schizophrenia (proportion of respondents recommending a particular treatment method). ES – Estimated proportion

Table 1 Meta-regression analyses of time trends in recommendations of sources of help and treatments in studies using case vignettes (1990-2011)

	Change per year adjusted for country, depression					Change per year adjusted for country, schizophrenia				
Recommendations	**%**	**95% CI**	**p**	**N studies**	**N sites**	**%**	**95% CI**	**p**	**N studies**	**N sites**
Psychiatrist	0.77	0.27-1.27	0.007	14	5	0.65	0.20-1.12	0.013	11	4
Psychologist/Psychotherapist	0.86	0.31-1.41	0.007	14	5	0.94	0.47-1.41	0.003	11	4
General practitioner	0.47	0.01-0.93	0.045	14	5	0.70	0.01-1.40	0.048	11	4
Medication	1.10	0.38-1.83	0.007	15	5	1.45	0.78-2.12	0.001	12	4
Psychotherapy	0.97	0.001-1.93	0.049	10	3	0.81	0.19-1.44	0.019	10	3

Belgium, Sweden and Australia found general practitioners being named more frequently than psychiatrists or psychologists/psychotherapists for treating both depression and schizophrenia[44,47,56,141]. Only a study from Japan found psychiatrists mentioned more frequently than a general practitioner for both depression and schizophrenia[38].

Attitudes towards psychiatric medication and psychotherapy

Figures 4 and 5 show forest plots for psychiatric treatments, namely psychotherapy and medication. Again, only studies eliciting both treatment modalities for either schizophrenia or depression are included, to enable a direct comparison of the subtotal and overall recommendation rates within one disorder. Medication was recommended by 49% for depression and 67% for schizophrenia. Psychotherapy was clearly more popular, being recommended by 76% for depression and 85% for schizophrenia. The general preference for psychotherapy was thus even more marked for schizophrenia than for depression. Only studies from Canada[52,109,119] found medication being slightly more popular than psychotherapy for treating depression.

Using a ranking approach, a similar picture emerged for both depression and schizophrenia: psychotherapy was more frequently than medication named as first choice[30,40,80,103].

Attitudes towards psychiatric inpatient care

Few studies examined attitudes towards psychiatric inpatient care. Generally, inpatient care was more accepted for schizophrenia than for depression or other mental disorders, that were perceived as less severe[38,80,92]. For example, in the US, inpatient care was recommended by 66% for a person with schizophrenia and by 27% for a person with depression[92].

Findings on whether psychiatric hospitals or psychiatric wards at general hospitals are preferred were inconsistent, with some studies showing a preference for specialized hospitals, particularly for patients with schizophrenia[80], others showing preferences for general hospitals[67], and still others demonstrating similar attitudes towards both forms of psychiatric inpatient care[146].

Evolution of attitudes towards psychiatrists and psychiatric treatments

Table 1 shows the results of our meta-regression analyses of time trends in recommending different sources of help. Trend data from vignette-based studies were available from Germany, Australia and the US[65,71,74,109,129]. All analyses showed a significant increase in treatment recommendations over time for medication and psychotherapy as well as for general practitioners, psychiatrists and psychologists/psychotherapists. The strongest increase in recommendations was visible for medication, increasing by 1.10% per year for depression (95% CI: 0.38-1.83) and 1.45% per year for schizophrenia (95% CI: 0.78-2.12).

Other studies specifically examined the evolution of attitudes towards psychiatric medication without using a case vignette. In the US, attitudes towards psychotropic medication generally became more favorable between 1998 and 2006[78]. A study from Germany, covering the time period 1990-2001, showed a similar trend, with increasingly positive attitudes towards medication[24]. The same holds for a study in a Swedish community, where between 1976 and 2003 a marked improvement of attitudes towards medication was observed[59].

A trend analysis of attitudes towards psychotherapy in Germany showed growing positive outcome expectations and a decline in negative evaluations between 2003 and 2012 also for this treatment modality[126].

Approval of restrictions for persons with mental illness – such as compulsory admission in Germany[149] and involuntary medication in the US[106] – remained largely stable over the last years, with three out of four respondents endorsing compulsory admission and one in four endorsing involuntary medication. However, closer examination of accepted reasons for compulsory admission showed a remarkable lowering of thresholds for admitting persons with mental illness in those who generally approved of compulsory admission. For example, while 29% recommended compulsory admission if a per-

son did not take prescribed medication in 1993, this proportion rose to 40% in 2011[149].

The image of the psychiatric hospital improved considerably between 1990 and 2011 in Germany[130]. Both in the US and Australia, the proportion recommending hospital care for schizophrenia or depression increased in recent years[65,92,119]. In contrast, approval of community services, such as group homes in one's neighborhood, decreased between 1990 and 2011 in Germany, with 35% welcoming such a service in their neighborhood in 1990, compared to 24% in 2011[128], while it remained stable in the UK[135].

Mental health literacy and attitudes towards seeking help from a psychiatrist and psychiatric treatments

Studies conducted in Germany, Belgium, Slovak Republic, Russia and Japan examined the relationship between identifying symptoms of schizophrenia or depression and help-seeking attitudes. Across all studies, recognition of a mental disorder or correct identification of the specific diagnosis was accompanied by a greater willingness to recommend visiting a psychiatrist[31,40,71,141] or higher expectations for the effectiveness of the treatment offered by a psychiatrist[121]. With one exception, in all Western countries participating in the Stigma in Global Context – Mental Health Study, the lay diagnosis of schizophrenic symptoms as "mental illness" increased the likelihood that seeking psychiatric help was considered important[107].

The picture concerning attitudes towards psychiatric treatments was rather mixed. In Germany, Slovak Republic and Russia, seeing symptoms of schizophrenia or depression as indicating mental illness was associated with recommending psychotherapy but not with recommending psychotropic medication[31,40,71]. Similarly, in Belgium and Turkey, recognition of mental illness increased the likelihood that psychotherapy was seen more favorably[66,166]. By contrast, in Japan, the lay diagnosis of depression was significantly associated with a high expectation of the effectiveness of antidepressants[121], and in Australia accurate recognition of depression or schizophrenia was associated with a stronger belief in helpfulness of antidepressants or antipsychotics, respectively[109,119].

In Germany, Slovak Republic and Russia, the attribution of mental disorder to biogenetic causes was associated to recommending a psychiatrist[31,40,71]. In the US, a neurobiological conceptualization of mental illness, i.e., attributing its cause to either chemical imbalance or a genetic problem, tended to increase the odds of endorsing help from a psychiatrist[92]. Only in Belgium no such relationship was observed[141].

Across all studies, attributing mental illness to biogenetic causes[31,40,71,120,143], holding a neurobiological conceptualization[92] or endorsing a biomedical illness representation model[100] were associated with more favorable attitudes towards psychotropic medication. As regards attitudes towards psychotherapy, results were less consistent: in two studies endorsement of brain disease was associated with lower readiness to recommend psychotherapy for the treatment of depression, but not schizophrenia[31]; in one study it was associated with even stronger recommendation of psychotherapy for the treatment of both disorders[40].

Stigma and attitudes towards seeking help from a psychiatrist and psychiatric treatments

Among the different stigma components, self-stigma – i.e., negative attitudes about oneself as a result of internalizing stigmatizing ideas held by society – seems of particular importance for attitudes towards seeking help from a psychiatrist. In a study in Australia, 44% of respondents reported they would feel embarrassed to see a psychiatrist, and there was a significant negative association between self-stigma and help-seeking[42]. Similarly, in studies from the Netherlands and Belgium, self-stigma was negatively related to the intention to seek help from a psychiatrist[155,158].

In addition, anticipated shame tends to decrease the likelihood of endorsing a psychiatrist as source of help[81,158]. Not only the application of negative stereotypes to oneself, but also negative attitudes towards other people with mental illness seem to play a role, as shown in a study from Germany, where greater desire for social distance was associated with weaker intentions to see a psychiatrist[81].

In contrast to self-stigma, perceived stigma – i.e., the awareness of negative stereotypes held by the general public about people receiving psychiatric help – and the anticipation of discrimination seem to have less impact on help-seeking. Only in an Australian study[42] perceived stigma had a negative effect, while in Germany[81], Belgium[155], the Netherlands and Flanders[158] no association with help-seeking was observed.

The relationship between stigma and attitudes towards medication did not show a consistent pattern. In Germany, Slovak Republic and Russia, endorsing lack of will power as cause of schizophrenia or depression had no effect on the recommendation of psychotropic medication. The same applied to the treatment of depression, with the exception of Slovak Republic, where lack of will power was related to greater reluctance to recommend drugs[31,40]. In Flanders and the Netherlands, self-stigma and perceived stigma were unrelated to the willingness to take medication[158]. In a study from the US, perceived stigma had also no impact on the preference for medication only[100].

Only three studies examined the association between stigma and attitudes towards psychotherapy. In one study the endorsement of lack of will power as cause of schizophrenia or depression was related to less readiness to recommend psychotherapy[40]; in the other two studies no such relationship was observed[31].

DISCUSSION

Some limitations of the present study should be acknowledged. First, our systematic review focused on depression and schizophrenia, as we were unable to identify sufficient num-

bers of research reports focusing on other mental disorders. Second, our review only included papers written in English or other European languages, which may have resulted in an underrepresentation of countries where other languages are used for disseminating research results. Third, in order to ensure a minimum quality of selected studies, we only included peer-reviewed papers and excluded grey literature, online research reports and doctoral theses. Having said that, our review comprises the largest body of population studies on attitudes towards help-seeking so far analyzed, and our meta-analyses allow identification of both different and similar patterns of attitudes across the world.

From a global perspective, our results suggest that the help provided by psychiatrists is held in high esteem by the public, being recommended by over 80 percent of respondents for the treatment of schizophrenia and by 70 percent for the treatment of depression. In the sixteen countries participating in the Stigma in Global Context – Mental Health Study, the proportion of those opting for psychiatric treatment in case of schizophrenia or depression amounted even to over 90 percent. Psychiatrists are slightly preferred over general practitioners for the treatment of schizophrenia, while the opposite holds for the treatment of depression. The public's readiness to recommend seeking help from a psychiatrist has increased over the past 25 years. Thus, our findings do not support the notion that psychiatry is currently exposed to strong discrimination and, as a consequence, shunned by the public. The gap between the attitudes of the public and those perceived by psychiatrists could be seen as an indication of psychiatrists' inclination to self-stigmatization[175], which, in the end, may result in low morale and a sense of entrapment[1].

However, this rather optimistic appraisal needs some qualification when comparing attitudes towards psychiatrists with those towards psychologists/psychotherapists. These groups of professionals work closely together and, with doctors working as psychotherapists in several countries, the line between them is not always clear cut. However, in some instances the public seems to prefer one group over the other. Psychologists/psychotherapists are more recommended than psychiatrists for the treatment of depression, at least in Europe and America. According to our meta-analysis, psychologists/psychotherapists are recommended as much as psychiatrists even for the treatment of schizophrenia – a disorder which is at the heart of psychiatry. This high standing of psychologists/psychotherapists seems to mirror the fact that, as our meta-analysis has shown, psychotherapy is the favorite treatment method among the general public, while pharmacotherapy, which is considered to be the main treatment offered by psychiatrists[89,176], is less appreciated. Although medication has gained popularity in recent years, there remains a large gap in public acceptance between the two treatment options.

The public's preference for psychotherapy is in sharp contrast to real-world clinical practice in many countries, where pharmacotherapy is the primary treatment for most mental disorders and psychotherapy is rather on the decline[177]. In the US, for instance, from 1998 to 2007, there was a significant increase in the percentage of outpatients who received pharmacotherapy alone to treat their mental disorder, which was mirrored by a significant decline in the use of psychotherapy alone as well as psychotherapy in combination with pharmacotherapy. By 2007, over half of outpatients, regardless of their mental health condition, received only pharmacotherapy[178].

The general public prefers psychotherapy not only for treating depression but also for treating schizophrenia, which might seem counterintuitive and conflicting with professional treatment recommendations. A possible explanation for this rather surprising result may be that the term "psychotherapy" does not necessarily mean the same for lay people as it does for mental health professionals. In a study from Austria, respondents who had endorsed psychotherapy were asked what kind of psychotherapy they had in mind. Two thirds of them mentioned "talk therapy" or simply "talking", and only a tiny minority named established forms of psychotherapy like cognitive behavioral or psychodynamic psychotherapy[179].

This indifference to the specific forms of psychotherapy might indicate that, instead of being treated by means of a certain technique, people have the (quite legitimate) need to be listened to by someone who takes them seriously and who is trying to understand them with their problem. Accordingly, the reason why psychologists/psychotherapists are in some instances preferred over psychiatrists could be that, in the eyes of the public, psychologists and psychotherapists are more ready to provide patients with an opportunity to talk over their problems[89,176]. As M. Maj[180] has recently pointed out, the role of empathetic communication in psychiatry has been underestimated in the past few decades, "ignoring the fact that without communicative interaction no person will allow any professional to genuinely access his/her personal world". A good strategy to improve the public image of psychiatry would thus be to point out that, of course, personal interaction, talking and empathetic understanding are at the core of psychiatric care, and not just prescribing medication.

Although we found no indication that psychiatry as a medical discipline is stigmatized, stigma is still a relevant problem for help-seeking. Similar to a recent extensive review of stigma and help-seeking[181], the studies included in our analyses point out that particularly self-stigma and individual stigmatizing attitudes are a prominent barrier to seeking help. It is our contention that, rather than seeing themselves as victims and spending their scarce resources on combating the stigma allegedly attached to their profession, psychiatrists would be better advised to fully engage in the fight against the stigma attached to those suffering from mental illness[182].

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Persistence of psychosis spectrum symptoms in the Philadelphia Neurodevelopmental Cohort: a prospective two-year follow-up

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Prospective evaluation of youths with early psychotic-like experiences can enrich our knowledge of clinical, biobehavioral and environmental risk and protective factors associated with the development of psychotic disorders. We aimed to investigate the predictors of persistence or worsening of psychosis spectrum features among US youth through the first large systematic study to evaluate subclinical symptoms in the community. Based on Time 1 screen of 9,498 youth (age 8-21) from the Philadelphia Neurodevelopmental Cohort, a subsample of participants was enrolled based on the presence (N=249) or absence (N=254) of baseline psychosis spectrum symptoms, prior participation in neuroimaging, and current neuroimaging eligibility. They were invited to participate in a Time 2 assessment two years on average following Time 1. Participants were administered the Structured Interview for Prodromal Syndromes, conducted blind to initial screen status, along with the Schizotypal Personality Questionnaire and other clinical measures, computerized neurocognitive testing, and neuroimaging. Clinical and demographic predictors of symptom persistence were examined using logistic regression. At Time 2, psychosis spectrum features persisted or worsened in 51.4% of youths. Symptom persistence was predicted by higher severity of subclinical psychosis, lower global functioning, and prior psychiatric medication at baseline. Youths classified as having psychosis spectrum symptoms at baseline but not at follow-up nonetheless exhibited comparatively higher symptom levels and lower functioning at both baseline and follow-up than typically developing youths. In addition, psychosis spectrum features emerged in a small number of young people who previously had not reported significant symptoms but who had exhibited early clinical warning signs. Together, our findings indicate that varying courses of psychosis spectrum symptoms are evident early in US youth, supporting the importance of investigating psychosis risk as a dynamic developmental process. Neurocognition, brain structure and function, and genomics may be integrated with clinical data to provide early indices of symptom persistence and worsening in youths at risk for psychosis.

Key words: Psychosis spectrum symptoms, psychotic-like experiences, schizotypy, persistence, youth, follow-up, predictors

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Subclinical psychotic-like experiences are relatively common in the general population of children and adolescents, occurring in as many as 22% of youths[1,2]. Yet, they only develop into distressing and impairing psychotic disorders in a minority of them[3]. Increasing evidence supports psychosis as a continuum in the general population[4], in which the experience and expression of multiple dimensions of symptoms can be detected in childhood or adolescence[5]. Examination of these early symptoms may enrich our knowledge of biobehavioral and environmental risk and protective factors associated with the psychotic disorder end of the continuum[6]. In turn, this line of research can inform early interventions and pathways to care for youths who are in the process of developing psychotic disorders.

Prospective studies in community youths suggest that 75-90% of psychotic-like experiences are transient[1,7]. Some early psychotic-like experiences may reflect vulnerability for psychotic disorders, with onset of sub-threshold symptoms occurring as long as 7-8 years prior to a first episode of psychosis[8,9]. However, other early experiences may be "transdiagnostic" and "incidental" to other mental disorders such as depression and anxiety[4]. In other youths, early symptoms may reflect trait-like characteristics that later manifest as schizotypy, consistent with a broadly defined risk state[5]. Finally, in some youths, symptoms may never be associated with a clinical disorder and thus never come to clinical attention, possibly due to their low severity and/or to protective factors[10]. The field has increasingly sought to explicate predictors and mechanisms of symptom course that may differentiate such varying developmental trajectories.

General population cohort studies conducted outside of the US have suggested that more severe and persistent subthreshold psychotic symptoms are associated with greater risk of conversion to psychotic disorders[1,11-13]. In adolescents, the longer subclinical symptoms persist, the greater the likelihood of impairment[1]. Persistence of psychotic-like experiences in youths has also been associated with other forms of psychopathology[14,15], cannabis use, childhood trauma, developmental problems, ethnic minority status, and mental health help seeking[13]. Such findings have been interpreted as supporting a proneness-persistence-impairment model of psychosis[16], in which early expressions of psychotic-like experiences may persist and subsequently become clinically impairing, depending on genetic vulnerability interacting with exposure to environmental risk factors and/or stressors. Evidence that varying trajectories of sub-threshold positive and negative/disorganized symptom domains may differentially predict functional impairment and help-seeking behavior has further supported the importance of a multi-dimensional and developmental view of psychosis spectrum symptoms[17].

In the US prospective investigations of psychosis spectrum symptoms in the general non-help-seeking youth population have been limited to schizotypal features among adolescent/

early adult college students[18] and young twins[19]. Though considerable research has centered on prospective investigations of help-seeking clinical high-risk youth[20], there is a gap in our understanding of risk and resilience factors that influence psychosis outcomes among the general population of US youth. Moreover, as detection of psychosis spectrum experiences has continued to extend earlier in the lifespan, there is an increasing need to differentiate early stable traits from subclinical psychotic-like states that may portend risk for psychosis[5].

Through the Philadelphia Neurodevelopmental Cohort, we aimed to investigate the predictors of persistence or worsening of psychosis spectrum features in the first large systematic community sample of US youths. As previously reported[21], we found that, among medically healthy youths aged 11-21, 3.7% reported threshold psychotic symptoms (delusions and/or hallucinations). An additional 12.3% reported significant subpsychotic positive symptoms. Odd/unusual thoughts and auditory perceptions, followed by reality confusion, were the most discriminating and widely endorsed attenuated symptoms.

In a series of investigations, we have found baseline psychosis spectrum status to be associated with reduced global functioning, and increased odds of depression, anxiety, behavioral disorders, substance use and suicidal ideation[21], as well as minority ethnic group membership[22]. Youths with psychosis spectrum symptoms had reduced accuracy across domains of neurocognitive function[21] and were neurocognitively delayed across the age range compared to asymptomatic youths[23].

Our neuroimaging studies have identified patterns of structural[24,25] and functional[26] abnormalities in the psychosis spectrum group, including novel evidence for functional dysconnectivity[27], similar to patterns observed in adults with psychotic disorders. Aspects of prefrontal executive system dysfunction and limbic hyperactivation to threat appear to be selectively associated with psychosis spectrum symptoms in comparison with other psychopathology dimensions[28].

To date, few community cohorts have evaluated a wide array of biobehavioral predictors of the persistence of psychosis risk symptoms. The Philadelphia Neurodevelopmental Cohort is uniquely suited to widening the window of investigation of neurobehavioral risk and protective factors associated with varying psychosis spectrum trajectories and outcomes among US youth. Here we conducted a two-year follow-up of a large subsample (N=503) of youth from the cohort, selected on the basis of presence or absence of psychosis spectrum features at baseline and neuroimaging eligibility. The aim of this first report from the follow-up study is to evaluate clinical patterns and predictors of symptom persistence.

METHODS

Participants

Participants were recruited for follow-up based on Philadelphia Neurodevelopmental Cohort Time 1 (baseline) psychosis spectrum screening[21,29]. Briefly, at Time 1, prospective participants (N=50,293) were recruited through the Children's Hospital of Philadelphia pediatric clinical health care network, extending to over 30 clinical community sites in the Philadelphia tri-state area (Pennsylvania, New Jersey and Delaware). Participants were not recruited from psychiatric clinics. Initial review of electronic medical records for preliminary eligibility yielded a pool of 19,161 participants between the ages of 8 and 21, who had provided written informed consent/assent to be re-contacted for future studies, were proficient in English, and did not appear to have significant developmental delays or physical conditions that would interfere with their ability to complete study procedures.

From the recruitment pool, 13,598 participants were invited, 9,498 were enrolled, and 9,421 completed the assessment. Time 1 assessment consisted of psychopathology screen, including screen for psychosis spectrum symptoms, and computerized neurocognitive testing for all participants[21]. A subset of 1,601 participants completed the imaging procedures.

From the cohort of 9,498 youths aged 8-21 at Time 1, participants (N=1,486) were identified for follow-up assessment if they screened either positive or negative for psychosis spectrum symptoms (as detailed below), were physically healthy at Time 1 (no moderate or severe physical conditions requiring multiple procedures and monitoring[30]), had completed the neuroimaging protocol ≥18 months previously, and had good quality neuroimaging data[31]. To maximize the number of subjects scanned at Time 2, a small subset of participants screening positive for psychosis spectrum symptoms who had not previously completed neuroimaging were also included in the recruitment pool.

From this pool, 61% (N=910) could be reached for further screen and invitation to participate. Among those invited, 56% (N=510) completed study procedures, 21% (N=182) declined (e.g., lived too far, away at school, not interested), 15% (N=118) were excluded due to conditions precluding imaging or cognitive testing (e.g., orthodontic braces, metal in body, pregnant, serious central nervous system disease), and 8% (N=55) had recurrent cancellations/no-shows for scheduled appointments. The current investigation included the 503 participants with complete Time 2 clinical data at the time of our analyses.

After complete description of the study, written informed consent was obtained for participants aged at least 18, and written assent and parental permission were obtained from children aged less than 18 and their parent/legal guardian. All procedures were approved by the University of Pennsylvania and the Children's Hospital of Philadelphia Institutional Review Boards.

Psychopathology measures

Time 1

Interviews

Probands (age 11-21) and collaterals (parent or legal guardian for probands aged 8-17) were administered a computerized

structured interview (GOASSESS)[21]. This instrument assessed psychiatric and psychological treatment history, and lifetime occurrence of major domains of psychopathology – including mood, anxiety, behavioral and eating disorders – and suicidal thinking and behavior.

Three screening tools to assess psychosis spectrum were embedded within the psychopathology screen. Positive subpsychotic symptoms in the past year were assessed with the 12-item assessor administered PRIME Screen-Revised (PS-R)[32,33]. Items were self-rated on a 7-point scale ranging from 0 ("definitely disagree") to 6 ("definitely agree"). The participant then rated the duration of each endorsed symptom. Positive psychotic symptoms (lifetime hallucinations and delusions) were assessed using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS)[34] psychosis screen questions, supplemented with structured questions to reduce false positives. Negative/disorganized symptoms were assessed using six embedded assessor rated items from the Scale of Prodromal Symptoms (SOPS)[35].

Psychopathology summary measures

Psychopathology was summarized into dimensions using factor analyses. For previous analyses, we used psychopathology summary measures[21,29] or a bifactor model with individual items that produced orthogonal scores[28]. For the current analyses, we wished to use and interpret Time 1 psychopathology scores as potential predictors of Time 2 psychosis spectrum status. However, there is a debate in the field regarding the validity of bifactor sub-factor scores used in this way[36,37]. Consequently, we used a correlated-traits model to generate oblique scores. Specifically, we performed exploratory factor analyses (EFAs)[38] on 112 individual GOASSESS items. Four factors were extracted, and we used various combinations of extraction (maximum likelihood, least squares, etc.) and rotation (oblimin, geomin, promax, etc.) methods to test for consistency across methods. The four-factor model was based on the finding of Krueger[39] that common mental disorders tend to group into three main categories, which he termed "anxious-misery", "fear", and "externalizing", and we additionally included GOASSESS items assessing psychosis, making four symptom clusters.

All extraction/rotation combinations yielded highly consistent results, with items almost never switching from one symptom cluster to another when a different extraction/rotation combination was used. Based on these EFA results, we performed a confirmatory factor analysis with four factors, each comprising the same items suggested by the EFAs. This model was used to calculate scores for each of the four correlated factors: anxious-misery, fear, externalizing, and psychosis. All EFAs were performed using the psych package[40], and the confirmatory factor analysis was performed using the mean- and variance-adjusted weighted least squares estimator in Mplus[41].

Finally, history of exposure to traumatic stressors was tabulated from the post-traumatic stress disorder section of the GOASSESS, in which participants were asked about lifetime history of experiencing eight categories of events (i.e., natural disasters, witnessed violence, attacked physically, sexually assaulted/abused, threatened with weapon, experienced serious accident, witnessed serious physical injury/death, observed dead body).

Individuals meeting any one of the following three criteria were classified as having significant psychosis spectrum symptoms[21]: a) positive-subpsychosis: either age-deviant PS-R total scores (as defined by extreme total scores, $z \geq 2$, compared with age mates) or extreme agreement on the PS-R ($\geq$1 item rated 6, definitely agree; or $\geq$3 items rated 5, somewhat agree[32]); b) positive-psychosis: possible or definite hallucinations or delusions based on K-SADS screen, with duration $\geq$1 day, occurring outside the context of substance use, illness and medicines, and accompanied by significant impairment or distress (rating $\geq$5); c) negative/disorganized: age deviant negative/disorganized total scores on the SOPS, as defined by $z \geq 2$ compared with age mates.

Additional measures

All measures were computerized locally. The Wide Range Achievement Test (WRAT-4) Reading subscale[42] provided an estimate of IQ. The majority of participants (N=6,298) completed an abbreviated version of a widely used self-report measure[43] assessing lifetime use of cannabis, alcohol, tobacco and illicit substances[44].

As previously described[45], neighborhood socioeconomic status scores were derived by factor analysis. This summary score reflects several socioeconomic characteristics of the participants' neighborhoods (census blocks). Specifically, high scores reflect a high percent of residents who are married, low percent in poverty, high median family income, high percent with at least a high school education, low population density, high percent employed, low percent of vacant lots, and high median age. Low scores reflect the opposite.

Time 2

Interviews

Psychopathology was assessed using a custom protocol consisting of modules of the K-SADS, the Structured Interview for Prodromal Syndromes (SIPS, version 4.0[34]), and the psychotic and mood differential diagnosis modules (C/D) of the Structured Clinical Interview for DSM-IV[46]. Collateral versions of the instruments were constructed and were identical to the standard proband versions, except that the wording of question stems was altered as appropriate for the informant (e.g., "Did you. . .?" was converted to "Did your child. . .?").

In contrast to Time 1, when we employed highly structured screens, all Time 2 sections were administered in a semi-structured manner, allowing follow-up probing and clarification of endorsed items, as well as reconciliation of experiences

across the interview. The K-SADS modules provided a standardized and comprehensive assessment of DSM-IV Axis I psychopathology (mood, attention deficit and hyperactivity, and substance use), including symptom and episode information for differential diagnoses of disorders, and clinical information about the diagnostic context of any reported sub-psychotic symptoms.

Psychosis spectrum symptoms were assessed using the SIPS, in which selected symptom items from the K-SADS were integrated to facilitate differential diagnosis. The SOPS[35], embedded within the SIPS, describes and rates the severity of prodromal, psychotic and other symptoms occurring within the past 6 months. Dimensional symptom domains include positive (e.g., unusual thought content, persecutory ideas), negative (e.g., avolition), disorganized (e.g., odd behavior or appearance), and general (e.g., sleep disturbance). To provide a common psychosis spectrum measure across Time 1 and Time 2, the PS-R was administered following the SIPS.

Social and role function was rated using the SIPS Global Assessment of Function[35]. Additional sections included construction of a timeline of major life events to facilitate accuracy of dating onset/offset of endorsed symptoms, demographics and medical history, psychiatric treatment history, history of suicidal thoughts and attempts, and current mental status (Mini-Mental State Examination[47]). An abbreviated version of the Family Interview for Genetic Studies (FIGS)[48], administered to collaterals (of probands < age 18) and adult probands, screened for presence or absence of first-degree family history of major domains of psychopathology, with more detailed assessment of possible psychotic disorders following affirmative responses to psychosis-related screening items. To avoid influence of proband status on judgments about psychosis family history, presence/absence was coded by the first author based on FIGS data contained in a blinded file, without reference to proband status at either Time 1 or Time 2.

All assessment tools were administered via a laptop computer using locally computerized versions in Filemaker to allow live data capture, verbatim recording of participant responses, and interactive checks of skip-outs and section completion. Where relevant, releases for medical and psychiatric records were requested to supplement interview assessed information.

Following each evaluation, assessors integrated information from probands, collaterals and available medical records to provide combined ratings across symptom domains. Integrated clinical information was then summarized in a narrative case history, and presented at a case conference attended by at least two doctoral level clinicians with expertise in psychosis and/or child psychopathology. A strict blind was maintained such that recruiters, assessors and clinicians determining consensus ratings and diagnoses were naïve to the Time 1 psychosis spectrum screening status of all participants. To avoid biasing case assignment or symptom ratings, family history of psychopathology was not disclosed during case conference.

Each SOPS clinical rating ≥3 underwent consensus review, and clinical risk status and best estimate final diagnoses for Axis I disorders were determined. We also made consensus "prodromal" diagnoses according to standard SIPS attenuated prodromal syndrome (APS) criteria[35], in which APS is diagnosed if at least one positive symptom rated 3-5 had frequency ≥1 time a week in the past month as well as onset or worsening (≥1 or more SOPS scale point) within the past year. We created a parallel attenuated negative/disorganized syndrome (ANDS) classification to reflect recent onset or worsening of negative or disorganized symptoms with comparable frequency and onset/worsening criteria as for APS, but requiring ≥2 negative or disorganized symptoms to meet these criteria. Individuals were classified as meeting psychosis spectrum criteria if they had either a) a DSM-IV psychotic disorder or mood disorder with psychotic features, or b) at least one SOPS positive symptom currently (past 6 months) rated 3-5 or at least two negative and/or disorganized symptoms rated 3-6.

Interviews were administered by bachelor's or master's level assessors who underwent formal training conducted by the first author. The training protocol consisted of a structured program of lectures, supervised practice sessions and mock interviews. Trainees then administered ≥5 interviews under direct observation by a certified observer until competency and consistency were established by scoring ≥85% on a standardized 60-item rating scale assessing proficiency in administration. In addition, trainees were required to be completely reliable with the observer in determination of clinical significance (≥3) on all SOPS items, and within one scale point with observer on all other SOPS ratings. Ongoing calibration of ratings was achieved through case conference meeting attendance by all assessors, and periodic re-training and direct observation.

Additional measures

Computerized assessment of substance use and estimated IQ (WRAT-4) were identical to Time 1 assessment. To provide convergent and supplemental dimensional assessment of psychosis spectrum symptoms, a subset of participants (N=418) was administered a modified and computerized version of the Schizotypal Personality Questionnaire (SPQ). The SPQ is a multi-dimensional true/false self-report measure assessing each of the nine major features of schizotypal personality disorder as defined by the DSM[49]. Seven items modeled after the Infrequency Scale of the Personality Research Form were interspersed among SPQ items to assess random or careless responding[50].

When completing the SPQ, participants were instructed to refrain from considering episodes when they were under the influence of drugs or alcohol, and periods when they were just falling asleep or awakening. Scores for the total SPQ and individual scales were based on an unweighted linear combination of the SPQ items endorsed in the psychopathological direction. Because the subscales differ in the number of constituent items (ranging from seven to nine), percentages of endorsed

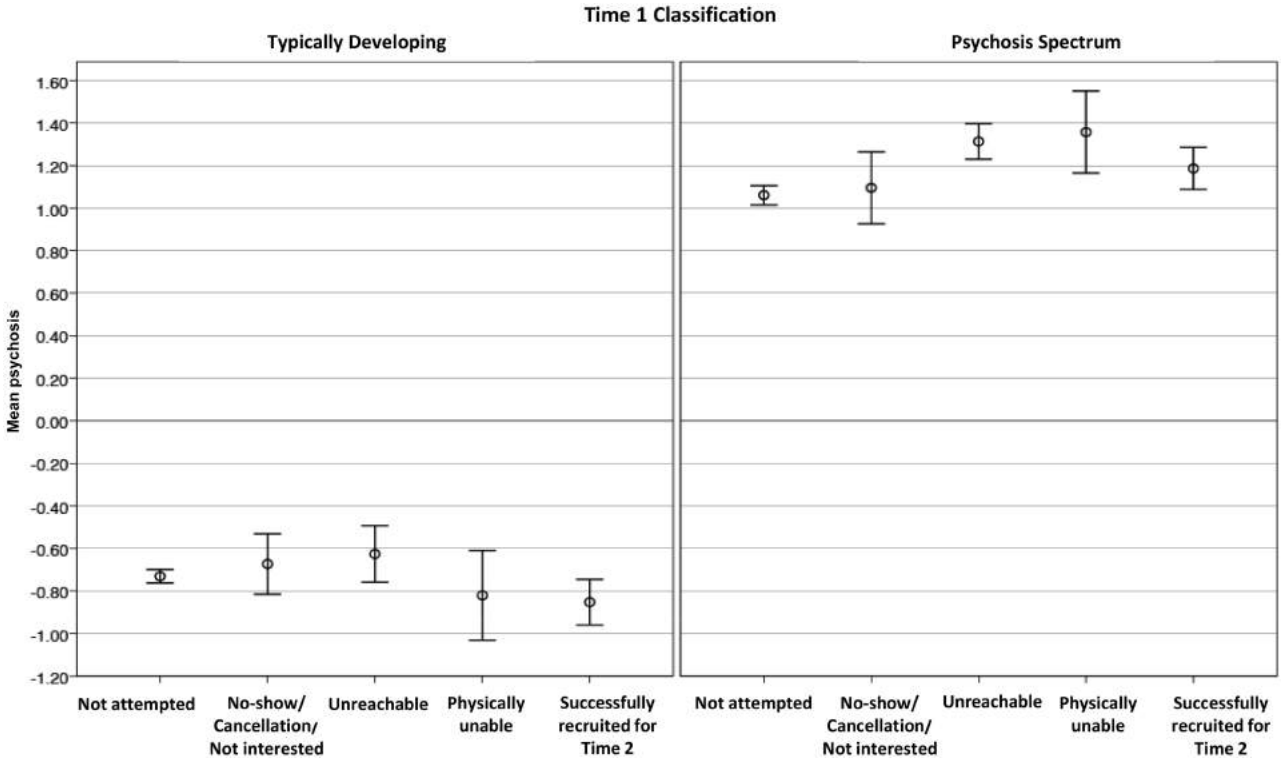

Figure 1 Mean psychosis scores at Time 1 by recruitment results at Time 2. Results are presented according to classification at Time 1 as Typically Developing (left panel) and Psychosis Spectrum (right panel)

items per subscale were calculated to allow comparison of relative endorsements across subscales.

Statistical analysis

To first assess the representativeness of the enrolled sample with regards to the broader Philadelphia Neurodevelopmental Cohort, we compared Time 1 psychopathology indices of enrolled and non-enrolled participants using t-tests of factor scores. We then classified individuals into four groups based on psychosis spectrum classifications at Time 1 and Time 2: Persistent (psychosis spectrum symptoms at both Time 1 and Time 2); Resilient (psychosis spectrum symptoms at Time 1 but not Time 2); Emergent (psychosis spectrum symptoms at Time 2 but not Time 1); Typically Developing (psychosis spectrum symptoms at neither Time 1 nor Time 2).

We evaluated differences among these groups using ANOVA's and Cohen's d (quantitative variables) or chi-square (categorical variables). Logistic regression then examined Time 1 demographic, psychopathology and substance use predictors of persistence vs. resilience (Statistical Package for Social Sciences, SPSS, version 22). Finally, we performed item analysis of positive sub-psychosis items comparing endorsements between groups, summarizing symptom endorsement count, and conducting multivariate analysis of variance (MANOVA) of differences in mean item ratings. Receiver operating characteristic curve analyses identified positive sub-psychosis items most predictive of Persistent vs. Resilient classification.

RESULTS

Recruitment analysis

Within Time 1 group, t-tests of mean Time 1 overall psychosis spectrum factor scores indicated that participants successfully recruited for Time 2 follow-up were comparable to those who were not enrolled ($p=0.14$; see Figure 1). They also did not differ in positive and negative psychosis symptoms ($p=0.14$ and 0.29, respectively), anxious-misery ($p=0.22$), externalizing ($p=0.29$), and fear ($p=0.29$) scores. Note that all p values are corrected for the false discovery rate[51].

Psychosis spectrum classification

Time 2 assessment results are depicted in Figure 2. Among youths screening positive at Time 1 ($N=249$), psychosis spectrum features persisted or worsened in 51.4% (Persistent, $N=128$), including 6.8% ($N=17$) diagnosed with threshold psychosis disorders (four with schizophrenia, one with schizoaffective disorder, one with delusional disorder, three with major depressive disorder with psychotic features, eight with psychotic

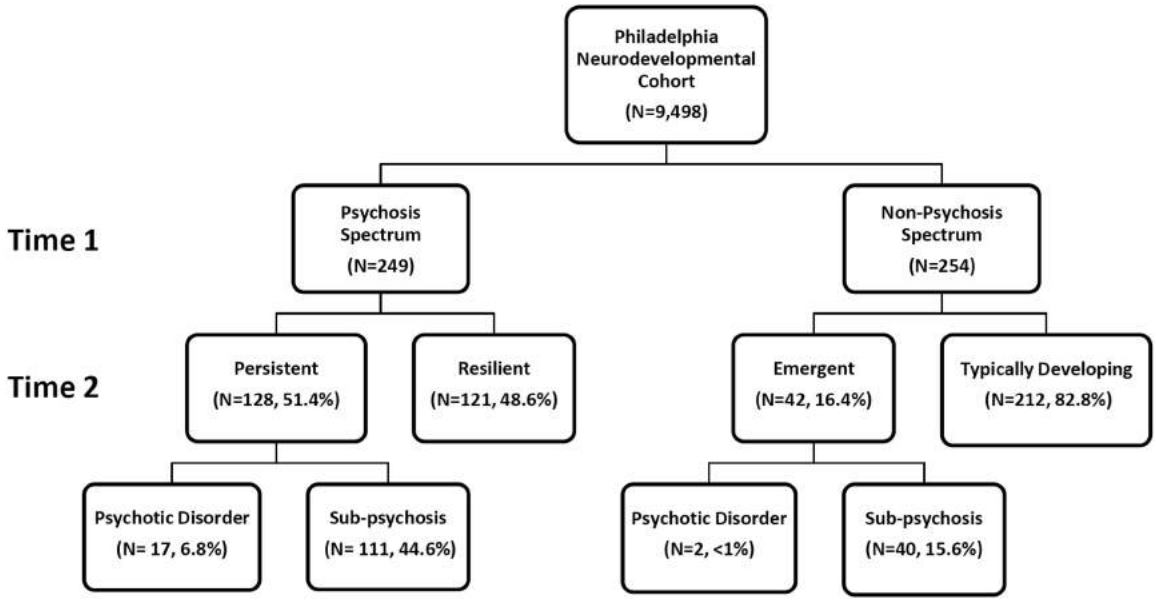

Figure 2 Assessment results at Time 2 in relation to psychosis spectrum classification at Time 1

disorder not otherwise specified). The remainder (N=121, 48.6%) did not have symptoms at Time 2, and were classified as Resilient, reflecting the absence of current clinically significant symptoms despite the history of elevated risk assessed at Time 1.

The majority of youths screening negative at Time 1 (N=254) remained asymptomatic at Time 2 (Typically Developing, N=212). Psychosis spectrum symptoms emerged in 16.4% (Emergent, N=42), including two diagnosed with a psychotic disorder not otherwise specified.

Sensitivity and specificity of Time 1 screening measures were 0.75 and 0.64 respectively, corresponding to a positive predictive value of 0.51, and a negative predictive value of 0.83.

Characteristics of the sample

Demographic and clinical characteristics of the sample are presented in Table 1. The four groups were comparable in age at both Time 1 (range: 14.8 to 15.5 years) and Time 2 (range: 16.6 to 17.5 years). Although the mean follow-up interval was approximately two years for all groups, the interval was, on average, two months longer for the Resilient group. Sex ratio and mean parental education (mother, father) did not differ among the groups. Neighborhood socioeconomic status at Time 1 was higher in Typically Developing youths than in all three groups reporting psychosis spectrum symptoms at either time point.

Participants' Time 2 classification was determined by positive and negative sub-threshold psychosis spectrum endorsements at Time 1. Thus, the Persistent and Resilient groups had higher baseline PS-R and SOPS scores compared to Emergent and Typically Developing. Notably, participants in the Persistent group also showed higher baseline Time 1 symptoms across psychopathology domains compared to the Resilient group. The Persistent group also showed comparatively lower baseline global functioning, and increased treatment seeking, including consulting a professional, inpatient hospitalizations, and prescription psychiatric medications. A minority of individuals in the Persistent group (N=8) were prescribed antipsychotic medicines.

The Resilient group also had higher levels of psychopathology and lower functioning at Time 1 than the Emergent and Typically Developing youths. Similarly, youths of the Emergent group had higher positive and negative/disorganized symptom levels and reduced functioning at Time 1 compared to youths who remained Typically Developing at follow-up. Importantly, reported exposure to traumatic stressors was lower in Typically Developing youths than the other three groups, with the highest mean number of stressors experienced by those with persisting symptoms.

At Time 2, a greater number of youth in the Persistent group had comorbid mood disorders, attention-deficit/hyperactivity disorder (ADHD), and alcohol and other substance abuse than the Resilient and Typically Developing groups. Major depressive disorder was least common in the Typically Developing group, and the groups did not differ in substance dependence rates. Youths who were never symptomatic had higher Mini-Mental State Examination scores than those who previously or currently exhibited psychosis spectrum symptoms. Global functioning was lower in the Persistent than the other three groups, and both the Resilient and Emergent groups showed reduced global functioning compared to Typically Developing.

As shown in Table 1, the Persistent group showed the highest level of SOPS symptoms across symptom domains, though

Table 1 Demographic and clinical characteristics of youth at Time 1 and Time 2

	Persistent, P (N=128)	Resilient, R (N=121)	Emergent, E (N=42)	Typically Developing, T (N=212)	p	Pairwise
Age, years (mean±SD)						
Time 1	15.5 ± 2.5	15.0 ± 2.5	14.7 ± 2.9	14.8 ± 2.8	n.s.	
Time 2	17.5 ± 2.6	17.1 ± 2.8	16.7 ± 2.9	16.6 ± 3.7	n.s.	
Follow-up interval, months (mean±SD)	23.2 ± 7.9	25.8 ± 7.3	23.7 ± 5.3	23.2 ± 6.7	0.009	R>P,T
Male/female	61/67	55/66	22/20	100/112	n.s.	
African-American/Other (%)	76.6	63.6	76.2	42.5	0.001	P>R,T
						R>T
						E>T
Parental education, years (mean±SD)						
Mother	13.2 ± 3.4	12.7 ± 4.9	12.5 ± 4.4	13.7 ± 4.6	n.s.	
Father	10.9 ± 5.6	11.7 ± 5.3	11.1 ± 5.2	12.2 ± 6.1	n.s.	
Neighborhood socioeconomic status factor score (mean±SD)	−0.6 ± 1.0	−0.4 ± 1.0	−0.6 ± 1.0	0.0 ± 1.0	0.001	P,R,E<T
Time 1 psychopathology factor scores (mean±SD)						
Psychosis	1.4 ± 0.9	1.0 ± 0.8	−0.2 ± 1.0	−0.6 ± 0.8	0.001	P>R,E,T
						R>E,T
						E>T
Anxious-Misery	1.1 ± 0.9	0.7 ± 0.9	−0.1 ± 1.0	−0.6 ± 0.9	0.001	P>R,E,T
						R>E,T
						E>T
Fear	0.9 ± 1.0	0.6 ± 1.0	−0.1 ± 1.1	−0.6 ± 0.9	0.001	P>R,E,T
						R>E,T
						E>T
Externalizing	0.8 ± 0.8	0.6 ± 0.8	0.0 ± 1.1	−0.6 ± 0.8	0.001	P,R>E,T
						E>T
Time 1 PRIME-Screen Revised, total (mean±SD)	24.8 ± 14.0	18.4 ± 12.4	6.4 ± 7.4	2.4 ± 4.9	0.001	P>R,E,T
						R>E,T
						E>T
Time 1 PRIME-Screen Revised, z (mean±SD)	1.6 ± 1.4	1.0 ± 1.2	−0.1 ± 0.7	−0.4 ± 0.5	0.001	P>R,E,T
						R>E,T
						E>T
Time 1 Scale of Prodromal Symptoms, z (mean±SD)	1.1 ± 1.5	0.6 ± 1.4	−0.1 ± 0.8	−0.5 ± 0.4	0.001	P>R,E,T
						R>E,T
						E>T
Time 1 Trauma exposure (mean±SD)	1.6 ± 1.5	1.2 ± 1.3	1.0 ± 1.1	0.5 ± 0.8	0.001	P>R,E,T
						R, E>T
Time 1 Global Assessment Scale (mean±SD)	69.3 ± 13.4	76.5 ± 11.4	80.4 ± 10.2	85.7 ± 7.7	0.001	P<R,E,T
						R<E,T
						E<T
Time 1 treatment (%)						
Talked with professional	68.8	54.2	45.2	34.1	0.001	P>R,E,T
						R>T

Table 1 Demographic and clinical characteristics of youth at Time 1 and Time 2 *(continued)*

	Persistent, P (N=128)	Resilient, R (N=121)	Emergent, E (N=42)	Typically Developing, T (N=212)	p	Pairwise
Psychiatric medications	23.4	11.9	4.8	2.4	0.001	P>R,E,T
						R>T
Inpatient hospitalizations	7.8	1.7	2.4	0.9	0.003	P>R,T
Time 2 diagnosis (%)						
Psychotic disorder	13.3	0.0	4.8	0.0	0.001	P>R,T
						E>R,T
Major depressive disorder	18.8	13.2	16.7	3.8	0.001	P,R,E>T
Other mood disorder	15.6	2.5	4.8	3.3	0.001	P>R,T
Attention-deficit/hyperactivity disorder	21.9	9.9	7.1	4.7	0.001	P>R,E,T
Alcohol abuse	7.0	1.7	4.8	1.4	0.023	P>R,T
Alcohol dependence	3.1	1.7	0.0	1.4	n.s.	
Substance abuse	8.6	4.1	4.8	0.9	0.006	P>T
Substance dependence	6.3	5.0	2.4	1.9	n.s.	
Time 2 Scale of Prodromal Symptoms, total (mean±SD)						
Positive	9.6 ± 5.2	2.4 ± 2.5	7.4 ± 4.5	1.6 ± 2.2	0.001	P>R,E,T
						R>T
						E>R,T
Negative	7.6 ± 5.2	3.2 ± 3.4	7.3 ± 4.9	1.7 ± 2.3	0.001	P>R,T
						R>T
						E>R,T
Disorganized	4.6 ± 3.3	1.3 ± 1.7	3.4 ± 2.5	0.7 ± 1.3	0.001	P>R,E,T
						R>T
						E>R,T
General	4.0 ± 3.4	1.2 ± 2.2	4.2 ± 3.0	1.2 ± 1.9	0.001	P>R,T
						R>T
						E>R,T
Time 2 Mini-Mental State Examination (mean±SD)	31.4 ± 3.4	32.1 ± 2.3	31.5 ± 3.2	32.3 ± 2.2	0.001	P,E<T
Time 2 Global Assessment of Functioning (mean±SD)	59.7 ± 10.4	77.1 ± 13.1	64.6 ± 11.4	83.4 ± 10.0	0.001	P<R,E,T
						R<T
						E<R,T
Time 2 treatment history (%)						
Talked with professional	76.8	46.5	48.6	30.8	0.001	P>R,E,T
						R>T
						E>T
Psychiatric medications	22.3	8.0	18.2	4.7	0.001	P>R,T
						E>T
Inpatient hospitalization	11.5	3.4	10.8	1.0	0.001	P>R,T
						E>T
Time 2 family history of psychosis (%)	22.6	7.7	8.3	3.1	0.001	P>R,T

comparable to Emergent in negative and general symptoms. Examination of sub-classifications revealed that, among the Persistent group, the majority (77.5%) exhibited a combination of significant (SOPS ratings ≥ 3) positive, negative and disorganized symptoms at Time 2, with a minority exhibiting only positive (18.0%) or only negative/disorganized (4.5%) symptoms. A comparable pattern was observed in the Emergent group (combination: 55%; only positive: 27.5%; only negative/disorganized: 17.5%). APS criteria were met in 26.4% and 23.7% of the Persistent and Emergent groups, respectively. An additional 5.7% (Persistent) and 13.2% (Emergent) fulfilled ANDS criteria, reflecting increased negative or disorganized symptoms within the past year.

More than two-thirds of the Persistent group had spoken with mental health professionals, compared to close to one-half of the Resilient and Emergent groups, and approximately one-third of Typically Developing. The Persistent group was also more likely to have received psychiatric medications and undergone inpatient psychiatric hospitalization, but not more so than the Emergent group, who received these services at a higher rate than Typically Developing.

Sufficient family history data were available to determine presence or absence of first-degree family history of psychosis for 438 participants (Persistent = 106, Typically Developing = 192, Resilient = 104, Emergent = 36). The Persistent group was more likely than the Resilient and Typically Developing, but not Emergent, groups to have a first-degree family member with psychosis.

SPQ data were first screened for random or careless responding: 37 participants were excluded for endorsing three or more infrequency items, and the number was proportional across the groups (Persistent: 14/114, 12.3%; Resilient: 6/108, 5.6%; Emergent: 5/37, 13.5%; Typically Developing: 12/196, 6.1%; $\chi^2=18.2$, df=12, not significant). Following significant overall MANOVA of nine subscales (F=6.6; df=27,1224; $p<0.001$), tests of between-subjects effects for all nine subscales were significant (all p values <0.001). Mean endorsement is graphed in Figure 3.

Pairwise post-hoc tests of significance (all p values <0.05) revealed that the Persistent group endorsed more items than the Resilient, Emergent and Typically Developing groups on all subscales except social anxiety, on which they differed only from Typically Developing. Importantly, the Resilient group also endorsed more items across all subscales than Typically Developing, but did not differ from the Emergent group. The Emergent group differed from Typically Developing only in endorsing more items on Social Interpersonal subscales.

Predictors of persistence

The prediction success of Persistence vs. Resilience from demographic and clinical predictors was 68.6% (Persistent: 70.3%, Resilient: 67.0%; false positive: 16.6%, false negative: 14.8%). Receiver operator characteristic curve analysis revealed a moderate fit of the model (area under the curve = 0.74; 95%

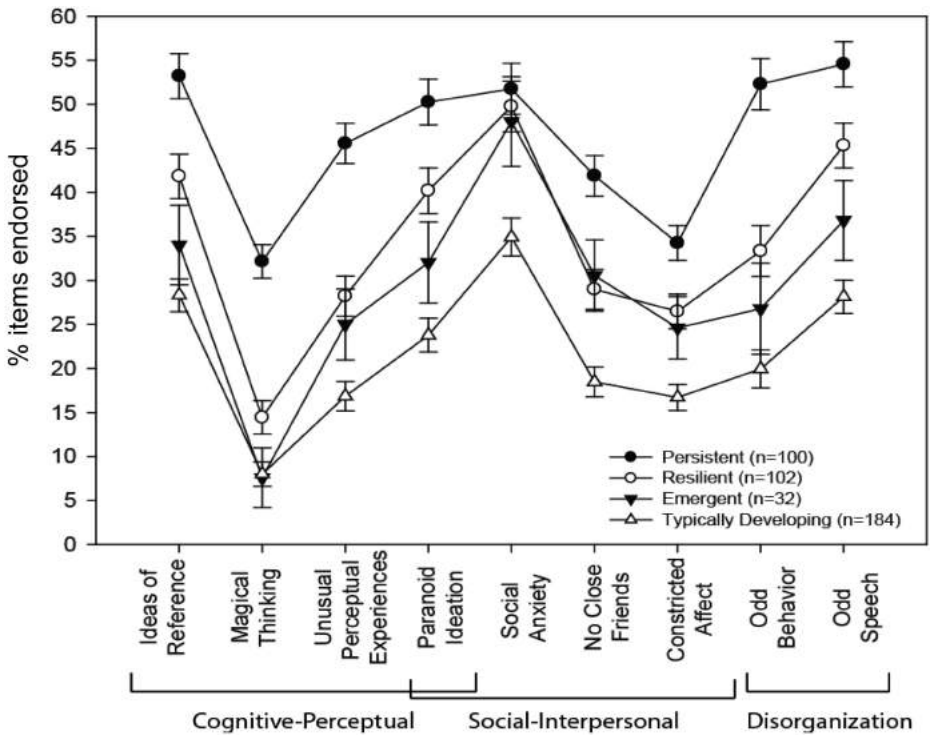

Figure 3 Items endorsed on subscales of the Schizotypal Personality Questionnaire by Time 2 classification

Table 2 Bivariate logistic regression predicting persistence vs. resilience from Time 1 demographic and clinical variables

							95% CI	
	Persistent	**Resilient**	**B**	**Wald chi-square**	**p**	**Odds ratio**	**Lower**	**Upper**
Demographics								
Gender (% female)	52.3	54.5	−0.28	0.73	n.s.	0.78	0.40	1.43
Age at Time 1, years (mean±SD)	15.5 ± 2.5	14.9 ± 2.6	0.07	1.13	n.s.	1.07	0.94	1.22
Ethnicity (% African-American/Other)	76.6	63.6	0.77	2.89	n.s.	2.16	0.89	5.24
Mother education, years (mean±SD)	13.8 ± 2.2	14.1 ± 2.2	0.03	0.11	n.s.	1.03	0.88	1.21
Father education, years (mean±SD)	13.1 ± 2.2	13.4 ± 2.4	−0.02	0.07	n.s.	0.98	0.84	1.15
WRAT-4 Reading (mean±SD)	96.9 ± 16.6	98.5 ± 16.8	−0.01	0.01	n.s.	1.00	0.98	1.02
Neighborhood socioeconomic status	−0.6 ± 0.9	−0.4 ± 1.0	0.06	0.06	n.s.	1.06	0.68	1.63
Psychopathology factor scores (mean±SD)								
Psychosis	1.4 ± 0.9	1.0 ± 0.8	0.59	5.01	0.03	1.80	1.10	3.01
Anxious-Misery	1.1 ± 0.9	0.7 ± 0.9	0.44	2.37	n.s.	1.55	0.89	2.71
Fear	0.9 ± 1.0	0.6 ± 1.0	−0.12	0.25	n.s.	0.89	0.56	1.41
Externalizing	0.8 ± 0.8	0.8 ± 0.8	−0.26	1.28	n.s.	0.78	0.50	1.21
Trauma exposure	1.6 ± 1.5	1.2 ± 1.3	0.04	0.11	n.s.	1.04	0.82	1.32
Morbid thoughts (%)								
Thoughts of death/dying	38.1	29.8	−0.26	0.51	n.s.	0.77	0.38	1.57
Suicidal ideation	24.6	15.7	−0.15	0.13	n.s.	0.85	0.37	1.98
Treatment (%)								
Talked with professional	68.8	54.2	0.17	0.28	n.s.	1.18	0.63	2.21
Psychiatric medications	23.4	11.9	1.02	4.53	0.03	2.78	1.08	7.15
Inpatient hospitalization	7.8	1.7	0.24	0.06	n.s.	1.27	0.18	9.29
Global Assessment Scale (mean±SD)	69.3 ± 13.4	76.5 ± 11.4	−0.04	6.63	0.01	0.96	0.94	0.99

WRAT-4 – Wide Range Achievement Test, version 4

CI: 0.68-0.81). Among Time 1 psychopathology variables, only higher overall psychosis factor score was a significant predictor of persistence. Lower Time 1 global functioning and Time 1 treatment with psychiatric medications also predicted persistence. No demographic or other treatment variables were predictive (Table 2). This pattern of results was not significantly altered when repeating the analysis with the smaller sample (N=192) with available family history data. Family history of psychosis was not robustly predictive of persistence, although there was a trend towards significance (p=0.075, odds ratio = 2.71), and the prediction success of this model was slightly improved (72.4%).

In the subgroup of participants (N=123) who completed the substance use self-report at Time 1, lifetime ever use of substances reported at Time 1 was not predictive of persistence. Success of the model including demographic characteristics and ever use of twelve classes of substances was 59.3% (Persistent: 71.6%, Resilient: 44.6%; false positive: 34.3%, false negative: 13.6%). The fit of the model was reasonable (area under the curve = 0.66; 95% CI: 0.56-0.75). No individual substances were significantly predictive.

Item analysis

Among youths, the positive sub-psychosis items most frequently endorsed ("definitely agree") at Time 1 on the PS-R were odd/unusual thoughts, auditory perceptions, and reality confusion (Table 3). However, mean Time 1 scores on these items did not significantly differ between Persistent and Resilient groups (MANOVA), and receiver operator curve analyses revealed only modest ability for these items to discriminate between the groups (area under the curve values ranging from 0.54 to 0.57).

Though less frequently endorsed ("definitely agree"), items assessing thought control, mind tricks and persecutory/suspicious thinking had higher mean Time 1 endorsement by the Persistent group (Cohen's d range: 0.28-0.51), and modest to moderate discriminability (area under the curve range: 0.57 to 0.63).

The least frequently endorsed item by the Persistent group was mind reading, which nonetheless had a higher mean endorsement by the Persistent than the Resilient group (Cohen's d = 0.31). The remaining PS-R items (superstitions, grandiosity,

Table 3 Item analysis of Time 1 PRIME Screen-Revised in Persistent vs. Resilient youths

	Endorsing "Definitely agree"		Item mean ± SD		Pairwise F following significant MANOVA			ROC		
PRIME Screen-Revised item	Persistent	Resilient	Persistent	Resilient	F	P	Cohen's d	AUC	95% CI lower	95% CI upper
I may have felt that there could possibly be something controlling my thoughts, feelings, or actions (Thought control)	8.9	1.7	2.05 ± 2.16	1.05 ± 1.70	15.80	0.001	0.51	0.63	0.56	0.70
I think that I might feel like my mind is "playing tricks" on me (Mind tricks)	16.9	7.7	2.58 ± 2.34	1.82 ± 2.18	6.77	0.010	0.34	0.59	0.52	0.66
I wonder if people may be planning to hurt me or even may be about to hurt me (Persecutory/suspicious)	8.1	2.6	1.73 ± 2.14	1.17 ± 1.80	4.71	0.031	0.28	0.57	0.50	0.65
I think that I have felt that there are odd or unusual things going on that I can't explain (Odd/unusual thoughts)	18.5	13.7	3.33 ± 2.07	2.81 ± 2.16	3.63	n.s.	0.25	0.57	0.50	0.64
I have thought that it might be possible that other people can read my mind, or that I can read other's minds (Mind reading)	5.6	0.9	1.37 ± 2.05	0.80 ± 1.53	5.90	0.016	0.31	0.56	0.49	0.63
I have had the experience of doing something differently because of my superstitions (Superstitions)	9.7	10.3	2.25 ± 2.20	1.76 ± 2.14	3.06	n.s.	0.23	0.56	0.49	0.63
I have had the experience of hearing faint or clear sounds of people or a person mumbling or talking when there is no one near me (Auditory perceptions)	18.5	16.2	2.48 ± 2.43	1.94 ± 2.45	2.90	n.s.	0.22	0.56	0.49	0.64
I believe that I have special natural or supernatural gifts beyond my talents and natural strengths (Grandiosity)	9.7	9.4	1.93 ± 2.24	1.48 ± 2.14	2.52	n.s.	0.21	0.56	0.48	0.63
I think that I might be able to predict the future (Predict future)	7.3	3.4	1.73 ± 2.16	1.25 ± 1.78	3.62	n.s.	0.24	0.55	0.48	0.62
I think that I may get confused at times whether something I experience or perceive may be real or may be just part of my imagination or dreams (Reality confusion)	18.5	14.5	3.37 ± 2.09	3.03 ± 2.20	1.49	n.s.	0.16	0.54	0.47	0.62
I think that I may hear my own thoughts being said out loud (Audible thoughts)	12.9	9.4	2.15 ± 2.36	1.83 ± 2.18	1.16	n.s.	0.14	0.54	0.46	0.61

ROC – receiver operating characteristic analysis of PRIME Screen-Revised items; AUC – area under the curve, indicating the ability of the item to discriminate between the Persistent and Resilient groups

predict future, and audible thoughts), though showing marginally higher mean scores in the Persistent than Resilient group (Cohen's d range: 0.14 to 0.24), discriminated the groups only modestly (area under the curve range: 0.54 to 0.56).

DISCUSSION

In a 2-year follow-up of US youths from the community, psychosis spectrum symptoms persisted or worsened in approximately 51% of youths endorsing symptoms at baseline. When correcting for demographic characteristics and baseline psychopathology, persistence or worsening of psychosis spectrum symptoms was predicted by several baseline clinical features, including higher severity of subclinical psychosis, lower global functioning, and prior psychiatric medication.

Those with persistent or worsening symptoms demonstrated higher overall psychosis symptom severity at baseline than those whose symptoms did not meet threshold levels at follow-up, lending further support to the reported relationship between severity and persistence of psychotic-like experiences in the population[1,11]. In our study, baseline severity was greater in those with persisting symptoms across summary psychosis spectrum indicators, including overall psychosis, and positive and negative sub-threshold symptom domains. In addition, several items most frequently endorsed as "definitely agree" by youths with psychotic spectrum symptoms at baseline were still the most commonly endorsed at follow-up,

including the subjective experience of odd/unusual thoughts, auditory perceptions, and reality confusion. However, they were not discriminative or predictive of persistence. Rather, the Persistent group was discriminated from the Resilient group by persecutory thinking/suspiciousness, ideation related to thought control, and the experience of mind tricks.

These findings are particularly notable, given reports that suspiciousness/paranoia and unusual thought content are associated with increased risk of psychosis conversion among clinically high risk youth[20,52], and that persecution and bizarre experiences (including thought control) in community youths are more likely to be associated with distress/disability than paranormal beliefs/magical thinking[10]. The current findings not only support the clinical and functional significance of these particular symptoms, but they also reinforce the potential benefits of early screening, particularly for these most discriminating experiences.

Global functioning was lower in the Persistent group at both Time 1 and Time 2, and it was predictive of symptom persistence, a finding that accords with numerous lines of evidence associating poor functioning with psychosis risk symptoms in both community[1,16,53,54] and clinical high risk[55] cohorts. Of course, traditional global ratings, including those used here, are not independent of symptom severity. The use of separate social and role function scales[56] in future follow-ups will allow better differentiation of social/role functioning impairments and symptom severity for predictive purposes.

Increasing impairment over time relates to symptom persistence[1,16]. However, we were unable to evaluate longitudinal functional changes in the current investigation, because we used different scales to assess global functioning at Time 1 and Time 2 (Children's Global Assessment Scale from the K-SADS, and SIPS Global Assessment of Functioning, respectively). Nonetheless, the results provide convergent support that youths with both psychosis spectrum symptoms and lower global functioning are particularly vulnerable to symptom persistence or worsening.

Prior treatment with psychiatric medications predicted persistence, consistent with overall higher level of treatment seeking at both Time 1 and Time 2. Our findings align with others suggesting that aspects of help-seeking behavior are common but not ubiquitous in youths with persisting psychotic-like experiences[13] and in some cases may precede the onset of psychotic disorders[7]. To more fully evaluate this finding, we are currently analyzing specific treatment history data, which will delineate the types of treatment that youths are seeking and receiving. Prior psychiatric medication suggests that a subset of youths with persisting symptoms are coming to the attention of health care providers, but it is unknown whether the psychosis spectrum symptoms are detected and adequately treated and/or monitored, especially since the context is likely to include comorbid psychopathology. For those at most imminent risk of psychosis or who have already entered a first episode, the importance of initiating specialized care aiming to reduce the duration of untreated psychosis is well documented[57].

Several other characteristics distinguished youths whose symptoms persisted, including a first-degree family history of psychosis, consistent with evidence from clinical high risk[20] and college student[18] studies, and more generally with the well-documented genetic risk for psychosis[58]. Although baseline anxious-misery, fear and externalizing domains were not uniquely predictive of persistence, the latter was associated with later mood disorders, ADHD and alcohol abuse. These findings are consistent with a prior community study of youths with psychotic-like experiences that evidenced a higher risk of internalizing and externalizing problems at 2-year follow-up[15]. They also provide further support for the suggestion that persisting psychotic-like experiences may be increasingly predictive of multiple domains of diagnosable psychopathology as young people age[59].

Although ethnic minority status was more common in the Persistent, Resilient and Emergent groups than in the Typically Developing, it was not a significant predictor of symptom persistence when correcting for other demographic and clinical features, including psychosis spectrum severity and global functioning. This finding appears inconsistent with other lines of evidence from non-US cohorts suggesting that ethnic minority status is a significant predictor of symptom persistence[13]. The experiences of ethnic minority groups in the US may differ in salient ways from those in other countries[60], yet some effects of being an ethnic minority could be similar. Ongoing follow-up of the Philadelphia Neurodevelopmental Cohort sample will allow us to further investigate the stability of our current finding, as well as additional risk and protective factors that may differentially impact ethnic groups.

We used the term "resilient" to refer to individuals with a risk factor, here defined by baseline endorsement of psychosis spectrum symptoms, who are not currently experiencing symptoms meeting severity criteria based on clinical interview. However, results suggest that individuals in this group are not asymptomatic, as reflected by comparatively elevated Time 2 scores on both SOPS and SPQ, lower global functioning, and higher levels of help-seeking behavior compared to typically developing youths. This finding supports the suggestion that "false positive" status does not necessarily imply an absence of risk[11]: "resilient" individuals may be in a transient state of low symptom level, still vulnerable to symptom exacerbation. Some of the "resilient" individuals may instead experience relatively stable schizotypal traits that will not evolve into psychosis; the likelihood of this is yet unknown, as very few studies have simultaneously investigated "schizotypal" and "prodromal" symptoms[61,62].

Sensitivity of assessment methods could also play a role. It has long been suggested that diagnostic interviews by trained assessors may reduce false positives by allowing follow-up probing to determine the clinical significance and context of endorsed symptoms[7]. Conversely, with some notable exceptions[7], self-report measures are often more feasible in large-scale studies than time and resource intensive semi-structured clinical interviews. Self-reported psychotic experiences that

are not judged significant upon clinical interview may be the "softest expression" of the psychosis spectrum extended phenotype[11], perhaps identifying those at an earlier point in progression to the disorder. Cross-sectional multi-modal assessment at Time 2 conducted here suggests that some self-report measures may be sensitive to aspects of symptoms that were either not disclosed or observed by the interviewer or, conversely, not severe enough to warrant significant clinical ratings upon interview.

These considerations notwithstanding, our current findings can be viewed as supporting the convergent validity of "prodromal" and "schizotypal" scales as measures of the overarching psychosis vulnerability construct[61]. For many individuals, the distinction between "schizotypy" and "psychotic-like experiences" may be a function of symptom duration, stability and/or intensity. Ultimately, the potential of differing trajectories highlights the value of indexing risk using multiple methods[61] to assess a multi-dimensional continuum[11] from a developmental perspective[62]. The inclusion of both self-report and interview-based assessments in ongoing follow-up studies will allow us to determine the ultimate clinical significance of "false positives".

Psychosis spectrum symptoms "emerged" in a small group of youths previously classified as typically developing. The number (N=42) was too small to allow formal analyses of predictors. The "emergent" category could reflect individuals for whom symptoms developed between Time 1 and Time 2. An alternative interpretation, that symptoms were experienced at Time 1 but at lower levels than were considered threshold at that time point, appears to be supported by close examination of Time 1 data. Compared to typically developing youths, those with subsequently emergent symptoms exhibited slightly elevated baseline PS-R scores, increased family history of psychosis, lower global functioning, and trends towards increased help-seeking behaviors that resolved to significance at Time 2. This result accords with previous findings that approximately 40% of adolescents with emergent symptoms had endorsed subclinical symptoms up to 8 years earlier[1]. It also further underscores the developmental aspect of the psychosis dimension, and the importance of the relationship between clinical and subclinical symptoms[1].

Some additional considerations and limitations should inform interpretation of the findings presented here. First, as for any longitudinal study, there is a potential selection bias among those who returned for follow-up versus those who did not. Although we cannot exclude the possibility that follow-up results would differ between those who were enrolled compared to those who were unreachable or refused, our recruitment analyses indicate that at least baseline psychosis levels did not differ between those who were recruited and those who were not.

Second, an obvious limitation is that our cohort is still young and developing, on average just entering or still passing through the period of risk for psychotic disorders[13]. Establishing predictors of trajectories of psychosis spectrum symptoms requires multiple measurements over a wider age span. A recently completed 4-year follow-up of a subset of Philadelphia Neurodevelopmental Cohort youths will allow fuller understanding of predictors as young people age.

Third, to allow simultaneous consideration of many potential predictors implicated in prior studies, we included broad indicators of comorbid psychopathology, environment, substance use, and exposure to traumatic stressors, an approach that could obscure more nuanced relationships. We are currently evaluating relationships with more specific potential predictors in each of these categories to further inform our predictive models. Nevertheless, though not uniquely predictive, it is noteworthy that, without exception, each one of these variables was associated with psychosis spectrum status at baseline or follow-up.

Finally, the classification categories of persistence/resilience/emergence we employed are rationally derived for the convenience of communication of salient constructs. However, we are aware that they cannot fully capture the complexity of clinical states. We employed cut-offs at both time points based on generally accepted "clinical significance" of items, but certainly alternative cut points, and other methods to derive them, are important to investigate[13]. Any such categories can be significantly impacted by the assessment approach.

There is no single accepted psychosis spectrum screening tool[63], and it is possible, if not likely, that measurement differences contribute to variation among study findings[64]. Here we used a hybrid approach in which we screened a very large sample at Time 1 via self-report and highly structured interview, and conducted a smaller follow-up via semi-structured clinical interview, complemented by a self-report. This design allowed us to conduct comprehensive Time 2 assessments comparable to those employed with clinical high-risk samples. However, classification outcomes could in part reflect varying sensitivity of assessment methods at different time points rather than true severity of psychosis spectrum symptoms.

The sensitivity and specificity of our screening approach for subsequent longitudinal clinical interview status is not directly comparable to most studies, which typically have used a single screening instrument to assess positive sub-threshold symptoms, followed immediately or within a 6-month window by diagnostic interview in clinical groups[6]. Even under such circumstances, no one screening approach has consistently yielded both sensitivity and specificity above 0.70[6]. Our two-year predictive sensitivity (0.75) was consistent with prior studies including an investigation also using the PS-R and 6-month follow-up by SIPS clinical high risk/psychosis in a young clinical sample[65]. Moreover, our negative predictive value, reflecting a relatively low number of "emergent" individuals, suggests that the majority of those who screen negative do not develop psychosis spectrum symptoms within 2 years. Thus, though not without limitations, our findings lend further support to the validity of screening approaches to enrich community samples with at-risk individuals. Imperfect as they may be, both cut-offs and a continuum can be useful in understanding clinical and neurobehavioral predictors[66] that may distinguish patterns of persistence versus resilience.

Our findings of varying courses of psychosis spectrum symptoms in US youth confirm those of earlier studies, and highlight that psychosis risk is a dynamic process in young people[8,13]. Among demographic and clinical characteristics assessed here, symptom persistence at 2-year follow-up was predicted by higher severity of subclinical psychosis, lower global functioning and prior psychiatric medication at baseline. In addition, psychosis spectrum features emerged in a small group of young people who previously had not reported significant symptoms but who nonetheless, on average, had exhibited early non-specific clinical warning signs. The results underscore the existence of a wide developmental window of opportunity to investigate risk and protective factors – neurobehavioral, genetic and environmental – associated with varying clinical outcomes. Although our prediction accuracy was better than chance using only demographic and clinical characteristics, it may be improved by select biobehavioral measures.

Given the young age of participants, continued follow-up will assist in evaluating the validity of the screening approach for predicting conversion to psychosis, as will incorporation of other potential predictors assessed in this cohort, including neurocognition, brain structure and function, and genomics, that may serve as early differentiators of symptom persistence and worsening. Moreover, investigations of points along the psychosis continuum are not only important as they relate to risk for clinical disorder, but also as an area of study that can inform our understanding of the neurobiology of psychosis[67].

The Philadelphia Neurodevelopmental Cohort public domain resource can accelerate collaborative research and advance our understanding of the complex inter-relationships among genes, cognition, brain and behavior involved in the development of common mental disorders.

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Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis

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Antipsychotic polypharmacy in schizophrenia is much debated, since it is common and costly with unclear evidence for its efficacy and safety. We conducted a systematic literature search and a random effects meta-analysis of randomized trials comparing augmentation with a second antipsychotic vs. continued antipsychotic monotherapy in schizophrenia. Co-primary outcomes were total symptom reduction and study-defined response. Antipsychotic augmentation was superior to monotherapy regarding total symptom reduction (16 studies, N=694, standardized mean difference, SMD=–0.53, 95% CI: −0.87 to −0.19, p=0.002). However, superiority was only apparent in open-label and low-quality trials (both p<0.001), but not in double-blind and high-quality ones (p=0.120 and 0.226, respectively). Study-defined response was similar between antipsychotic augmentation and monotherapy (14 studies, N=938, risk ratio = 1.19, 95% CI: 0.99 to 1.42, p=0.061), being clearly non-significant in double-blind and high-quality studies (both p=0.990). Findings were replicated in clozapine and non-clozapine augmentation studies. No differences emerged regarding all-cause/specific-cause discontinuation, global clinical impression, as well as positive, general and depressive symptoms. Negative symptoms improved more with augmentation treatment (18 studies, N=931, SMD=–0.38, 95% CI: −0.63 to −0.13, p<0.003), but only in studies augmenting with aripiprazole (8 studies, N=532, SMD=–0.41, 95% CI: −0.79 to −0.03, p=0.036). Few adverse effect differences emerged: D2 antagonist augmentation was associated with less insomnia (p=0.028), but more prolactin elevation (p=0.015), while aripiprazole augmentation was associated with reduced prolactin levels (p<0.001) and body weight (p=0.030). These data suggest that the common practice of antipsychotic augmentation in schizophrenia lacks double-blind/high-quality evidence for efficacy, except for negative symptom reduction with aripiprazole augmentation.

Key words: Antipsychotics, polypharmacy, augmentation, monotherapy, schizophrenia, clozapine, aripiprazole

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Management options for patients with schizophrenia remain suboptimal, as indicated by insufficient symptom control in a sizable subgroup of patients and low response rates, frequently leading to functional impairment[1-5]. Recommendations after inadequate antipsychotic response include waiting for a delayed response, dose adjustment, switching to another antipsychotic, and – in case of treatment resistance to at least two adequate antipsychotic trials – clozapine treatment[6-11].

Another adopted strategy is antipsychotic polypharmacy[12]. Limited data on clinicians' reasoning suggest various motivations for this strategy, including attempts to increase/speed up efficacy, treat residual positive symptoms, or reduce adverse effects allowing dose reduction of the first antipsychotic[13]. Antipsychotic polypharmacy has been reported as a common clinical practice[12,14,15], sometimes implemented by clinicians before or instead of trying clozapine[13,16]. Although the frequency of antipsychotic polypharmacy varies according to patient, illness, setting and provider variables[17], rates in schizophrenia commonly range between 10 and 30%[12,14,17-19].

Despite common use, the evidence for the efficacy and tolerability of antipsychotic polypharmacy is weak[20-22]. In fact, guidelines reserve augmentation with a second antipsychotic as a last-stage treatment option after clozapine failure, intolerability or rejection[6-10]. Additionally, concerns about antipsychotic polypharmacy include the potential for drug-drug interactions, decreased adherence due to complex drug regimes, higher cost[23-25], and increased adverse effects[10,22,26-29].

Meta-analyses aggregate the information of conceptually similar studies and consolidate their quantitative outcomes using statistics. The derived pooled estimates of treatment efficacy and safety are more robust compared to primary study results. Moreover, meta-analyses enable researchers to contrast results from multiple studies and to identify patterns of common effects across studies, or reasons for outcome variability. However, to facilitate informative results and meaningful subgroup and meta-regression analyses, the study methodology should be as homogeneous as possible; study quality should be taken into account; and the total population studied should be sufficiently large (≥1000 subjects)[30].

Although four meta-analyses examined the efficacy of antipsychotic polypharmacy, either irrespective of the antipsychotics used[20] or restricted to clozapine-treated patients[21,31,32], their results remained somewhat inconclusive, possibly influenced by: a) mixing together antipsychotic augmentation (adding a second antipsychotic after non-response to the first) and co-initiation (combination of two antipsychotics from the

beginning) strategies[20]; b) lack of separating lower from higher quality studies[20], and c) the relatively low number of available studies and patients treated in an augmentation paradigm[20,21,31,32].

In one of those meta-analyses, polypharmacy was associated with significantly greater response than monotherapy, with a number-needed-to-treat of 7[20]. However, the improved response was moderated by studies lasting at least ten weeks, conducted in China, examining co-initiation and involving clozapine. Further, that meta-analysis only included six studies of antipsychotic augmentation (N=197), and did not assess symptom reduction due to lacking data.

The three remaining meta-analyses focused on combination treatments with clozapine, either mixing co-initiation and augmentation studies together[21], or focusing on augmentation studies but analyzing only individual drug combinations[32], or focusing only on symptom reduction and not response rates[31]. One meta-analysis found clozapine co-treatment to be superior to clozapine monotherapy, but this finding was only apparent in open-label studies[21]. In one other meta-analysis, augmentation of clozapine with a second antipsychotic was associated with a small benefit (effect size = 0.239, p=0.028), but only 14 trials and 714 patients provided data, and higher versus lower quality studies were not analyzed separately[31].

Due to the limitations of those prior meta-analyses, the frequent use of antipsychotic polypharmacy in ordinary practice, and the recent publication of many additional studies, we conducted a new systematic review and meta-analysis comparing the efficacy and adverse effects of antipsychotic augmentation vs. monotherapy. Based on the prior literature[20,21,31-34], we hypothesized that antipsychotic augmentation would not be superior to monotherapy regarding efficacy (measured as total and specific symptom reduction as well as response/remission/relapse) when focusing on augmentation trials and those with higher quality, but that antipsychotic augmentation might confer a higher risk of adverse effects (except for reduction of specific adverse effects when adding a partial D2 agonist to D2 antagonists).

METHODS

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard[35,36]. At least two independent authors searched PubMed/MEDLINE, PsycINFO, Chinese Journal Net, Wangfan, and China Biology Medicine databases from inception until May 25, 2015, without language restrictions, supplemented by a manual review of reference lists from eligible publications and relevant reviews. Authors were contacted for additional information if needed.

We included randomized controlled trials with samples consisting of at least 20 adults with a diagnosis of schizophrenia or schizoaffective disorder; in which patients were assigned to augmentation of the current antipsychotic with a different antipsychotic versus augmentation with placebo (in blinded studies) or continuation of existing antipsychotic monotherapy; and in which meta-analyzable data were reported, including symptomatic/functional or adverse effect outcomes. We excluded studies comparing antipsychotic monotherapy versus two antipsychotics started concurrently, as well as those comparing antipsychotic augmentation with antipsychotic switch instead of continuation of the original antipsychotic monotherapy.

Co-primary outcomes were total symptom reduction, as assessed by the Positive and Negative Syndrome Scale (PANSS)[37] or the Brief Psychiatric Rating Scale (BPRS)[38], and study-defined treatment response. Secondary outcomes were all-cause and specific-cause discontinuation (inefficacy, intolerability); reduction of positive symptoms (as assessed by the PANSS positive, the BPRS positive, or the Scale for the Assessment of Positive Symptoms, SAPS[39]), of negative symptoms (as assessed by the PANSS negative, the BPRS negative, or the Scale for the Assessment of Negative Symptoms, SANS[40]), and of general symptoms (as assessed by the PANSS general); reduction of global illness severity (as assessed by the Clinical Global Impression Scale - Improvement, CGI-I[41]); reduction of depressive symptoms (as assessed by the PANSS/BPRS anxiety/depression, the Hamilton Scale for Depression, HAM-D[42], or the Calgary Depression Scale for Schizophrenia, CDSS[43]); improvement of functioning (as evaluated by the Global Assessment of Functioning Scale, GAF[44]); and frequency and severity of adverse effects.

Data of each study were independently identified, checked and extracted by at least two authors, including information relevant for the Cochrane risk-of-bias tool[45]. Inconsistencies were resolved by consensus/involvement of a third reviewer.

We conducted a random effects[46] meta-analysis of outcomes using Comprehensive Meta-Analysis V3 (www.meta-analysis.com). Study heterogeneity was explored using I^2 statistics and chi-square test of homogeneity, with $I^2>50\%$ and $p<0.05$ indicating significant heterogeneity. All analyses were two-tailed with alpha=0.05, without adjustments for multiple comparisons.

For "total" and "specific" psychopathology (except depression and negative symptoms) and for inefficacy-related discontinuation, all studies except those focusing on the amelioration of adverse effects were analyzed. The reason for using this restricted data set was that studies focusing on the amelioration of adverse effects could have included treatment responders, leaving little or no room for improvement. In contrast, for depression and negative symptoms and for individual adverse effects, all-cause discontinuation and intolerability-related discontinuation, all available data were analyzed, including studies focusing on the reduction of adverse effects.

Group differences in continuous outcomes were analyzed as the pooled standardized mean difference (SMD) in either change from baseline to endpoint (preferred) or endpoint scores (only preferred if change score results were skewed, i.e., SD > twice the mean). Additionally, weighted mean difference (WMD) was calculated for weight change in kilograms. Dichotomous data were analyzed calculating the pooled risk ratio (RR). Intention-to-treat (ITT) data were always preferred, but observed cases (OC) data were also allowed.

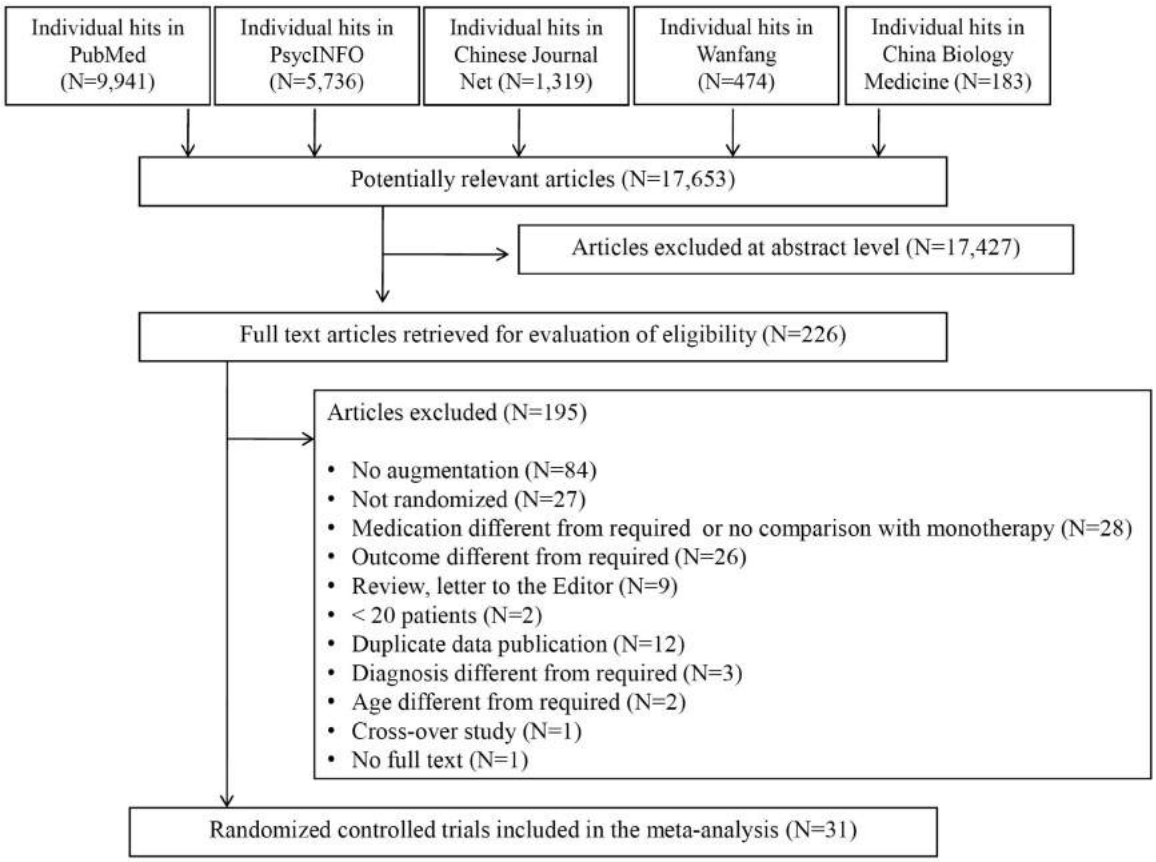

Figure 1 PRISMA diagram of the literature search

All outcomes were analyzed for the pooled sample and for high-quality studies separately. The latter were defined *a priori* as double-blind studies using ITT/last-observation-carried-forward (LOCF) analyses, as opposed to open-label studies and those using OC data. In two studies with more than one active augmentation arm[47,48], the number of patients in the monotherapy group was divided by the number of active study arms to avoid double-counting of control subjects.

For meta-regression analyses, the baseline BPRS total scores were converted to PANSS total scores using equipercentile linking[49]. Exploratory subgroup and meta-regression analyses were added *post-hoc* for negative symptom change (the only overall significant outcome in both low- and high-quality studies) in studies using partial D2 agonists.

We inspected funnel plots, used Egger's regression test[50] and the Duval and Tweedie's trim and fill method[51] to quantify whether publication bias could have influenced the results.

RESULTS

The initial search resulted in 17,653 hits. Altogether, 17,427 studies were excluded at the title/abstract level. Of the remaining 226 references, 195 were excluded after full text review, yielding 31 studies that were included in the meta-analysis (Figure 1).

Efficacy of antipsychotic monotherapy vs. augmentation (efficacy data set)

Details on the 22 meta-analyzed studies with efficacy as the primary outcome (N=1,342) are provided in Table 1. They included 13 double-blind and ITT/LOCF "high-quality" studies and 9 open-label and/or OC "low quality" ones.

Antipsychotic augmentation was superior to monotherapy regarding total symptom reduction (16 studies, N=694, SMD =–0.53, 95% CI: −0.87 to −0.19, p=0.002), but only in open-label (n=6, N=285, SMD=–0.81, 95% CI: −1.18 to −0.43, p<0.001) and low-quality (n=7, N=316, SMD=–0.83, 95% CI: −1.16 to −0.50, p<0.001) studies, not in double-blind (n=10, N=409, SMD=–0.37, 95% CI: −0.83 to 0.10, p=0.120) and high-quality (n=9, N=378, SMD=–0.30, 95% CI: −0.78 to 0.19, p=0.226) ones (Figures 2 and 3). The funnel plots and Egger's test did not indicate publication bias (p=0.320).

In subgroup analyses, antipsychotic augmentation was superior in certain settings (only inpatients: n=6, N=316, SMD=–0.82, 95% CI: −1.22 to −0.43, p<0.001; only outpatients: n=5, N=247, SMD=–0.76, 95% CI: −1.49 to −0.03, p=0.042) and regions

Table 1 Study, patient and treatment characteristics

Study	Agents	No. patients	Risk of bias*	Blinding	Primary outcome	Analysis	Trial duration (weeks)	Setting	Monotherapy dose, mg/d: mean (range)	Augmentation group dose, mg/d: mean (range)	
Clozapine + first-generation antipsychotic											
Liu et al[52] (China)	CLZ + FLU	T: 60 M: 30 A: 30	1	OL	Efficacy	ITT	24	Inpatients	CLZ: NR (375-500)	CLZ: NR (375-500)	FLU: NR (25-50)
Friedman et al[53] (US)	CLZ + PIM	T: 53 M: 28 A: 25	3	DB	Efficacy	ITT	12	Inpatients (64.2%) and outpatients (35.8%)	CLZ: 478.1 (NR)	CLZ: 518.8 (NR)	PIM: 6.48 (2.0-8.9)
Gunduz-Bruce et al[54] (US)	CLZ + PIM	T: 28 M: 14 A: 14	4	DB	Efficacy	ITT	12	Outpatients	CLZ: NR (NR)	CLZ: NR (NR)	PIM: 4 (fixed)
Clozapine + second-generation antipsychotic											
Chang et al[55] (Korea)	CLZ + ARI	T: 61 M: 32 A: 29	5	DB	Efficacy	ITT	8	Inpatients and outpatients (% NR)	CLZ: 290.6 (NR)	CLZ: 304.3 (NR)	ARI: 15.5 (5-30)
Fan et al[56] (US)	CLZ + ARI	T: 38 M: 18 A: 20	2	DB	Adverse effects	OC	8	Outpatients	CLZ: 400 (NR)	CLZ: 397 (NR)	ARI: 15 (fixed)
Fleischhacker et al[57] (Europe, South Africa)	CLZ + ARI	T: 207 M: 99 A: 108	4	DB	Adverse effects	ITT	16	Outpatients	CLZ: 363 (163-900)	CLZ: 384 (200-900)	ARI: 11.1 (5-15)
Guan[58] (China)	CLZ + ARI	T: 60 M: 30 A: 30	1	OL	Efficacy	ITT	16	Inpatients	CLZ: NR (300-500)	CLZ: NR (200-300)	ARI: NR (20-30)
Muscatello et al[59] (Italy)	CLZ + ARI	T: 40 M: 20 A: 20	5	DB	Efficacy	OC	24	Outpatients	CLZ: 341.2 (200-450)	CLZ: 310.7 (200-450)	ARI: 12.5 (10-15)
Sun et al[60] (China)	CLZ + ARI	T: 62 M: 30 A: 32	1	OL	Efficacy	ITT	6	Inpatients	CLZ: 368.2 (200-450)	CLZ: 168 (75-300)	ARI: 21.6 (10-30)
Lin et al[61] (China)	CLZ + PAL	T: 70 M: 35 A: 35	3	DB	Efficacy	ITT	12	Inpatients	CLZ: 217.9 (NR)	CLZ: 231.7 (NR)	PAL: 8.2 (6-12)
Freudenreich et al[62] (US)	CLZ + RIS	T: 24 M: 11 A: 13	2	DB	Efficacy	ITT	6	Outpatients	CLZ: 456 (200-700)	CLZ: 456 (200-700)	RIS: 4 (NR)
Anil Yagcioglu et al[63] (Turkey)	CLZ + RIS	T: 30 M: 14 A: 16	6	DB	Efficacy	ITT	6	Inpatients (20.0%) and outpatients (80.0%)	CLZ: 414.3 (300-900)	CLZ: 515.6 (300-900)	RIS: 5.1 (NR)

Table 1 Study, patient and treatment characteristics *(continued)*

Study	Agents	No. patients	Risk of bias*	Blinding	Primary outcome	Analysis	Trial duration (weeks)	Setting	Monotherapy dose, mg/d: mean (range)	Augmentation group dose, mg/d: mean (range)	
Honer et al[64] (International)	CLZ + RIS	T: 68 M: 34 A: 34	6	DB	Efficacy	ITT	8	Inpatients (38.2%) and outpatients (61.8%)	CLZ: 487 (NR)	CLZ: 494 (NR)	RIS: 3 (NR)
Josiassen et al[65] (US)	CLZ + RIS	T: 40 M: 20 A: 20	3	DB	Efficacy	ITT	12	Inpatients (26.1%) and outpatients (73.9%)	CLZ: 403 (NR)	CLZ: 529 (NR)	RIS: 4.4 (NR)
Hu[66] (China)	CLZ + RIS	T: 60 M: 30 A: 30	1	OL	Efficacy	ITT	12	Inpatients	CLZ: 253.6 (NR)	CLZ: 126.3 (NR)	RIS: 2.9 (2-6)
Weiner et al[67] (US)	CLZ + RIS	T: 69 M: 36 A: 33	2	DB	Efficacy	ITT	16	Inpatients (26.1%) and outpatients (73.9%)	CLZ: NR (NR)	CLZ: NR (NR)	RIS: 4 (fixed)
Nielsen et al[68] (Denmark)	CLZ + SER	T: 50 M: 25 A: 25	6	DB	Efficacy	ITT	12	Outpatients	CLZ: 435 (NR)	CLZ: 394 (NR)	SER: 16 (fixed)
Shiloh et al[69] (Israel)	CLZ + SUL	T: 28 M: 12 A: 16	5	DB	Efficacy	ITT	10	Inpatients	CLZ: 446 (NR)	CLZ: 403 (NR)	SUL: NR (100-600)
Jiang et al[70] (China)	CLZ + ZIP	T: 24 M: 12 A: 12	2	OL	Efficacy	ITT	12	NR	CLZ: 597.2 (75-600)	CLZ: 489.7 (75-600)	ZIP: NR (20-160)
Muscatello et al[71] (Italy)	CLZ + ZIP	T: 40 M: 20 A: 20	6	DB	Efficacy	ITT	16	Outpatients	CLZ: 462.5 (350-600)	CLZ: 428.7 (350-600)	ZIP: 80.0 (fixed)
First-generation + second-generation antipsychotic											
Shim et al[72] (US, Korea)	HAL + ARI	T: 54 M: 28 A: 26	2	DB	Adverse effects	ITT	8	NR	HAL: 24.8 (NR)	HAL: 20.7 (NR)	ARI: 22.5 (15-30)
Second-generation + second-generation antipsychotic											
Chen et al[47] (China)	RIS + ARI	T: 119 M: 30 A: 89	3	DB	Adverse effects	ITT	8	Inpatients and outpatients (% NR)	RIS: 4.93 (NR)	RIS: 4.63 (NR) RIS: 4.79 (NR)	ARI: 5 (fixed) ARI: 10 (fixed)

Table 1 Study, patient and treatment characteristics *(continued)*

Study	Agents	No. patients	Risk of bias*	Blinding	Primary outcome	Analysis	Trial duration (weeks)	Setting	Monotherapy dose, mg/d: mean (range)	Augmentation group dose, mg/d: mean (range)	
										RIS: 5.07 (NR)	ARI: 20 (fixed)
Kane et al[73] (US)	QTP/RIS + ARI	T: 323 M: 155 A: 158	1	DB	Efficacy	ITT	16	Outpatients	QTP/RIS: 516/4.8 (400-800/4-8)	QTP/RIS: 513/4.6 (400-800/4-8)	ARI: 10.3 (2-15)
Lee et al[74] (Korea)	RIS + ARI	T: 35 M: 18 A: 17	2	DB	Adverse effects	ITT	12	Inpatients	RIS: 3 (NR)	RIS: 3 (NR)	ARI: 10 (fixed)
Liu et al[48] (China)	RIS + ARI	T: 86 M: 27 A: 59	1	DB	Adverse effects	ITT	4	Inpatients	RIS: NR (>4)	RIS: NR (>4)	ARI: 5 (fixed) ARI: 10 (fixed)
Ou et al[75] (China)	OLZ + ARI	T: 70 M: 35 A: 35	1	OL	Efficacy	OC	8	Inpatients	OLZ: 18.2 (NR)	OLZ: 17.8 (NR)	ARI: 10 (fixed)
Yasui-Furukori et al[76] (Japan)	RIS/OLZ + ARI	T: 36 M: 18 A: 18	1	DB	Adverse effects	OC	12	Outpatients	RIS/OLZ: 5.0/12.5 (3-8/5-20)	RIS/OLZ: 5.9/12.1 (2-12/2.5-20	ARI: 15.2 (6-30)
Zhao[77] (China)	RIS + ARI	T: 56 M: 28 A: 28	1	OL	Adverse effects	NR	12	Inpatients and outpatients (% NR)	RIS: NR (3-8)	RIS: NR (3-8)	ARI: 10 (fixed)
Zhou et al[78] (China)	RIS + ARI	T: 100 M: 50 A: 50	0	OL	Adverse effects	NR	24	Inpatients	RIS: NR (4-6)	RIS: NR (4-6)	ARI: 5 (fixed)
Liang & Liu[79] (China)	ARI + CLZ	T: 65 M: 33 A: 32	1	OL	Efficacy	ITT	8	NR	ARI: NR (20-30)	ARI: NR (20-30)	CLZ: NR (25-100)
Kotler et al[80] (Israel)	OLZ + SUL	T: 17 M: 8 A: 9	2	OL	Efficacy	ITT	8	Inpatients	OLZ: 22.5 (20-30)	OLZ: 22.2 (20-30)	SUL: 600 (fixed)

*number of low risk judgements, T – total, M – monotherapy, A – augmentation, OL – open label, DB – double blind, ITT – intent to treat, OC – observed cases, CLZ – clozapine, FLU – fluphenazine, PIM – pimozide, ARI – aripiprazole, PAL – paliperidone, RIS – risperidone, SER – sertindole, SUL – sulpiride, ZIP – ziprasidone, HAL – haloperidol, QTP – quetiapine, OLZ – olanzapine, NR – not reported

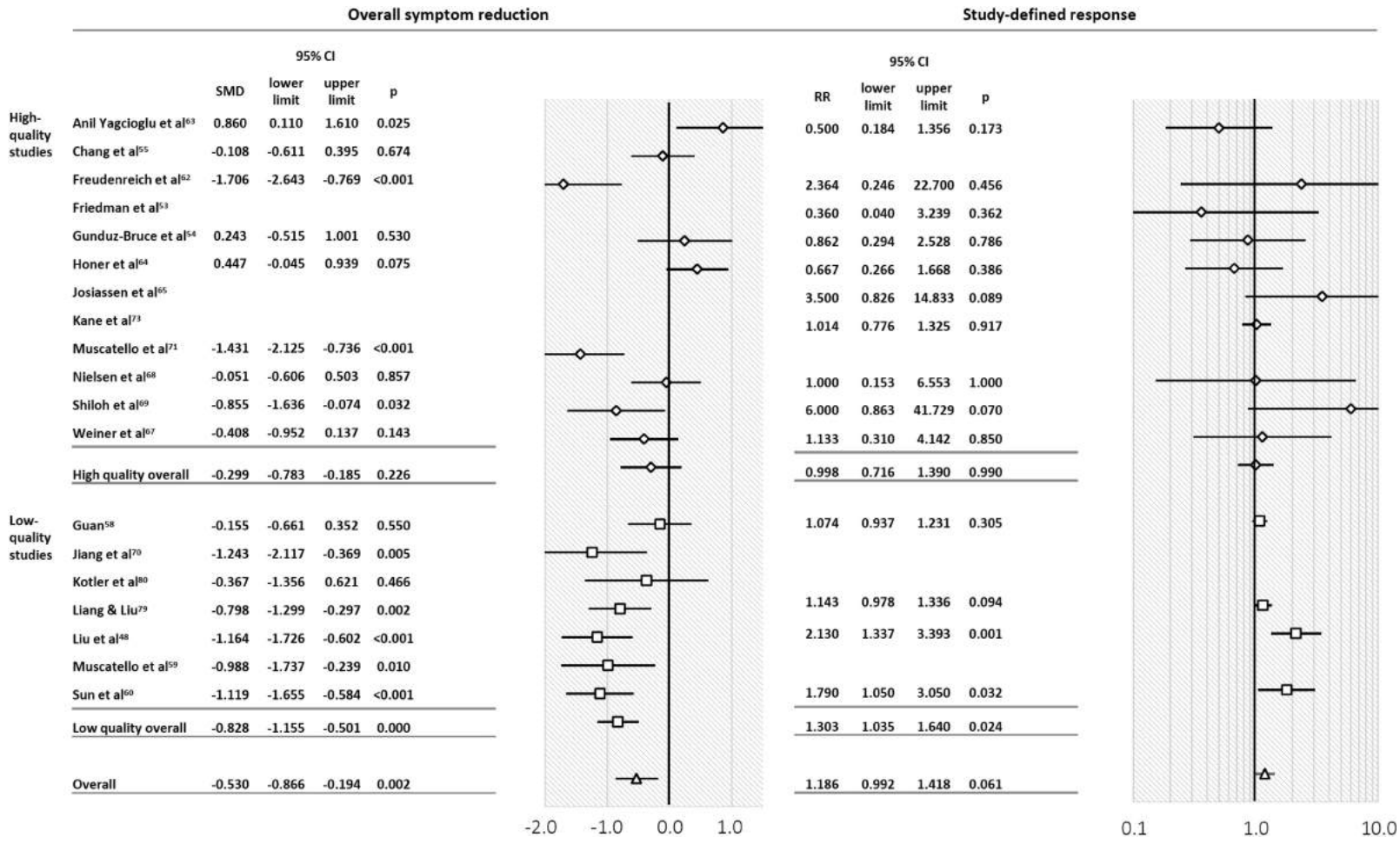

Figure 2 Forest plots of overall symptom reduction and study-defined response. SMD – standardized mean difference, RR – risk ratio

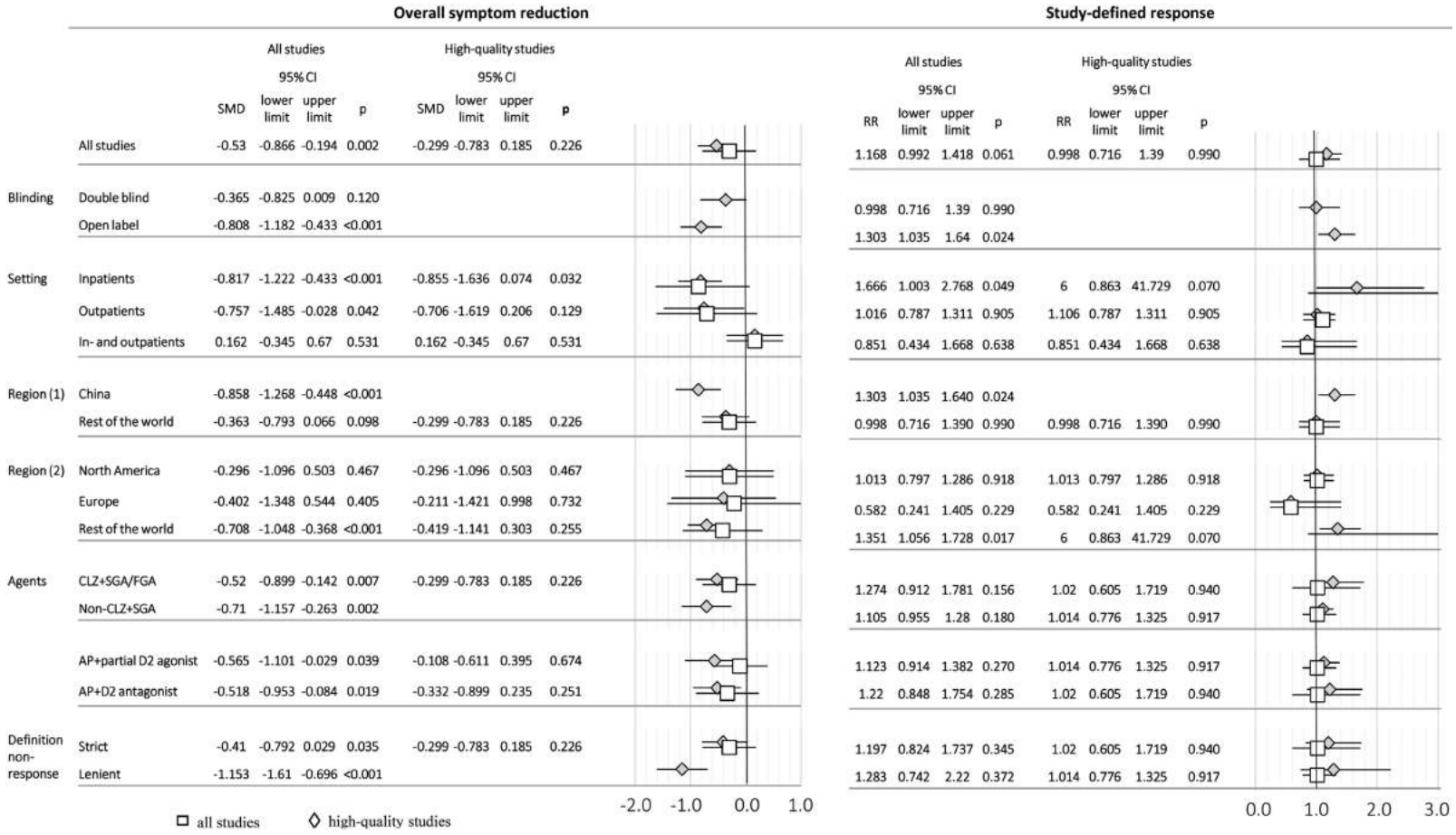

Figure 3 Primary outcomes, subgroup analyses and meta-regression in studies with efficacy as primary outcome. SMD – standardized mean difference, RR – risk ratio, CLZ – clozapine, SGA – second generation antipsychotic, FGA – first generation antipsychotic, AP – antipsychotic

(China: n=5, N=269, SMD=−0.86, 95% CI: −1.27 to −0.45, p<0.001; non-North American/European countries: n=8, N=374, SMD=–0.71, 95% CI: −1.05 to −0.37, p<0.001). However, superiority in these subgroups was not apparent in high-quality studies (Figure 3).

Findings regarding symptom reduction were replicated in augmentation studies of clozapine with a second generation antipsychotic (SGA) or a first generation antipsychotic (FGA) (n=14, N=612, SMD=–0.52, 95% CI: −0.90 to −0.14, p=0.007), clozapine with a SGA (n=12, N=528, SMD=–0.52, 95% CI: −0.93 to −0.11, p=0.012), and non-clozapine SGA with a SGA (n=2, N=82, SMD=–0.71, 95% CI: −1.16 to −0.26, p=0.002); studies augmenting with a partial D2 agonist (n=4, N=214, SMD=–0.57, 95% CI: −1.10 to −0.03, p=0.039), and those augmenting with D2 antagonists (n=12, N=480, SMD=–0.52, 95% CI: −0.95 to −0.08, p=0.019). Results persisted independent of the non-response definition (strict, ≥2 adequate trial failures vs. lenient, ≥1 adequate trial failure): respectively, n=13, N=542, SMD=–0.41, 95% CI: −0.79 to 0.03, p=0.035; and n=2, N=86, SMD=–1.15, 95% CI: −1.61 to −0.70, p<0.001). However, again, differences were non-significant when analyzing only high-quality studies (Figure 3).

In meta-regression analyses, a higher augmentation-to-monotherapy ratio of chlorpromazine equivalent dose (p=0.019) and higher baseline PANSS/converted BPRS scores (p=0.011) were associated with less symptom improvement, while studies with high risk of bias near-significantly moderated greater improvement with antipsychotic augmentation (p=0.050). The influence of the PANSS/converted BPRS scores was replicated in high-quality studies (p=0.033), whereas the other factors were non-significant.

Response, as defined by ≥20% PANSS/BPRS reduction (n=10), ≥25% PANSS reduction (n=3), and ≥20% PANSS reduction or CGI-I of 1 or 2 (n=1), did not differ between antipsychotic augmentation and monotherapy (n=14, N=938, RR=1.19, 95% CI: 0.99 to 1.42, p=0.061). In subgroup analyses, antipsychotic augmentation was superior in open-label/low-quality studies (n=4, N=245, RR=1.30, 95% CI: 1.04 to 1.64, p=0.024), but not in double-blind/high-quality ones (n=10, N=693, RR=1.00, 95% CI: 0.72 to 1.39, p=0.990) (Figure 2). The funnel plots and Egger's test did not indicate publication bias (p=0.508).

Antipsychotic augmentation was again superior in inpatient only studies (n=4, N=207, RR=1.67, 95% CI: 1.00 to 2.77, p=0.049), Chinese studies (n=4, N=245, RR=1.30, 95% CI: 1.04 to 1.64, p=0.024) and non-North American/European studies (n=5, N=273, RR=1.35, 95% CI: 1.06 to 1.73, p=0.017) (Figure 3). In these subgroups, the number of high-quality studies was ≤1, not allowing for separate analyses. There was no advantage of any specific antipsychotic combination, or depending on non-response definition. No significant moderator of treatment response emerged. No between-group differences were observed regarding inefficacy-related discontinuation (n=6, N=596, RR=1.08, 95% CI: 0.44 to 2.67, p=0.870), global clinical impression (n=8, N=403, SMD=–0.01, 95% CI: −0.32 to 0.30, p=0.947), positive symptoms (n=14, N=604, SMD=–0.25, 95% CI: −0.66 to 0.16, p=0.230), general symptoms (n=4, N=144, SMD=–0.73, 95% CI: −1.91 to 0.46, p=0.229), and functioning (n=2, N=80, SMD=–0.36, 95% CI: −1.19 to 0.47, p=0.389).

Efficacy and tolerability of antipsychotic monotherapy vs. augmentation (complete data set)

The complete data set (efficacy-focused plus adverse effect-focused studies) included 31 trials (N=2,073) (see Table 1). The mean PANSS/converted BPRS score was higher in efficacy-focused studies (total sample = 79.7 ± 10.8, clozapine studies = 79.3 ± 9.6, non-clozapine studies = 81.7 ± 15.9) than in adverse-effect focused ones (total sample = 67.4 ± 9.2, clozapine studies = 71.5, non-clozapine studies = 66.6 ± 9.9).

All-cause discontinuation (n=22, N=1,482, RR=1.13, 95% CI: 0.90 to 1.42, p=0.284), and intolerability-related discontinuation (n=11, N=949, RR=0.87, 95% CI: 0.50 to 1.50, p=0.611) did not differ between antipsychotic augmentation and monotherapy.

Negative symptoms improved with antipsychotic augmentation (n=18, N=931, SMD=–0.38, 95% CI: −0.63 to −0.13, p=0.003), but in subgroup analyses this effect was only significant in studies augmenting D2 antagonists with a partial D2 agonist (n=8, N=532, SMD=–0.41, 95% CI: −0.79 to −0.03, p=0.036), not when combining two D2 antagonists (n=10, N=399, SMD=–0.36, 95% CI: −0.72 to 0.01, p=0.055). These findings were replicated in high-quality studies (4 trials augmenting D2 antagonists with a partial D2 agonist, N=355, SMD=–0.28, 95% CI: −0.55 to −0.009, p=0.043). In exploratory subgroup and meta-regression analyses, no relevant moderator of negative symptom improvement with a partial D2 agonist emerged.

Antipsychotic augmentation and monotherapy did not differ regarding depressive symptoms (n=10, N=351, SMD=−0.69, 95% CI: −1.42 to 0.05, p=0.066).

Few differences in adverse effects emerged. D2 antagonist augmentation was associated with less insomnia (n=3, N=169, RR=0.26, 95% CI: 0.08 to 0.86, p=0.028), but more prolactin elevation (n=2, each representing augmentation with risperidone, N=74, SMD=2.20, 95% CI: 0.43 to 3.96, p=0.015), while aripiprazole augmentation of D2 antagonists was associated with reduced prolactin levels (n=9, N=450, SMD=–1.60, 95% CI: −2.19 to −1.01, p<0.001) and body weight (n=6, N=260, WMD=–0.93, 95% CI= −1.77 to −0.09, p=0.030).

DISCUSSION

While some prior meta-analyses have examined the efficacy of combination or "polypharmacy" strategies in schizophrenia[20,21,31,32], this is the first meta-analysis of randomized controlled trials focusing exclusively on augmentation strategies (i.e., the addition of a second antipsychotic after non-response to the first) versus continued treatment with one antipsychotic (with addition of placebo in the blinded studies), irrespective of the baseline antipsychotic.

Although our prior meta-analysis, published in 2009[20], included 19 studies and 1,229 patients, merely 6 studies with only 197 patients were "augmentation" studies, which are the ones that are truly relevant, as they clinically reflect the management of refractory/non-responsive patients. In the current study, we increased the meta-analyzed data from 6 to 31 studies and 197 to 2,073 patients. This greater number of studies allowed for an evaluation of various symptom domains beyond study-defined response, plus the assessment of adverse effects and subgroup and meta-regression analyses, including examination of the effect of open versus blinded trials.

In contrast to that prior meta-analysis[20], in which response rates had been significantly greater in the antipsychotic polypharmacy group that mixed co-initiation and augmentation trials (number-needed-to-treat = 7), the current meta-analysis did not provide any evidence for enhanced efficacy of antipsychotic augmentation in high-quality, blinded studies for either antipsychotic response or symptom reduction. This finding suggests that expectation and salience biases, also present in clinical care, may underlie observed improvements and decision making when augmenting one antipsychotic with a second one.

Although in efficacy-focused studies total symptoms decreased significantly more in the augmentation group, this effect was driven by open-label studies and those using OC analyses. Notably, the non-significance regarding total symptom reduction in high-quality studies was not driven by fewer studies and widening of the confidence intervals. Rather, more high-quality than low-quality studies were included (nine vs. seven), and the confidence intervals remained almost identical, whereas the between-group effect size was much smaller in high-quality studies. Furthermore, in efficacy-focused studies, no difference between antipsychotic augmentation and monotherapy was found regarding response rate, but, again, in the subgroup of low-quality studies superiority of the augmentation arm was observed.

Evidence regarding symptom improvement and treatment response was lacking for augmentation of either clozapine or non-clozapine antipsychotics (with the latter studies being surprisingly uncommon). The previously identified benefit regarding augmentation of clozapine with a second antipsychotic[31] could not be confirmed in blinded trials and those using ITT data. Prior meta-analyses that focused on antipsychotic co-treatment strategies involving clozapine[21,31,32] had much fewer studies (augmentation studies: 5-14 vs. 20 in our meta-analysis; patients: 187-734 vs. 1,112 in our meta-analysis) and in one instance[21] combined antipsychotic augmentation and co-initiation trials.

Despite the overall unfavorable results in high-quality studies for total, positive and general symptoms, global clinical impression, depression, treatment response and study discontinuation, augmentation of D2 antagonists with a partial D2 agonist was associated with significantly reduced negative symptoms, a finding that was confirmed in high-quality studies. Since the treatment of negative symptoms remains a big challenge in schizophrenia[81,82], these findings, based on eight studies (including four high-quality trials) clearly require further investigation, especially comparing augmentation with a partial D2 agonist versus switching to a partial D2 agonist. Since two new partial D2 agonists, brexpiprazole[83] and cariprazine[84], were recently approved for schizophrenia, it will be of interest to see if the potential benefits for negative symptoms extend to these other agents.

Different from the generally held notion that antipsychotic polypharmacy carries a greater risk of adverse effects[22], this was only found regarding greater prolactin elevation when combining two D2 antagonists. Rather, combination of two D2 antagonists was associated with less insomnia, whereas augmentation with the partial D2 agonist aripiprazole resulted in lower prolactin levels and reduced body weight.

The lack of superior efficacy of antipsychotic augmentation in high-quality studies is in contrast to common clinical belief and practice, where antipsychotic co-treatment is often implemented for non-response to antipsychotic monotherapy[12]. However, the clinical evaluation of improvement with antipsychotic augmentation mirrors the findings from open-label studies, suggesting that in clinical settings the expectations of patients and clinicians may translate into perceived favorable outcomes. Large pragmatic randomized controlled trials of antipsychotic augmentation strategies conducted in generalizable settings and samples are needed to confirm the lack of efficacy advantages of antipsychotic augmentation, as we cannot fully rule out a selection bias of less severely ill patients agreeing to participate in blinded trials. However, this possibility seems relatively low, since mean baseline PANSS/converted BPRS total symptom severity was around 80 in these pretreated individuals, and PANSS/converted BPRS total symptom severity did not significantly moderate the results.

In meta-regression analyses, less symptom improvement was associated with a higher chlorpromazine equivalent dose in the augmentation versus monotherapy arms, and a greater baseline symptom severity, with the latter relationship remaining significant in high-quality studies. These findings suggest that antipsychotic augmentation is even less effective in the sicker patients and those requiring higher antipsychotic doses. Alternatively, the higher total antipsychotic doses in the combination groups may be a reflection of lack of initial improvement, prompting dose escalation. This relationship might also be due to greater dopamine blockade resulting in less improvement due to secondary negative symptoms or other unfavorable effects.

Although the moderation of less efficacy by higher baseline symptom severity contradicts a recent meta-analysis[85], those results pertained to acutely exacerbated patients in whom greater baseline symptom severity created more room for improvement. Conversely, in our meta-analysis, a substantial number of patients had likely benefitted to some degree from antipsychotic monotherapy in the past, so that higher residual symptom severity is probably a marker of less treatment responsiveness.

The results of this study need to be interpreted within some limitations. These include: a) the still relatively small number

of double-blind studies comparing antipsychotic augmentation with monotherapy in schizophrenia, particularly for augmentation of non-clozapine antipsychotics and for specific antipsychotic co-treatment pairs; b) the heterogeneous study origin, design, definition and degree of insufficient response to monotherapy, measurements and outcomes; c) the limited number of studies reporting negative and depressive symptoms as well as adverse effects, which were often not comprehensively assessed or reported; d) the potential influence of cultural or ethnic differences (although we addressed regional effects in pre-planned subgroup analyses, yet the effect of studies from China overlapped almost 100% with an efficacy signal only detected in open-label/low-quality studies); e) the exclusion of studies focusing on adverse effects from the efficacy analyses to reduce heterogeneity (supported by a >10-point lower mean PANSS/converted BPRS symptom severity in side effect-focused versus efficacy-focused studies); f) the combination of studies augmenting clozapine and non-clozapine antipsychotics, potentially representing different patient subgroups (although mean baseline PANSS/converted BPRS total scores were comparable, and subgroup analyses replicated results in both clozapine and non-clozapine studies); g) the restriction of the distinction between high-quality and low-quality to blinding and data analysis (although risk-of-bias tool clearly confirmed quality differences without having a significant influence in the meta-regression analysis, suggesting that major influencing biases were captured through blinding/ITT categorization); h) the lack of adjustment for multiple comparisons (yet, adjustment for multiple comparisons would only have increased the level of non-significance of differences between groups); i) the potential effect of non-adherence, and j) the lack of detailed data to determine whether the effect of partial agonist augmentation was mainly on primary or secondary negative symptoms.

In summary, data from this study suggest that high-quality evidence is lacking for antipsychotic augmentation in patients with schizophrenia, which applies also to patients with inadequate response to clozapine. The clinical relevance of the negative symptom advantage of adjunctive partial D2 agonist treatment needs to be further assessed. Additionally, effects of augmentation with a partial D2 agonist versus a switch to a partial D2 agonist on negative symptoms need to be compared before these results can be considered for clinical care. Antipsychotic augmentation treatment should also be compared with high-dose antipsychotic monotherapy or augmentation with psychosocial interventions. Furthermore, non-clozapine antipsychotic augmentation strategies should be compared against a switch to clozapine or to improving adherence, including monotherapy with a long-acting injectable antipsychotic, which are each more rational choices for addressing antipsychotic non-response. Another gap is the systematic assessment of adverse effects of antipsychotic augmentation, extending also to cognition, functioning and subjective well-being. Finally, more high-quality trials are needed that examine antipsychotic augmentation in non-clozapine-treated patients across relevant outcome domains, including patients with carefully defined insufficient response to antipsychotic monotherapy.

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Has increased provision of treatment reduced the prevalence of common mental disorders? Review of the evidence from four countries

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Many people identified as having common mental disorders in community surveys do not receive treatment. Modelling has suggested that closing this "treatment gap" should reduce the population prevalence of those disorders. To evaluate the effects of reducing the treatment gap in industrialized countries, data from 1990 to 2015 were reviewed from four English-speaking countries: Australia, Canada, England and the US. These data show that the prevalence of mood and anxiety disorders and symptoms has not decreased, despite substantial increases in the provision of treatment, particularly antidepressants. Several hypotheses for this lack of improvement were considered. There was no support for the hypothesis that reductions in prevalence due to treatment have been masked by increases in risk factors. However, there was little evidence relevant to the hypothesis that improvements have been masked by increased reporting of symptoms because of greater public awareness of common mental disorders or willingness to disclose. A more strongly supported hypothesis for the lack of improvement is that much of the treatment provided does not meet the minimal standards of clinical practice guidelines and is not targeted optimally to those in greatest need. Lack of attention to prevention of common mental disorders may also be a factor. Reducing the prevalence of common mental disorders remains an unsolved challenge for health systems globally, which may require greater attention to the "quality gap" and "prevention gap". There is also a need for nations to monitor outcomes by using standardized measures of service provision and mental disorders over time.

Key words: Common mental disorders, depression, anxiety disorders, prevalence, antidepressants, psychological therapies, treatment gap, quality of treatment, prevention

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National surveys in a range of countries have found that mental disorders are common and are a major source of disability[1]. However, many cases are untreated, even among people with the most serious disorders. In industrialized countries, 36-50% of serious cases are untreated in the previous year, whereas in developing countries the situation is even worse, with 76-86% untreated. It has been proposed that treatment services need to be expanded to reduce the prevalence and impact of mental disorders[2].

The "treatment gap" is of such concern that the 2001 World Health Report made ten recommendations for addressing it, including making mental health treatment more accessible in primary care, making psychotropic drugs more available, and increasing the training of mental health professionals[3]. Simulation data suggested that extending the provision of evidence-based treatment would reduce the population burden of mental disorders[4] and provide an economic return on investment[5].

The aim of the present paper is to review evidence from four industrialized English-speaking countries – Australia, Canada, England (most of the UK population) and the US – on whether increases in treatment provision have been associated with a reduction in prevalence of common mental disorders. These countries were chosen because they have the necessary data, have mental health systems familiar to the authors, and provide a suitable test of whether increasing services improves population mental health.

The focus is on mood and anxiety disorders in adults, which are the major source of disease burden from mental disorders. Both diagnostic measures and symptom scale data were reviewed. While both lay diagnostic interviews and self-report symptom scales are imperfect measures of these mental disorders, consistency of findings across assessment methods supports conclusions about whether any changes have occurred.

Papers were identified by a search in PubMed for studies published from 1990 to 2015 using the terms: (Australia OR Canada OR "Great Britain" OR England OR "United Kingdom" OR "United States") AND ("stress, psychological" OR depression OR "depressive disorder" OR anxiety OR "anxiety disorder") AND (epidemiology OR therapeutics) AND trends.

Papers were considered relevant if they covered time trends in prevalence or treatment and were based on assessments at more than one time point. Studies based on analyses of lifetime reports from different cohorts in the same survey were not considered. Reports selected were supplemented by manual search of references of the retrieved articles and the authors' knowledge of any grey literature from their respective countries.

AUSTRALIA

Changes in treatment

In Australia there has been an overall substantial growth in the resources allocated to mental health care, with total

government expenditure increasing by 178% in real terms between 1992-1993 and 2010-2011[6]. This change in expenditure has been accompanied by a 35% increase in the *per capita* mental health workforce employed by the states and territories.

Antidepressant use showed a 352% increase (in terms of daily doses per 1,000 people per day) from 1990 to 2002, mainly associated with the introduction of selective serotonin reuptake inhibitors (SSRIs)[7]. This trend continued in the 2000s, with a 95% increase from 2000 to 2011[8]. By 2011, Australia had the second highest consumption of antidepressants among 23 countries which are part of the Organization for Economic Co-operation and Development (OECD)[9].

The availability of psychological therapies increased in 2001 and then further in 2006 with the introduction of new funding arrangements. These programmes provided subsidies for evidence-based psychological services, mainly delivered by psychologists, leading to a rapid uptake of psychological treatments. It has been estimated that the 12-month treatment rate for mental disorders increased from 37% in 2006-2007 to 46% in 2009-2010[10]. Australia has also seen rapid growth in the availability of e-therapy since 2002[11].

Changes in prevalence

Australia had national mental health surveys in 1997 and 2007, both using the Composite International Diagnostic Interview (CIDI). Direct comparison of prevalences is difficult because of differences in methodology. However, no reduction in prevalence was observed, with 18% having an anxiety, affective or substance use disorder in 1997 compared to 20% in 2007[6].

Other relevant data come from national surveys that used symptom scales. A comparison of surveys in 1995, 2003-2004 and 2011, using the 4NS scale, found no change[12]. Comparison of the Kessler Psychological Distress Scale (K10) data in the 1997 and 2007 national mental health surveys showed an increase in anxiety symptoms, but no change in depressive symptoms[13]. Another national health survey series showed no change in the K10 data between 2001, 2004-2005 and 2007-2008[14]. There are also relevant time series data from a health survey in the state of South Australia, which compared the prevalence of major depression according to the Patient Health Questionnaire in 1998, 2004 and 2008, and found a significant increase from 7% to 10%[15].

Conclusion on Australia

Australia has had increasing resources allocated to mental health care, with an increased mental health workforce, increased use of antidepressants and, more recently, increased provision of psychological therapies, including e-therapy. However, there is no evidence for any reduction in prevalence of disorders or reduction in symptoms. If anything, trends are in the opposite direction.

CANADA

Changes in treatment

In Canada, several national surveys have collected data on self-reported current (past 2-day) antidepressant use. A meta-regression analysis of survey data collected between 1994 and 2012 identified substantial increases, more than three-fold, in the 1990s, but no change between 2002 and 2012[16]. By 2011, Canada ranked third among OECD countries (behind Australia and Iceland) in antidepressant consumption[9].

Another indicator of access to clinical care is the proportion of people reporting that they have been professionally diagnosed with a mood or anxiety disorder. This was assessed in three national surveys between 2003 and 2007, increasing both in men and women in each year[17]. This trend has continued up to 2014, with the percentage reporting that they had been diagnosed with a mood or anxiety disorder increasing from 5.1% in 2003 to 7.5% in 2013[18].

Due to lack of detailed data, it is not possible to estimate the frequency of participation in evidence-based psychotherapies for common mental disorders in Canada. However, the proportion of respondents with past-year major depression who reported six or more visits to a health professional for mental health reasons (a pattern that is at least consistent with receipt of an evidence-based psychotherapy) increased from 27.6% to 39.5% between 2002 and 2012[19]. When antidepressant use was included in this definition, 52.2% of respondents received potentially adequate treatment in 2012, up from 41.3% in 2002.

Changes in prevalence

A brief lay-administered interview for major depressive episodes has been consistently included in large, representative national health surveys conducted in Canada over the past 20 years. Also, two national mental health surveys, in 2002 and 2012, used a Canadian adaptation of the CIDI. A recently reported meta-regression analysis that examined estimates from this data library (consisting of eleven national surveys) found no change in prevalence between 1994 and 2012, the slope of the meta-regression line over time being nearly exactly zero[20].

While Canadian prevalence data are most readily available for major depressive episodes, the same data sources have often included the K6 scale (an abbreviated version of the K10) for non-specific distress[21]. This scale may provide broader coverage of common disorders in community populations. There was no evidence of change over time either in the prevalence of elevated distress or in mean distress ratings[17].

Conclusion on Canada

In Canada, there is evidence of increasing access to clinical care and treatment with antidepressant medications. Despite this change, there is no evidence that the prevalence of common

mental disorders, as reflected by the past-year occurrence of major depressive episodes or by non-specific distress ratings, has diminished over time.

ENGLAND

The UK has since 1948 provided universal health care free at the point of need, funded through central taxation, which provides an interesting opportunity to study the effects of health care unencumbered by the barrier of cost.

In the British National Psychiatric Morbidity Survey (NPMS) programme, adults living in private households were recruited using population-based multi-phase probability sampling, and evaluated by lay interviewers. While improvements were made in successive surveys, the emphasis was on using identical instruments wherever possible. In consequence, rates of mental disorders, health service use and treatment delivery at different time points over a 15 year period can be directly compared. Most data are available for England, which includes the vast majority of people living in the UK. As the 2007 survey covered only England, current analyses are restricted to the English population in all the surveys.

Changes in treatment

Data on trends in treatment over time have been collected by the NPMS in 1993, 2000 and 2007, using standardized and essentially unchanged methods[22-26]. The surveys asked respondents directly about using treatments and consulting with professionals for a mental health problem over specific time periods.

There was little change in primary care physician contact for a psychological problem over the period from 1993 to 2007[27]. However, the receipt of antidepressants increased significantly, nearly trebling between 1993 and 2000[28], following which there was no further increase between 2000 and 2007[27]. Increasing hypnotic use[29] and antidepressant prescribing[30] has also been reported. There was limited evidence of an increase in talking treatments between 1993 and 2007.

Changes in prevalence

Recent analyses of the NPMS found no clear secular trend in the prevalence of common mental disorders in general or in depressive episodes in particular between 1993 and 2007[31]. The prevalence of common mental disorders was 10.9% in men and 18.1% in women in 1993, while it was 11.8% and 18.9%, respectively, in 2007.

Conclusion on England

England has had an increasing use of antidepressants, hypnotics and possibly talking treatments since 1993. However, there is no evidence for any decrease in prevalence of disorders or reduction of symptoms in adulthood. If anything, trends are in the opposite direction.

UNITED STATES

Changes in treatment

A 2001 study by Zuvekas[32] compared data from the 1987 National Medical Expenditure Survey (NMES) and its successor, the 1996 Medical Expenditure Panel Survey (MEPS) – two representative general population surveys. The prevalence of any mental health treatment use increased from 6.9% to 8.5% (a 23.3% increase). The increase in use of psychiatric medications was much larger: from 3.4% to 5.6% (a 63.4% increase). The total number of ambulatory visits increased by 29.2% in this period, whereas the population only increased by 12.3%.

A 2005 study covered a more recent time period and recorded a larger increase by comparing 1990-1992 data from the National Comorbidity Survey (NCS) and 2001-2003 data from the National Comorbidity Survey - Replication (NCS-R)[33]. The increase in overall prevalence of treatment in adults aged 18-54 was over 65% (from 12.2% in 1990-1992 to 20.1% in 2001-2003). The relative increase was similar when the sample was limited to individuals who met the criteria for a DSM-IV mental disorder based on a structured interview: from 20.3% to 32.9%.

Other studies have examined trends in use of treatments for specific conditions (such as depression[34,35] and anxiety disorders[36]) or specific types of treatments (such as antidepressants[37,38] and psychotherapy[39]).

Two studies based on 1987 data from NMES and 1997, 1998 and 2007 data from MEPS recorded a significant increase in treatment for depression over the 1987 to 2007 period[35,39]. The increase was more marked in the 1987-1997 period (220% increase, from 0.73% to 2.33%) than the 1998-2007 period (22% increase, from 2.37% to 2.88%).

Marked growth in antidepressant medication treatment appears to have been the major driver of the increase in depression treatment in the earlier period: 74.5% of those who received treatment for depression in 1997 were treated with antidepressants, compared to 37.3% in 1987. In contrast, the use of psychotherapy for treatment of depression declined from 71.1% to 60.2%[36]. Antidepressants remained the major form of treatment in the later period, with 80.1% of individuals treated for depression in 1998 and 81.9% in 2007 receiving these treatments. The downward trend in the use of psychotherapy in treatment of depression also continued in the later period, going from 53.6% of those treated for depression in 1998 to 43.1% in 2007[39].

Similar patterns of increased prevalence of treatment, increased use of antidepressants and decreased use of psychotherapy were observed for anxiety disorders[36].

Changes in prevalence

Few studies have examined trends in prevalence of common mental disorders in the US, mainly because assessments and diagnostic criteria used in mental health surveys of general population have changed over the years, making comparisons difficult if not impossible. Yet, there is no evidence from available studies that the prevalence of these disorders has declined over the past two or three decades[33,40].

Indeed, one study based on two large national surveys found a more than two-fold increase in the prevalence of major depressive episodes between 1991 and 2002[41]. Another study based on consecutive waves of National Health and Nutrition Examination Survey (NHANES) also found increases in depressive symptoms over the 2005-2010 period[42]. Other studies based on 1991-1992 NCS and 2001-2003 NCS-R data found essentially similar prevalence estimates of major depression and other common mental disorders in this period[33,40]. A more recent study did not find evidence of any significant decrease in 12-month prevalence of major depressive episodes or psychological distress in the years since 2001[43].

Conclusion on the United States

Virtually all studies that have examined trends in use of mental health treatments in the US have recorded an increasing trend since early 1990s. The increase was sharpest between early 1990s and early 2000s and more marked for antidepressant medication treatment, especially SSRIs.

However, there is no evidence for any corresponding reduction in prevalence of mental disorders or psychological distress among US adults in this same period. Some evidence even points to possible increases in prevalence of depression and in disability due to mental health problems[44].

HAS A REDUCTION IN PREVALENCE BEEN MASKED?

We now consider the possibility that treatment has really had a population impact, but this effect is difficult to detect. Two hypotheses are considered: masking by changes in risk factors and masking by increased awareness or willingness to report symptoms.

Masking by changes in risk factors

It is possible that there has been an increase in exposure to risk factors that has masked any decrease in prevalence of common mental disorders due to increased treatment.

Australia

Australia has been affected by a number of natural disasters over the period, particularly drought, floods and fires, but these have been regional and time limited and unlikely to have had a national impact. There have been no major economic changes that could plausibly drive prevalence up. The global financial crisis, for example, has had a limited impact on Australia. Comparison of exposure to specific traumatic events in 1997 and 2007 showed no change[45].

Changes in physical health are also unlikely to have masked changes in mental health. Physical health has overall improved, with increased life expectancy, more years free of disability and slightly improved self-rated health[46]. However, some health problems, in particular obesity and diabetes, have increased.

Canada

During the past two decades, parts of Canada have been affected by natural disasters such as ice storms, forest fires and floods. However, these have been regional events. There were no natural disasters affecting the national population. The global financial crisis has had a relatively limited impact in Canada.

England

In common with many high-income economies, the UK experienced a major recession beginning in 2007. Cuts in most public services (but not in health care) began in 2010 and continue. Unemployment rates rose, but have declined since. The most recent comparable data from the NPMS were collected in 2007. Further data will be available in 2016 (following a period of slight economic growth).

No major disasters, conflicts or other changes have occurred throughout England that could plausibly drive prevalence up since the NPMS data collection began in 1993.

United States

The US population has experienced a number of major social and economic stressors over the past two decades, ranging from terrorist attacks to economic recession and hurricanes, impacting large portions of the population. Although the short-term mental health impact of these events on specific population groups or specific outcomes has been studied[47-49], their overall and long-term impact on the prevalence of mental disorders and psychological distress is not clear.

A study covering the periods before and after the 2008 economic downturn did not detect any clear effects on mental health of the US population[43]. There is also little evidence that the physical health of the US adults has declined over this period, as evidenced by a decrease in all-cause mortality across virtually all age groups[50].

Masking by increased awareness or reporting of symptoms

The measures used to monitor prevalence involve self-report of symptoms or lay diagnostic interviews. If public

awareness of common mental disorders or willingness to disclose symptoms increased over time, this might lead to an artefactual increase in reporting.

Australia

There is evidence that Australians have become more open about mental health problems. Between 1995 and 2011, there was an increase in the percentage of adults who reported having had a problem similar to a depressed person described in a vignette[51]. There was also an increase in the percentage who reported knowing a family member or friend who had a similar problem.

Associated with this increase, Australian adults have shown improvements in the ability to give psychiatric labels to vignettes[52] and a reduction in the belief that depression is due to weakness of character[53]. While there is no evidence linking these changes to prevalence rates, it is possible that the public has become more willing to report symptoms.

Canada

While studies of mental health literacy[2] and perceived stigma[54] have been conducted in Canada, repeated measurements over time have not been made. Therefore, temporal trends cannot be evaluated.

While there have been no changes in symptom-based measures of mental health, there has been a slight increase in the proportion of Canadians reporting that their mental health is merely fair or poor[55]. If this trend reflects an increasing willingness to disclose mental health concerns, then the sensitivity of instruments such as structured diagnostic interviews or the K6 scale may be increasing over time, which would lead to larger prevalence estimates. Speculatively, such an effect could offset gains that might otherwise result from better delivery of treatment.

England

Response rates for the household NPMS were 79% in 1993, 69% in 2000, and 57% in 2007, which is in line with international trends. The paper-and-pencil questionnaires used in 1993 were replaced by computer assisted interviewing in subsequent surveys; this is not thought to affect the results substantially[56]. Willingness to report symptoms has not been specifically assessed in the UK survey programme. The absence of significant change in responses to identically worded questions on symptoms argues against such a change.

The increased use of treatments by men between 1993 and 2000 might suggest some change in attitudes or self-perception, but no further such change was seen between 2000 and 2007. There has been an increased focus in other research on examining the effects of stigma, for example on the under-use of treatments[57], which has not yielded information on trends over time.

United States

Little research has focused on any possible changes in Americans' willingness to disclose mental health problems. One study, recording increased reports of "impending nervous breakdown" among the US general population between 1957 and 1996, concluded that the change could be due either to an increase in psychological problems, or a decrease in the stigma associated with admitting that one is going to have a nervous breakdown, or both[58]. Other studies indicate that younger adults were more willing to disclose mental health problems and to seek professional help in more recent years[59]. Yet, it remains unclear whether people who participated in more recent surveys were more likely than those who participated in earlier years to identify their psychological distress as indicative of a mental health problem.

A recent study found that middle-aged and older Americans tend to rate themselves and cases presented in standard vignettes as more depressed than their European counterparts[60]. When the self-ratings were adjusted for vignette ratings, American participants were not more depressed than the Europeans. While this finding highlights the importance of expectations and norms in labeling one's mental status, it is not clear if the expectations and norms of American adults regarding their mental health have changed over time.

WHY HAS PREVALENCE NOT DECREASED?

Given that prevalence has not shown the expected decrease, we next discuss possible reasons. Two possibilities are examined: that the quality of treatment is too poor to affect prevalence or is too poorly targeted, and that too little has been done to reduce incidence through prevention.

Is treatment of poor quality or poorly targeted?

Australia

In Australia, there is evidence that treatments provided are often not consistent with clinical practice guidelines. It has been estimated that 39% of cases of mood or anxiety disorders sought professional help, 26% received an evidence-based intervention, and 16% received minimally adequate treatment[61]. There is also evidence that only 50% of people prescribed antidepressants receive them for at least six months as recommended in clinical guidelines[62]. Similarly, while the perceived needs of service users were better met in 2007 than in 1997, most of the gains were in partially met rather than fully met needs, suggesting that quality of services may still be lacking[63].

There have been specific questions raised about the use of antidepressants. It has been noted that the age distribution of antidepressant use aligns poorly with the age distribution of

mood and anxiety disorders, with antidepressants more likely to be prescribed to older people, among whom prevalence is lower[64]. There are also data showing that general practitioners, who are the major prescribers, use antidepressants to treat "chronic mild depression", whereas the evidence indicates that these drugs are more appropriate for severe disorders[65]. The use of antidepressants for milder cases is also inconsistent with clinical guidelines that recommend psychological therapies as the first line of treatment[61].

Canada

A survey conducted in the province of Alberta in 2005 and 2006 found that only 40.5% of those with major depression were taking an antidepressant. The frequency was 28.5% in those with anxiety disorders. Among those with major depression, only 14.3% reported receiving psychotherapy as a treatment[66].

In the Alberta survey, 67.2% of those who reported taking antidepressants had no active mood or anxiety disorder diagnosis at the time of the survey. However, some of these respondents may have had successful outcomes, such that they no longer met diagnostic criteria at the time of the interview. They may have been taking medications to safeguard a remission rather than for acute treatment. In this particular survey, 81% of those taking antidepressants reported doing so for more than one year.

In the most recent national mental health survey (which was conducted in 2012), 85% of respondents with past year major depressive episodes reported a perceived need for mental health care, 63% reported that they had actually seen a health professional about their mental health and only 58% of these reported that their health care needs were completely met[67]. These results suggest that there is much progress to be made in the timeliness and quality of treatment, factors that affect the impact of treatment on population health.

England

Adherence to guidelines has not been a specific focus of the UK survey programme, in part because surveys do not provide an opportunity to evaluate practice at a sufficiently detailed level. Furthermore, guidelines are updated periodically, making checks on adherence over time more problematic. Thresholds for diagnosis by primary care physicians have become progressively lower[22], but whether this is a good development depends on how such cases are managed. Two studies showing trends in primary care physician assessments away from diagnosis of depression and of anxiety disorder towards diagnosing symptoms of depression and of anxiety could reflect reduced quality of care, possibly related to increased demand pressures on physicians[68,69].

Note has been taken of the increasing use of antidepressants by adults not currently depressed[28], but this could indicate either inappropriate over-diagnosis and over-prescribing or it could be a positive indicator that antidepressant treatments are not being withdrawn too quickly following remission.

United States

A large and growing body of evidence points to the poor quality of mental health treatments as offered in usual care settings in the US[70-78]. Many patients who start treatment for common mental disorders drop out before they could experience the full benefit of treatment[73]. Indeed, prevalence of "minimally adequate" treatment is often much lower than the prevalence of treatment contacts overall. In one study, less than 40% of the participants who reported having received any mental health treatment for a serious mental illness were rated as having received minimally adequate treatment[75]. This means that the current prevalence estimates of mental health treatments based on population surveys greatly exaggerate the prevalence of *effective* treatments received.

While there is little data on trends in quality of mental health treatments nationally, there is some evidence that the mix and nature of treatments has changed over time[34-36]. For example, over the 1987 to 2007 period, the proportion of patients treated for depression who received any psychotherapy or psychotherapy in conjunction with medication treatment declined greatly[35,39].

Furthermore, a large number of people who do not clearly meet the diagnostic criteria for a mental disorder routinely use mental health treatments in the US. Between 1990 and 2003, the increase in the prevalence of treatments in the past year was slightly larger among adults who did not meet the criteria for any 12-month mental disorder than those who met these criteria (65% vs. 62%)[33].

Other data indicate that, among adults treated with antidepressants, the proportion of those who met the criteria for a 12-month mental illness declined during the 1990s and later years[79,80]. Of course, many of those who did not meet the criteria for mental disorder in the past 12 months had met the criteria before that time and were in remission or in partial remission[81]. Treatment may be clinically justified in this group to prevent relapse. Others may be suffering from subthreshold symptoms or mild disorders, and treatments may reduce the risk of future severe illness or chronicity[40].

Is more emphasis needed on prevention?

Prevalence is a function of incidence and duration, with treatment services primarily focused on reducing duration[82]. It is possible that reducing prevalence requires greater emphasis on reduction of incidence through prevention approaches.

Australia

While difficult to quantify, the resources allocated to prevention have been very small compared to those for treatment[83].

The 2014 National Review of Mental Health Programmes and Services recommended greater emphasis on prevention, but this remains to be implemented[84].

Canada

Canada's first national mental health strategy was published in 2012 and referred prominently to mental health promotion and prevention as key actions[85]. In particular, school-based programmes were emphasized, drawing upon the observation that common mental disorders often manifest for the first time during childhood. However, implementation of preventive interventions has not been documented either in terms of its extent or effectiveness.

England

Evidence-based depression prevention programmes for adults are not funded in the UK. Responsibility and a small budget for what is termed mental health promotion has now been transferred from national to local government. Funding targeted on the research priority of prevention of mental disorders has only just begun in 2015, with non-health care settings being the preferred location for proposed studies.

Sure Start Centres to support disadvantaged young families were established from 1997 onwards, but are now gradually losing funding. It is too soon to be able to say what, if any, long-term benefits might accrue for conditions like depression that mainly begin to become common from puberty onwards.

United States

A 2009 report by the US Institute of Medicine called on the nation to make prevention of mental and behavioural disorders a priority[86].

While various agencies across the country have implemented programmes aimed at prevention of mental and behavioural health problems, including school and college programmes sponsored by the Substance Abuse and Mental Health Services Administration[87], these efforts remain disjointed and do not amount to a national strategy.

CONCLUSIONS

Common mental disorders remain a major source of disability globally. According to the Global Burden of Disease 2013 study, major depression ranks second and anxiety disorders rank ninth[88] among all non-communicable diseases. This disability burden did not change substantially over the period 1990-2013, with age-standardized years lived with disability estimated to have increased by 4.7% (95% uncertainty: 2.7 to 6.7) for major depression and to have decreased by 0.2% (95% uncertainty: −1.6 to 1.3) for anxiety disorders. Similarly, age-standardized prevalence was estimated to have increased by 4.2% (95% uncertainty: 2.4 to 6.2) for major depression and to have decreased by 0.5% (95% uncertainty: −1.7 to 0.8) for anxiety disorders[88], consistent with a meta-analysis of prevalence studies over the period[89].

The four countries examined here provide a test of the capacity of current treatment approaches to reduce prevalence of common mental disorders. All four countries have had increases in rates of treatment for these disorders since the 1990s. This has been consistently seen for use of antidepressants, with large increases in all countries. For psychological therapies, there has been more variability, with increases in Australia and possibly England, decreases in the US and no evidence available in Canada. Despite these changes, none of the four countries had any evidence for a reduction in prevalence of disorders or symptoms over the period. If anything, there were indications of changes in the opposite direction in Australia, England and the US.

In pointing out that there have not been population mental health gains, we are not suggesting that pharmacological and psychological treatments for common mental disorders do not work. There is abundant evidence from systematic reviews of randomized controlled trials that they do. Rather, this review indicates that there may have been problems of implementation or other factors that may have counteracted their impact. Furthermore, this review is concerned with the situation in high-income countries. We do not know what the impact of increasing availability of treatment would be in low- and middle-income countries.

Considering the various hypotheses to account for a lack of improvement, we found no support for a masking of a decrease in prevalence due to treatment by an increased exposure to risk factors. We also examined the hypothesis that people have become more aware of common mental disorders or willing to report symptoms in surveys, but found little relevant evidence. This is an area that requires further work, perhaps using clinician-based measures or psychometric techniques for assessing item and test bias.

We considered two possible explanations for a real lack of improvement. Firstly, we examined whether treatment might be of poor quality or might not be well targeted. In Australia, Canada and the US, there was evidence that treatment was frequently not of an adequate standard, as indicated by short duration and continuing unmet need. England lacked relevant data. There were also data from Australia, England and the US that treatment is often received by people who do not meet criteria for a diagnosis, although in some cases this may be appropriate, for example to prevent relapse.

Secondly, we examined whether there has been too little emphasis on reducing incidence through prevention. There is evidence from randomized controlled trials that psychological interventions can have preventive effects in both young people and adults[90,91], and that these can be cost-effective[92]. There is also considerable potential for prevention through risk factor modification, including parenting behaviours, school environments, workplace conditions, diet and lifestyle behaviours[93]. Social

determinants such as poverty and unemployment are also important for mental health[94]. In all four countries, prevention is receiving piecemeal efforts, with no country having a coordinated national approach, despite calls to do so in several of them.

Despite the remarkable consistency in trends across the four countries, there are a number of limitations in the available data that need to be considered. Survey methodologies, diagnostic criteria and response rates have varied over time within countries, limiting the comparisons that can be made. The data available come from lay diagnostic interviews or self-report symptom questionnaires rather than the gold standard of standardized clinical instruments. There are also limited data available on some issues, including whether there have been changes in awareness of common mental disorders or willingness to report symptoms in surveys in all four countries, use of psychological therapies in Canada, and quality of treatment in England. Furthermore, the timing of data points for changes in services does not always match that for changes in prevalence (e.g., the largest increases in use of psychological therapies in Australia have occurred after the most recent national survey of prevalence).

Efforts to reduce the burden of disease due to common mental disorders have emphasized the importance of reducing the "treatment gap". Modelling of the impact of reducing this gap indicated that this approach would produce measurable reductions in disease[4]. However, it now appears that this modelling was optimistic. The present analysis suggests that, in order to reduce the prevalence of common mental disorders, we may also need to reduce a "quality gap"[95]. This gap has two components: providing treatments that meet the minimal standards of clinical practice guidelines, and targeting treatments optimally to those in greatest need. There may also be a "prevention gap", where resource allocation to reducing incidence through prevention has lagged efforts to reduce duration of disorders through treatment. However, if prevention is to have an impact, it needs to also be rigorously evidence based and implemented to a high standard, so that it does not end up having its own quality gap.

In order to properly evaluate the future impact of closing these gaps, nations need to use standardized measures of service provision and mental disorders over time. There would be merit in future work attempting to quantify changes in services and prevalence of mental disorders across countries using meta-analytic techniques, as have been applied in Canada[16,20].

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Irritability in children: what we know and what we need to learn

Irritability can be defined as increased proneness to anger, relative to peers. Clinically, it manifests as developmentally inappropriate temper outbursts and sullen, grouchy mood; thus, it includes both behavioral and mood components. Related constructs are mood dysregulation, which is broader than irritability, and aggression, which encompasses only behavioral manifestations.

Anger proneness has a defined developmental trajectory, peaking in the preschool period and declining thereafter, with a modest increase during adolescence[1]. Irritability is a common reason for mental health evaluation in children, and pediatric irritability is associated with both concurrent and future impairment.

In the 1990s, American researchers suggested that pediatric bipolar disorder does not present with distinct manic episodes as in adults, but instead with severe, chronic irritability. However, *post-hoc* analyses of epidemiological studies found associations between pediatric irritability and risk for subsequent anxiety and depression, but not for bipolar disorder[2]. Similarly, in studies comparing the two dimensions of oppositional defiant disorder (ODD) (i.e., irritability and headstrong behavior), irritability predicts subsequent anxiety and depression, while headstrong behavior predicts attention-deficit/hyperactivity disorder (ADHD) and conduct disorder[2]. Thus, the diagnosis of bipolar disorder should be reserved for youth (and adults) with distinct manic episodes, rather than chronic irritability.

Genetically informative studies link irritability and depression[3]. Twin studies document that longitudinal associations between irritability and both anxiety and depression have a genetic component. These studies also find that the heritability of irritability is approximately 40-60%, similar to anxiety or unipolar depression.

Irritability is a diagnostic criterion for multiple disorders in youth, including anxiety disorders, major depressive disorder, and ODD. It is also common in youth with ADHD, bipolar disorder, conduct disorder, and autism. However, for children and adolescents, the validity and clinical utility of a diagnostic category characterized primarily by irritability remains an important and unanswered question. Historically, that category has been ODD, which is conceptualized as a disruptive behavior disorder. However, ODD consists of two dimensions, only one of which, irritability, has genetically mediated longitudinal associations with depression and anxiety. Also, severe irritability has significant cross-sectional associations with anxiety disorders. These considerations call into question the appropriateness of combining irritable and headstrong features into one disorder, and of categorizing a diagnosis characterized primarily by irritability as an externalizing, disruptive behavior disorder, rather than as a mood disorder.

Given these complexities, it is not surprising that DSM-5 and ICD-11 take different approaches to diagnosing youth whose primary problem is severe irritability. Reflecting the American controversy about pediatric bipolar disorder, the mood disorder section of DSM-5 includes a new diagnosis, disruptive mood dysregulation disorder (DMDD), characterized by severe, chronic irritability. DMDD captures youth whose irritability causes impairment comparable to that of youth with bipolar disorder and, hence, is more severe than that of most youth with ODD. Given overlap between DMDD and ODD, ICD-11 instead includes a specifier to the diagnosis of ODD denoting chronic irritability. To evaluate these different nosologic strategies, future research should focus on their utility in predicting treatment response.

Two neuroscience-based formulations can guide research on the pathophysiology of irritability. One conceptualizes irritability as an aberrant response to frustration, the emotion elicited when goal attainment is blocked, as when an expected reward is withheld[2]. The second conceptualizes irritability as an aberrant approach response to threat: whereas healthy organisms approach a threat (i.e., attack) only when it is inescapable, irritable individuals may attack in a broader range of contexts. In an animal model with translational potential for studying irritability, threat and frustration were found to interact in determining an animal's behavior. Specifically, compared to non-frustrated rodents, those who experienced "frustrative non-reward" (i.e., did not receive an expected reward) showed increased motor activity and were more likely to attack a conspecific[4]. Such hyperactivity and increased propensity for aggression may be analogous to the behavior exhibited by a frustrated child experiencing a temper outburst.

Functional magnetic resonance imaging research has examined associations between irritability and neural responses to frustration (e.g., rigged games) and threat (e.g., angry faces). Work with frustrating tasks shows associations between irritability and dysfunction in striatum, anterior cingulate cortex, amygdala, and parietal lobe, consistent with irritable youths' deficits in reward processing and in maintaining attentional control when frustrated[5,6]. Irritable youth are also more likely than their non-irritable peers to view ambiguous faces as angry and, like youth with anxiety disorders, to attend preferentially to angry faces[7,8]. One direction for future research would be identifying the extent to which abnormalities in reward or threat processing differentiate subtypes of irritable youth. Also, an important question is whether the brain mechanisms mediating irritability vary across diagnoses and/or when irritability co-occurs with another trait, such as anxiety. Early data suggest that the pathophysiology of irritability varies across such contexts[9].

Given the very recent inclusion of DMDD in DSM-5, limited controlled trials exist. However, tentative recommendations stem from studies focused on treating irritability in the context of other disorders, including ADHD and major depressive disorder. Considerable data indicate that stimulants reduce irritability in youth with ADHD[2]. This suggests that, while

stimulants are relatively contraindicated in bipolar disorder, they may be helpful for DMDD. Data support the use of atypical antipsychotic medication in youth with autism and irritability, and in youth with aggression[2]. However, recent increases in antipsychotic prescriptions may have resulted in part from attempts to treat pediatric irritability, perhaps without adequate exploration of alternative pharmacologic and psychotherapeutic approaches[10]. Selective serotonin reuptake inhibitors (SSRIs) may treat irritability in adults; such an approach in children is supported by the high comorbidity and longitudinal associations among irritability, anxiety and depression[2]. SSRIs are now being tested in youth with DMDD.

Psychotherapeutic approaches are likely to be important in the treatment of irritability. Parent training can decrease a child's aggression and might also decrease irritability[11]. Cognitive behavioral approaches are being tested, as is implicit training designed to alter irritable children's tendency to view ambiguous faces as angry[8].

In conclusion, the recent focus on irritability has yielded considerable knowledge about its longitudinal course and associations with psychopathology. Ongoing work is aimed at identifying the brain mechanisms mediating irritability and at using that knowledge to inform novel treatment approaches.

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Are there new advances in the pharmacotherapy of autism spectrum disorders?

Autism spectrum disorders (ASD) are heterogeneous neurodevelopmental disorders beginning early in childhood and characterized by social communication deficits and restricted patterns of repetitive/stereotypic behaviors. Associated symptoms such as hyperactivity, irritability, insomnia, seizures, gastrointestinal and immunological disturbances may be present. Some ASD children have exceptional (savant) abilities in isolated cognitive areas such as mathematical, artistic or musical skills. ASD are more common in boys than girls (ratio 4:1), but are under-diagnosed in the latter.

The etiology of ASD is quite complex. Genetic, epigenetic, infectious, autoimmune-immunologic, metabolic, nutritional and toxic factors may be involved. Different brain areas, neural circuits, neurotransmitters, neuropeptides, cytokines, synaptic and signal transduction molecules and processes may be affected.

Because of this complexity, the development of pharmacotherapy for ASD has proven quite challenging. The marked heterogeneity of these disorders suggests that different treatments will likely be beneficial for different patients. There is a need for early detection and intervention when the brain is more plastic and changes may be more easily reversible; however, some studies suggest that pharmacotherapy may also be useful in adults. Biomarkers may help stratify subgroups and predict response to therapy. The ultimate goal is to target the ASD core symptoms; however, most current pharmacotherapies target ASD-associated symptoms.

The atypical antipsychotics risperidone and aripiprazole are approved in the US for the treatment of disruptive behaviors (aggression, self-injury, temper tantrums) in childhood ASD. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and citalopram, have been studied in ASD: single-site trials demonstrated efficacy for repetitive behaviors in ASD children and adults[1,2], but multi-site trials failed to document efficacy, except in a subgroup of subjects with high irritability. Anticonvulsants have been studied for disruptive behaviors such as impulsivity, self-injury and aggression, common in ASD: valproate, acting by potentiating the inhibitory effect of the GABAergic system and by epigenetic effects, has shown benefit in reducing irritability and impulsive-aggressive behavior in ASD children[3]. Medications approved for attention-deficit/hyperactivity disorder (ADHD) have been studied in ASD: they have modest efficacy on symptoms such as hyperactivity (methylphenidate, dextroamphetamine, atomoxetine) and irritability (clonidine).

Newer ASD experimental pharmacotherapies target core ASD symptoms and are developed on the basis of knowledge of the molecular neurobiology and genetics of ASD.

One group of such drugs aims to restore the balance of excitation and inhibition in brain cortical regions. They include those targeting metabotropic glutamate receptors (such as mGlu5 antagonists), NMDA receptors (such as the NMDA receptor antagonist memantine), or AMPA receptors (such as

AMPA receptor potentiating drugs, ampakines)[4]. mGlu5 antagonists have been tested in ASD associated with fragile X syndrome, and showed promise in a subgroup of patients[5]. GABAergic agents, such as the GABA-B receptor agonist arbaclofen (STX209), have shown some effect on irritability and social withdrawal in ASD children[6].

The peptide hormone oxytocin is important in social cognition and behavior. In ASD adults, acute intravenous administration of oxytocin reduced repetitive behaviors[7] and improved accuracy of recognizing emotions in speech over time[8]. Intranasal administration improved social cognition in children, adolescents and adults with ASD[9]. A vasopressin 1a receptor antagonist had some effect on speech recognition of emotions such as fear and lust in high-functioning ASD adults.

Insulin-like growth factor 1 (IGF-1) is important in central nervous system maturation, development and connectivity, that are perturbed in ASD. Studies in Shank-3 deficient mice that model Phelan-McDermid syndrome (PMS), which may be associated with some cases of ASD, indicated that IGF-1 may reverse structural changes in ionotropic glutamate receptors, functional synaptic plasticity changes, and excitation/inhibition imbalance. A clinical trial with recombinant human IGF-1 in PMS children showed improvement in social impairment and restricted behaviors[10].

Agents modulating the immune system have been tested in ASD. The immune response induced by the whipworm Trichuris suis ova has shown benefit on the repetitive behavior domain in adult ASD. Immunosuppressive and protein synthesis inhibiting drugs such as the mTOR inhibitor rapamycin have been shown to improve social deficits in some forms of ASD.

The alpha-7 nicotinic acetylcholine receptor (nACR) gene is associated with autism and ADHD. nACR drugs tested in clinical trials include mecamylamine, transdermally administered nicotine, and donepezil. Some alpha-7 nACR antagonists such as galantamine have shown promise in animal models and clinical trials.

Drugs modulating the cannabinoid system, such as cannabidiol, have been found effective in childhood epilepsy, and may be worth studying in ASD due to their anti-anxiety, anti-epileptic, immunomodulating and cognitive-enhancing effects and good safety. Interestingly, social reward and oxytocin induce release of endocannabinoids in nucleus accumbens. In ASD animal models, cannabidiol has some impact on social deficits, repetitive behaviors and irritability.

Complementary and alternative medicine (CAM) treatments have been tested in ASD. However, they are not strictly regulated and have not been studied in large-scale clinical trials. Therefore, their safety and efficacy is not well determined. CAM treatments may complement rather than replace proven therapies for ASD. Melatonin may be used for sleep disorders, omega-3 fatty acids for reducing repetitive behaviors and improving sociability. Vitamin B12 supplements are believed to protect against the oxidative damage in ASD. Curcumin, an active ingredient of turmeric, may be beneficial in ASD, perhaps owing to its anti-oxidant and anti-inflammatory properties. Probiotics such as yogurt may have effects on the gut microbiome and on pro-inflammatory cytokines that may play a role in the pathogenesis of ASD.

In summary, the enormous heterogeneity in ASD complicates development of new pharmacotherapies. Personalized treatments are desirable, and studies of syndromal orphan populations may accelerate drug development. Design of future clinical trials needs to address patient stratification on the basis of biomarkers or etiology (for example, immune-inflammatory) and target populations stratified by clinical symptoms.

New pharmacotherapies such as oxytocin/vasopressin antagonists, anti-inflammatory agents, IGF-1, drugs regulating excitation/inhibition balance, protein synthesis inhibitors, and microbiome-targeting drugs may be of particular promise. Existing drugs such as anticonvulsants, SSRIs and atypical antipsychotics may be beneficial in some patients. It is important to test the effectiveness of drugs in younger children who may benefit most from early intervention. The ultimate goal of ASD pharmacotherapy will be to match the treatment to the underlying molecular mechanisms in individual patients.

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Nonmedical use of prescription drugs in adolescents and young adults: not just a Western phenomenon

Nonmedical prescription drug use, generally defined as use without a prescription or use for reasons other than what the medication is intended for, is a global concern, primarily driven by the high and rising phenomenon of nonmedical use of prescription opioids in young populations. Prescription drugs are legal and hence tend to be more easily available than most illegal drugs.

Nonmedical use merits particular attention given the high degree of abuse potential[1] and numerous ill-health consequences, that vary depending on the drug. Nonmedical use of prescription stimulants can lead to irregular heart rate, hypertension, cardiovascular system failure, stroke and seizures, while nonmedical use of prescription opioids can cause respiratory suppression and overdose[2]. Most of drug-related deaths worldwide are due to either prescription opioid or heroin overdoses. A recent review has illustrated worldwide increased rates of deaths from prescription opioids[3], with the exception of Australia. In Europe, prescription opioids account for three-quarter of overdose deaths, which represent 3.5% of total deaths among 15-39 year olds.

Nonmedical use of stimulants and prescription opioids among adolescents and young adults has also been linked to increased harmful use of other substances[4], reporting of psychiatric symptoms, psychiatric disorders and suicidal ideation[5].

Despite the undisputed worldwide concern, it is important to note the variability in the prevalence/patterns of nonmedical use of prescription drugs among young people. In the US, according to the 2014 National Survey on Drug Use and Health, past-year nonmedical use of prescription drugs (opioids, stimulants, tranquilizers and sedatives) was reported by 6.2% of 12-17 year-olds and 11.8% of 18-25 year-olds, mainly driven by nonmedical use of prescription opioids, which has remained stable in the past decade despite rising trends since the late 1990s. Data from the 2012 Canadian Alcohol and Drug Use Monitoring Survey showed that 4.9% of 15-24 year olds were past-year nonmedical users of the above cited prescription drug classes. Data from the 2013 Australian National Household Survey showed an increase in nonmedical use of prescription drugs since 1998, particularly among 14-19 year olds; the 2013 past-year estimates were 4% among 14-19 year olds, and 5.8% among 20-29 year olds. While comparability is hindered by the varying methodologies, definitions, and age categorizations, data clearly supports the global concern for the nonmedical use of prescription drugs among young vulnerable populations.

General household population data among young populations in other countries are not as readily available, but there is data from school-based and college-based surveys in Europe, Latin America, Asia and the Middle East. In Europe, data from 36 countries collected as part of the 2011 European School Survey Project on Alcohol and other Drugs showed that, on average, 6% of European school students (mean age of 15.8 years) reported lifetime nonmedical use of tranquilizers (data on other drug classes are unavailable).

Data on high school or university students from the Middle East or Arab world indicate that nonmedical use of prescription drugs warrants closer attention. In Beirut, Lebanon, past-year nonmedical use of any prescription drugs was 21.6% among private university students, and 10% among high school students. In both populations, prescription opioids were the drugs most commonly used nonmedically. In Saudi Arabia, a recent school-based survey showed a lifetime prevalence of 7.2% for the nonmedical use of any prescription drug.

In Brazil, the most recent national school-based survey, conducted in 2010, showed that the past-year prevalence of nonmedical use of prescription stimulants among middle/high school students in public and private schools was 1.6% and 2.2%, respectively. Only lifetime data on nonmedical prescription opioid use was collected (0.3% of all middle/high school students). One study from Southern China conducted in 2007-2009 revealed that 6% of the middle/high school students had tried any prescription medication nonmedically, mostly opioids, followed by cough medicine with codeine. A 2012 high school survey from Chongqing, China reported a lifetime prevalence of 11.3% for the nonmedical use of prescription opioids only. For comparison purposes, data from the 2015 US Monitoring the Future school and college-based surveys showed that 12.8% of 12th graders used any prescription drugs nonmedically.

It is important to shed light on important socio-demographic differences. College-based studies exclude significant proportions of minority or low socio-economic status young adults, who are at higher risk of developing a prescription drug use disorder once they start using the drugs. Evidence on gender differences among adolescents and young adults has been mixed: some studies have found no difference; others have found a higher prevalence in males or in females[6,7]. Early age of initiation of nonmedical use has been associated with higher likelihood of ill-health outcomes, including a higher probability of developing substance use disorders[8]. Individuals with previous nonmedical use of prescription opioids may be at greater risk of heroin use and heroin dependence[9]. Motives for nonmedical use also vary (i.e., to get high; to self-medicate), leading to the presence of several heterogeneous subgroups of nonmedical users that are at varying risks of other substance use[10].

Worldwide comparisons are hampered by the variations in the study methodologies, including definitions of nonmedical use or prescription drugs included. The impact is also different given the varied availability and cultural acceptance of the drugs worldwide. Prescription drug monitoring programs, recently implemented in the US, Canada and Australia, are not widely available globally and, where available, there is unevenness in how they operate. Today, the biggest challenge is balancing a country's need to make available prescription drugs to those in need (i.e., those with chronic pain) while simultaneously curbing diversion and nonmedical use. Pharmacists in some countries struggle between providing medical advice and service to those who cannot afford a doctor's prescription while meeting the requirements of their governmental regulations. Another challenge is controlling the top most reported sources of supply, including parents, doctors and friends, highlighting the need to target multiple sources simultaneously.

The greater "social acceptance" for using these medications (versus illegal substances) and the misconception that they

are "safe" may be contributing factors to their misuse. Hence, a major target for intervention is the general public, including parents and youth, who must be better informed about the negative consequences of sharing with others medications prescribed for their own ailments. Equally important is the improved training of medical practitioners and their staff to better recognize patients at potential risk of developing non-medical use, and to consider potential alternative treatments as well as closely monitor the medications they dispense to these patients.

The United Nations Office of Drugs and Crime is already assisting several governments in collecting epidemiologic data more efficiently as well as developing monitoring and training programs that ensure these drugs are available to those who need them while strictly avoiding diversion for nonmedical purposes.

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The concept of basic symptoms: its scientific and clinical relevance

The concept of basic symptoms originates from retrospective descriptions of the prodromal phase of schizophrenia, published in the first half of the 20th century and continuously developed through its second half[1]. It was not until the mid 1990s, however, that basic symptoms attracted a broad attention within two main lines of research: an empirical approach to early detection of psychosis[2] and a heuristic approach to define the Gestalt of schizophrenia by so-called "self-disorders"[3].

Basic symptoms are subtle, subjectively experienced disturbances in mental processes including thinking, speech, attention, perception, drive, stress tolerance, and affect[1,2,4]. Following training, they can be reliably assessed with a clinical interview from age 8 onwards using the youth and adult version of the Schizophrenia Proneness Instrument[5,6] (available at www.basicsymptoms.org). They have been reported in all stages of psychotic disorders, including prodromes and acute states of first episode and relapse, as well as residual states[1,2,4].

Basic symptoms are regarded as an immediate symptomatic expression of the neurobiological processes underlying psychosis and the earliest form of self-experienced symptoms – hence the term "basic". In contrast, attenuated and overt psychotic symptoms are assumed to develop later, as a result of poor coping with initial symptoms, such as basic symptoms, or stressors, when a vulnerable individual's protective mechanisms are overstrained[1,4]. With its focus on the emerging disorder, the concept of basic symptoms has been linked to a better understanding of the origins of psychoses, in particular schizophrenia, and to an improvement of their (early) diagnosis and treatment.

Initially, two criteria for the identification of basic symptoms were developed: cognitive-perceptive basic symptoms (COPER) and cognitive disturbances (COGDIS)[1,2,4]. COGDIS requires two of nine cognitive basic symptoms to occur at least once per week and is increasingly used as a clinical high-risk criterion in addition to ultra-high risk criteria[2,7]. The first meta-analysis comparing various clinical high-risk criteria found pooled conversion rates in COGDIS-defined samples of up to 61% at follow-ups of more than four years. Medium- and long-term pooled conversion rates of COGDIS samples were significantly higher than those of ultra-high risk criteria samples[7]. Thus, the European Psychiatric Association recommended ultra-high risk criteria and COGDIS to be used alternatively for psychosis risk assessment[7]. However, the presence of both COGDIS and ultra-high risk criteria appears to increase psychosis predictability compared to either criterion alone[2].

In spite of their neurobiological conceptual foundation, basic symptoms have only recently been considered in neurobiological studies of psychosis. Several correlates of these symptoms in psychotic and clinical high-risk individuals have been reported. These included changes in event-related potentials, neural oscillations, neurotransmitter systems, and large-scale networks as assessed with functional magnetic resonance imaging[4]. However, there is a need for further studies in clinical and non-clinical samples exploring the neurobiological correlates of individual basic symptoms and their relevance to the development of psychosis[4].

The basic symptoms concept has informed research on alterations of the very experience of the self as a core feature of schizophrenia[3,8]. Within this line of research, basic symptoms are an integral part of the so-called "anomalous self-experiences", "(basic) self-disturbances" or "self-disorders"[3]. Starting with E. Bleuler's characterization of schizophrenia as "a loss of unity of the personality", self-disturbances have always had a central role in the concept of schizophrenia, being explored by authors such as Minkowski and Blankenburg. Currently, alterations in self-disturbances, including the "development of an integrated sense of self" are believed to have common underlying neurobiological mechanisms[8]. Basic symptoms offer an empirical approach to test related hypotheses, such as perceptual incoherence or

progressive neurodevelopmental alterations (e.g., aberrant synaptic pruning) affecting the "neural circuitry of self"[8].

Another fundamental objective of research on basic symptoms has been to gain a better understanding of residual states. The assessment of basic symptoms can help evaluate the level of remission and guide treatment through combinations of pharmacological, psychological and rehabilitative interventions. Furthermore, treatment compliance might be improved by relating therapeutic strategies to basic symptoms that are self-recognized as deviations from "normal" mental processes. Finally, the recognition of basic symptoms can help educate patients and their families about the manifestation of psychosis and the expected changes that occur in the disorder, which is an important step towards stripping fear and unpredictability from "madness"[1,9].

In summary, the concept of basic symptoms has recently started to reveal its potential in psychosis research. So far, it is mainly recognized for its contribution to early psychosis detection and exploration of self-disorders as the assumed core Gestalt of schizophrenia. Deeper insight into the neurobiological origins of psychosis using the concept is only just emerging and will depend on its reliable assessment.

The benefit of the concept to psychosis treatment has unfortunately not been explored systematically. Furthermore, although basic symptoms are perceived as an integral part of psychotic disorders, several of them may also occur in other mental disorders, in particular organic and mood disorders[10]. However, the utility of the assessment of these symptoms outside the psychosis field has not yet been investigated. Thus, in many ways, the full potential of the concept remains unexplored.

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A renewed call for international representation in editorial boards of international psychiatry journals

In a 2003 letter to *The Lancet*, Saxena et al[1] reported on the international nature of the editorial and advisory boards of the top ten general psychiatry journals (excluding those focused primarily on biological psychiatry). They noted that "most journals claim to be international", but found that the actual journal leadership was overwhelmingly from high-income and Western countries. Only four editorial or advisory board members were from low- and middle-income countries (LMICs) across the top ten journals. The authors deemed this an "unsatisfactory situation" of underrepresentation and called for increased LMIC presence in those leading international journals. Subsequently, similar observations were made for other areas of medicine[2-4], including an editorial in *The Lancet* questioning whether "widespread systemic bias" in medical journals exemplified "institutional racism" in medicine[5].

Where do we stand now? Hoping to find an improvement in LMIC representation, we reviewed the editorial and advisory boards of the top ten psychiatry journals, ranked by impact factor, in 2016. Given the evolution of journal content, we included the top ten journals by ranking without regard to emphasis. This resulted in the additional inclusion of *World Psychiatry* (founded in 2002), *Molecular Psychiatry*, *Biological Psychiatry*, and *Psychotherapy and Psychosomatic*s, as well as the exclusion of *Journal of Clinical Psychiatry*, *Schizophrenia Research*, *Psychological Medicine*, and *Psychosomatic Medicine*. Consistent with the methodology of Saxena et al[1], we used the most recent World Bank country income groupings[6] to identify editorial and advisory board members from LMICs.

Our search revealed minimal improvement: 21 editorial board members from LMICs out of a total of 607 (3.46%) in 2016, as compared to 4 out of 470 (0.85%) in 2003. Although this is a small step in the right direction, the increase is largely due to *World Psychiatry*, which alone has ten LMIC members out of 31 editorial board members (32.26%). Among the remaining nine journals, LMIC representation is 11/576 (1.91%). In contrast, more than 80% of the world population lives in LMICs[6]. Clearly, the situation remains unsatisfactory – indeed, unacceptable.

We must address serious inequities as a field if we are to fully advance a global understanding of mental health, and scientific journals provide a critical leadership function. While the publication process is meritocratic in theory, lack of global representation in editorial boards represents a systemic disparity that may perpetuate a limited understanding of international issues, as well as a limited access and guidance for individuals from LMICs. This guidance could facilitate the capacity building necessary to increase research activity aligned with the global standards of those journals. Indeed, it has been reported that "the gap in scientific publications between low-income countries and the rest of the world has widened"[7] and "only about 6% (or less) of [mental health] publications are from low- and middle- income countries"[8]. More diversity among editorial board members can also help to ensure that published research accurately incorporates and represents data from LMICs through better understanding of the communities from which the data are drawn.

The lack of representation of LMICs in leadership positions is not unique to scientific journals. The most recent Egon Zehnder Global Board Index[9], an assessment that tracks and evaluates trends among US Standard and Poor's 500 companies in terms of board composition, global capability, and business performance, noted in 2014 that while 37% of the revenue of those companies comes from international sources, a mere 7.2% of the directors are foreign nationals. This has led to the development of the Board Global Capability Gap, a measure of the difference between global representation in the boardroom and global footprint of each company, intended to promote board membership that is more closely aligned with the current business market. An analogous metric for scientific journals could serve as an effective tool to help promote LMIC representation in editorial leadership.

Successful engagement of individuals from LMICs in editorial boards will require focused attention and intention. Possible steps for scientific journals include: a) setting a minimum goal of having at least 10% of editorial board members from LMICs by 2018; b) including a minimum number of members from LMICs of each of the World Health Organization (WHO) regions; c) inviting experts from LMICs to serve as guest editors for special sections throughout the course of the year; and d) developing a mentorship program to build capacity in editorial skills among individuals from LMICs. This may require journals to increase the number of members in their editorial boards or consider term limits to make room for increased diversity among their membership. The WHO can facilitate this process by identifying suitable advisors from LMICs and working with journals and editors to establish suitable training and mentorship opportunities[10].

It has been over 13 years since the first call to action for greater diversity of membership in the top editorial and advisory boards in our field. Global leaders are entrusted with the responsibility to use their positions of influence to set an example, and the world's premier international psychiatry journals are poised to demonstrate such leadership. Progress is long overdue, but it is achievable. The time to start is now.

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The relationship of subjective social status to mental health in South Korean adults

South Korea has witnessed an unprecedented rise in suicide rates following the 1997 Asian financial crisis. Unfortunately, the rate has not decreased and still remains the highest among the 34 countries which are part of the Organization for Economic Co-operation and Development (OECD).

Several researchers[1,2] have suggested that, in high-income countries, it is no longer the absolute level of one's socioeconomic status (SES) that is most important for health, but rather inequality or a sense of inequality. A number of studies have been undertaken to examine the relationship of inequality (at the country level) or a sense of inequality (at the individual level) to health. Some of these studies have focused on subjective SES, which measures one's perception of his/her own position in the social hierarchy[3].

We aimed to examine how both objective and subjective SES are related to mental health problems (suicidal ideation, depressive symptoms and psychological distress) in South Korea, using data from the 2013 Korea Health Panel survey. Subjective SES was measured using the MacArthur scale, a 10-rung ladder on which individuals indicate their perceived standing in the social hierarchy[1]. The assessment of suicidal ideation and depression was based on self-report ("yes" versus "no" in the past 12 months). Psychological distress in the past month was assessed using the Korean version of the Brief Encounter Psychosocial Instrument (BEPSI-K)[4]. A score $\geq$2.4 was defined as "severe stress". Of the 16,313 respondents aged 19 years or older, the 14,432 who had no missing data were included in this analysis. All data were weighted to represent the structure of the Korean population.

Of the 14,432 participants, 5.4% and 7.2% had suicidal ideation and depression, respectively, in the past 12 months, and 13.6% had severe psychological distress in the past month. A clear social gradient was found in the prevalence of these mental health problems, especially when SES was measured subjectively (subjective SES) rather than objectively (income quintile) ($p<0.001$). Notably, this pattern was more apparent in the case of severe psychological distress. Of those with the lowest subjective SES (i.e., a rating of 1 on the 10-rung ladder), nearly one in three (29.6%) reported the experience of severe psychological distress in the past month, while only 7.2% reported the same experience among those with the highest subjective SES (i.e., a rating $\geq$5). The equivalent rates were 19.3% in the lowest income quintile and 10.2% in the highest income quintile.

The associations with subjective SES appeared to far outweigh those with conventional measures of SES when considering both in logistic regression models. Subjective SES was the only factor that was consistently associated with any type of mental health problems. For instance, compared to the respondents with the lowest subjective SES (i.e., a rating of 1 on the 10-rung ladder), those with higher subjective SES were much less likely to report suicidal ideation (OR=0.60 in the group with a rating of 2, OR=0.40 in those with a rating of 3, OR=0.24 in those with a rating of 4, and OR=0.20 in respondents with a rating $\geq$5; $p<0.001$ for all). The same applied to depression (OR=0.50, 0.38, 0.26, and 0.20; $p<0.001$ for all), and severe psychological distress (OR=0.52, 0.32, 0.25, and 0.19; $p<0.001$ for all). Associations with objective SES measures (education, employment status, income quintiles) were infrequently observed.

Previous studies have shown that the strength of the association between subjective SES and health varies across countries[5]. Contextual factors such as social structure and culture are likely to strengthen or weaken the association between the two. What factors might then have strengthened the relationship between subjective SES and mental health in South Korea?

This country achieved rapid economic growth while maintaining a relatively equitable income distribution up until the mid-1990s. However, it fell into a severe recession following the 1997 Asian financial crisis, which in turn served as a major turning point in the Korean society. Massive structural reforms were undertaken to promote economic productivity and globalization. These reforms have had a significant impact on the labour market, increasing labour flexibility and job insecurity. As a result, the labor market has become highly segmented between regular and non-regular workers. Income inequality has also worsened since the 1997 crisis, despite the resurgence of economic growth (the average gross domestic product increased by 5.4% between 1999 and 2010[6]). The average Gini coefficient, a measure of income inequality, was 0.258 in the period 1990-1995, but increased to 0.298 in 1999 and peaked at 0.320 in 2009[7].

Concomitant to these social changes, a limited number of studies have demonstrated a worsening trend of SES-related inequalities in health. For example, our study published in this journal in 2011[8] showed a widening income-related inequality in the prevalence of depression and suicidal behaviour over the 1998-2007 period. Nevertheless, our current finding of a strong

link between subjective SES and mental health, above and beyond conventional measures of SES, suggests that some aspects of social changes which are strongly associated with mental health have not been fully captured by those conventional measures.

Some scholars have argued that income inequality and social polarization can heighten an individual's sense of relative deprivation, resulting in frustration, anger and resentment[2]. Our data suggest that how much one believes he/she has compared to others is more relevant than how much one actually has in understanding mental health problems in contemporary Korea. These findings may offer some lessons for the countries experiencing similar economic and social changes.

Further research is needed to better understand how subjective social status is formed and what mechanisms underlie the strong link between subjective social status and mental health problems.

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Nonsuicidal self-injury in men: a serious problem that has been overlooked for too long

Nonsuicidal self-injury (NSSI) refers to the act of deliberately destroying one's own body tissue without conscious intent to die and for reasons that are not socially sanctioned[1-3]. Common methods include cutting, scratching, and burning oneself. It is estimated that around 6% of adults in the general population have engaged in NSSI at least once during their lifetime[2]. While once thought to occur primarily within the context of borderline personality disorder, contemporary research demonstrates that NSSI is a transdiagnostic condition which is associated with significant functional impairment[3]. As a result, NSSI disorder has been included in DSM-5 as a condition for further study.

By definition, the function of NSSI is different from that of suicidal behavior, where the goal is to end one's life. The most common reason that patients provide for engaging in NSSI is that they believe that it helps them to regulate their emotions. Other commonly alleged reasons include self-punishment, physiological stimulation, and communication with others[1,2]. Although NSSI and suicidal behavior are clearly distinct, increasing evidence suggests that NSSI is a significant risk factor for suicidal behavior. NSSI is more strongly associated with history of suicide attempts than impulsivity, depression, anxiety, and borderline personality disorder. Actually, NSSI is a stronger prospective predictor of suicide attempts than history of suicide attempts[4-6].

Despite the significant implications that NSSI has for patients' health, well-being, and risk for suicide, this important clinical condition has been largely overlooked among men. This lack of attention is due in large part to the historical viewpoint that NSSI is far more common among females than males[7]. However, contemporary population-based studies of NSSI have consistently failed to find evidence for sex differences in rates of NSSI among adults[2,8]. A recent meta-analysis including many clinical studies concluded that "women are slightly more likely than men to engage in NSSI", but the overall rate of NSSI identified among males (26.36%) was still remarkably high[9].

In that meta-analysis, the observed sex difference appears to have been largely driven by the inclusion of clinical samples. The discrepancy in sex differences observed between clinical and population-based studies of NSSI may be due to the fact that women are more likely to seek out psychiatric treatment than men[9]. Sample selection practices might also help to explain this discrepancy, as clinical settings that have a preponderance of male patients (e.g., veterans' hospitals) are likely to be under-utilized in NSSI research. In support of this view, we found that 57% of male veterans seeking treatment for post-traumatic stress disorder reported a history of NSSI[10], suggesting that men who are actively seeking treatment for psychiatric issues may be just as likely as women to engage in NSSI.

Sex differences in the expression of NSSI could also affect prevalence estimates. The above-mentioned meta-analysis explored sex differences in NSSI methods and found that females were more likely than males to engage in cutting, biting, scratching, and hair pulling[9]. Wall/object punching was not included among the twelve NSSI methods considered in the meta-analysis. However, Whitlock et al[1] reported that wall/object punching is the single most common form of NSSI endorsed by college-aged men. Moreover, males who self-injure are significantly more likely to engage in wall/object punching than females who self-injure (44% vs. 19%, $p<0.001$).

Such findings are critically important, because the vast majority of NSSI research has not examined wall/object

punching as a possible NSSI method. Thus, it is entirely possible that the systematic exclusion of one of the most common NSSI methods for males to use has resulted in a significant underestimate of the true prevalence of NSSI among men. More importantly, the failure to include wall/object punching and other forms of NSSI in standard psychiatric risk assessment batteries has likely resulted in many individuals (particularly men) who engage in NSSI not being properly identified and treated, despite the fact that NSSI is one of the strongest predictors of suicide attempts identified to date.

In sum, NSSI is common among men and associated with high levels of clinical distress, significant functional impairment, and increased risk for suicide attempts. It is possible that prior research has underestimated the true prevalence of NSSI in men due to biased selection and assessment methods. It is time for clinicians and researchers to recognize that NSSI is a serious problem that warrants careful investigation in both men and women.

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5-HTTLPR and DISC1 risk genotypes for elevated PTSD symptoms in US military veterans

The serotonin transporter linked polymorphic region (5-HTTLPR) genotype is a candidate vulnerability factor for post-traumatic stress disorder (PTSD). Recently, Telch et al[1] reported in this journal that the 5HTTLPR-S' variant was associated with elevated levels of PTSD symptoms in military personnel deployed to Iraq, supporting similar findings in deployed military personnel by our group[2]. Variants in several other genes have been associated with greater severity of PTSD symptoms in civilian populations. In a further study, we screened a panel of nine candidate genetic variants with potential to influence the development of PTSD in veterans deployed in support of the wars in Afghanistan and Iraq.

Study subjects were male US military veterans registered to receive health care at the Central Texas Veterans Health Care System. The local institutional review board approved and monitored the study. Subjects who did not have a chart diagnosis of schizophrenia or bipolar disorder and who provided informed consent were enrolled in the study independent of their mental health status. Recruitment took place in a variety of venues, including the main lobby of the hospital and mental health waiting rooms.

Participants (N=102) completed the Impact of Events Scale Revised (IES) and donated saliva for genetic research. The IES has been increasingly used as a self-report instrument to assess current PTSD symptom severity. It yields a total symptom severity score and three psychologically and biologically relevant sub-factor scores: avoidance, intrusion and hyperarousal. Saliva samples were collected with Oragene DNA collection kits (DNA Genotek, Ottawa, Canada), and genomic DNA was extracted and purified.

5-HTTLPR genotyping was accomplished with a triplex/double digestion PCR protocol[2]. Alleles were re-classified using rs25531 into the triallelic classification. A Taqman SNP panel for COMT (rs4680), FKBP5 (rs1360780), DTNBP1 (rs9370822), PACAP receptor ADCYAP1R1 (rs2267735), 5-HT1A (rs6295), DISC1 S704C (rs821616), BDNF val66met (rs6265) and NTRK1 (rs6336) was performed using ABI TaqMan SNP Genotyping Assays (Applied Biosystems, Inc., Foster City, CA) on ABI PRISM 7900 HT Sequence Detection System (Applied Biosystems). Distributions did not vary from Hardy-Weinberg equilibrium (all p values >0.05).

Stepwise regression modeling identified two genetic variants that significantly contributed to variance in PTSD symptoms: 5-HTTLPR and DISC1 S704C. Risk genotypes selected by the regression (model cumulative $R^2=0.30$) were 5-HTTLPR-S' carriers (vs. 5-HTTLPR-L'L'; $p<0.031$) and DISC1 TT (vs. A carriers; $p<0.034$). The next closest gene to significance in the model was NTRK1 ($p<0.11$). When the stepwise procedure was repeated after removing 5-HTTLPR and DISC1, no other variant significantly contributed to PTSD symptom load. The

two genetic variants continued to be significant factors in the ANCOVA analysis, which included age and education as covariates. The model also remained significant in a follow-up analysis in which participants who identified as African-American (N=15) were excluded.

Carriers of the 5HTTLPR-S' allele had increased PTSD symptoms compared to individuals homozygous for the L' allele (IES mean score: L'L'=47.3 ± 5.3, S=59.8 ± 4.1). For DISC1, individuals homozygous for the T allele had increased PTSD symptoms compared to A carriers (A=45.3 ± 2.8, TT=61.9 ± 7.2). In ANCOVA analysis of symptom sub-factors, 5-HTTLPR and DISC1 selectively influenced intrusion and hypervigilance symptoms, but did not affect avoidance symptoms. PTSD symptom severity (total IES scores) increased by an average of 40% with each risk genotype (none=38.4, one=54.5, two=65.6).

These data support prior observations of 5-HTTLPR effects on PTSD symptoms in military veterans[1,2]. Although 5-HTTLPR has been identified as a potential contributor to PTSD susceptibility in civilian-based populations, its effect may be less robust in those populations, due to lower overall level of trauma exposure[3]. The effects of 5-HTTLPR on PTSD in military veterans after deployment to a war zone may be more robust because of a universal and constant exposure to threat, military training, and/or separation from family and home social support.

In addition to 5-HTTLPR, genetic variation in DISC1, a gene associated with susceptibility to multiple mental disorders, was found to contribute to PTSD symptom severity. Possessing both DISC1 and 5-HTTLPR risk genotypes resulted in a 1.7-fold increase in PTSD symptoms. Although this is the first report of DISC1 S704C TT allele as a risk factor for PTSD, the finding is not surprising, considering that this allele has been identified as a risk factor for major depression[4]. DISC1 variants interfere with a protein complex important for organelle transport and in tethering of mitochondria, interfering with dendritic development and reducing densities of dendritic spines in the frontal cortex, paralleling our recent report of spine density reductions in the frontal cortex in PTSD[5-7].

This study was powered to screen for candidate genes with relatively large effect sizes on PTSD symptoms in combat veterans, which may be different from sets of genes affecting PTSD in civilian populations. Study of the serotonin system in PTSD is motivated in large part by the therapeutic utility of serotonin uptake inhibitors to treat symptoms of PTSD. Our data provide additional impetus for continued study of this system in PTSD pharmacotherapy. In addition, antipsychotics such as risperidone have been shown to reverse DISC1-related behavioral deficits and pathophysiology in animal models, suggesting the possibility that such agents could be re-examined for use as alternative pharmacotherapies for PTSD[8,9].

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Cardiovascular risk and incidence of depression in young and older adults: evidence from the SUN cohort study

Cardiovascular disease (CVD) and depression are two leading causes of disability worldwide[1] and frequently co-occur. A higher load of cardiovascular risk factors without the presence of CVD may imply a higher risk of depression. To assess this hypothesis we evaluated the relationship between the predicted absolute cardiovascular risk and the subsequent observed incidence of depression. In a cohort of university graduates, the Seguimiento Universidad de Navarra (SUN) Project[2], we followed 16,739 participants (mean age: 38 years), initially free of depression and CVD, up to 14 years (mean follow-up 9 years).

Cardiovascular risk was estimated using a logistic regression model in which the incidence of CVD (myocardial infarction, stroke, and death from cardiovascular causes) during follow-up was the dependent variable, and age (linear and quadratic terms), sex, body mass index (linear and quadratic terms), smoking (never, current, former), type 2 diabetes, hypertension, hypercholesterolemia and hypertriglyceridemia were the independent variables. Once we had obtained the predicted probabilities of CVD (theoretically ranging from 0 to 100%), we categorized these estimated probabilities into sex-specific

quintiles. We assessed incident depression through the self-report of a medical diagnosis during follow-up. This definition had been previously validated[3].

We estimated hazard ratios (HRs) and 95% confidence intervals (95% CIs) of depression across sex-specific quintiles of predicted CVD risk. Models were adjusted for age, adherence to the Mediterranean dietary pattern (low/moderate/high), physical activity (quintiles), total energy intake (quintiles), menopause due to natural causes (yes/no), living alone (yes/no), employment status (employed, unemployed, retired), marital status (married or not), and personality traits (competitiveness, relaxation, dependence).

Over 151,125 person-years of follow-up, we identified 927 incident cases of depression. A higher predicted cardiovascular risk at baseline was significantly associated with higher risk of depression. Young adult participants (<40 years) in the highest quintile of CVD risk (mean risk: 0.30%) presented an adjusted HR of 1.47 (95% CI: 1.08-2.00) compared to those in the lowest quintile (mean risk: 0.05%). The second, third and fourth quintiles presented non-significant HRs of 1.05, 1.21, and 1.16, respectively. This association was even stronger for older participants (≥40 years): 1.65 (1.17-2.34) for the second quintile (mean risk: 0.54%), 1.68 (1.16-2.42) for the third quintile (mean risk: 0.85%), 1.85 (1.24-2.75) for the fourth quintile (mean risk: 1.43%), and 2.17 (1.33-3.54) for the fifth quintile (mean risk: 4.31%), all of them compared to the first quintile (mean risk: 0.31%).

So, a higher predicted CVD risk was strongly associated with a higher future incidence of depression, both in younger and older adults. This finding may support the hypothesis that CVD and depression share common pathophysiological mechanisms[4-6]. As an alternative, depression and CVD may share risk factors but not the mechanisms through which these risk factors act. Actually, there is a growing body of research on the bi-directional relationship between depression and metabolic syndrome[7], obesity[8] or type 2 diabetes[9].

The clinical implications of our findings are of great importance for public health and clinical practice. First, public health agencies may consider sharing efforts for the primary prevention of both depression and CVD, which may be synergic. Both CVD and depression are associated with a set of known and modifiable risk factors that it is worth to target from a public health perspective. Second, general practitioners should consider that both older and younger patients at higher risk of CVD may also be at higher risk of depression. Physicians can calculate the predicted cardiovascular risk using the Framingham risk score or other similar equations which are available in charts and user-friendly versions. Their interventions addressed to obtain improvements in these equations through changes in lifestyle are likely to also be an appropriate approach for the prevention of depression.

Finally, the knowledge that lifestyle factors are not only increasing the risk of CVD but also that of depression, even at younger ages, needs to reach the general public. This take-home message may be useful to achieve greater changes in unhealthy habits throughout the life cycle in the population at large.

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Depressive symptom profiles and glucose tolerance status

Depression is known to be two to three times more prevalent among individuals who have diabetes than among those without it[1]. The conventional hypothesis suggests that the higher prevalence of depression among individuals with diabetes is a consequence of the psychological distress created by the diagnosis, namely its stigmatizing effects and the long-term complications. However, there is contradictory evidence that an association can also be observed between insulin resistance and depression among individuals without diabetes[2]. To address this inconsistency, three recent reviews[3-5], including one published in this journal[5], have called for greater precision in studies, proposing that specific depression profiles (e.g., atypical depression) should be further investigated.

We conducted a population-level investigation on the importance of atypical and non-atypical depressive symptoms in specific pre-diabetic states as well as in previously undiagnosed and diagnosed diabetes mellitus. The 75 g oral glucose tolerance test was used to define each person's glucose tolerance status. Depressive symptom profiles were defined by using the 21-item Beck Depression Inventory (BDI-II). Participants who scored at least 14 points and responded positively (at least one point) to both reversed vegetative symptoms (oversleeping and overeating) were defined as having atypical depressive symptoms[6]. The rest of the participants with at least 14 BDI-II points were defined as having non-atypical depressive symptoms.

In the study sample (N=4838; Northern Finland Birth Cohort

1966 members with written consent who volunteered to participate in clinical examination at the age of 46 years), we found 379 (7.8%) and 74 (1.5%) participants with non-atypical and atypical depressive symptoms, respectively. The prevalence of normal glucose tolerance, defined as having a fasting plasma glucose (FPG) concentration <6.1 mmol/l and a two-hour glucose <7.8 mmol/l, was only 61% among those with atypical depressive symptoms, whereas it was 73% and 79% among those with non-atypical and no depressive symptoms, respectively.

The proportions of all abnormal glucose tolerance states were highest among participants with atypical depressive symptoms. The prevalence of impaired fasting glucose (FPG 6.1-6.9 mmol/l and a two-hour glucose <7.8 mmol/l) among those with atypical, non-atypical and no depressive symptoms was 8%, 7% and 7%, respectively. The corresponding prevalence of impaired glucose tolerance (FPG <7.0 mmol/l and a two-hour glucose of 7.8-11.0 mmol/l) was 15%, 11% and 8%, respectively. The prevalence of previously undiagnosed type 2 diabetes (FPG ≥7.0 mmol/l or a two-hour glucose ≥11.1 mmol/l) was 5%, 3% and 2%, respectively.

Previously diagnosed diabetes was designated if any of the following was observed: self-reported diagnosis of diabetes made by a physician; self-reported medication for diabetes; inpatient or outpatient visit at a hospital due to diabetes (all hospital visits were obtained from the Finnish Care Register for Health Care); or the right to purchase diabetes medication at a subsidized cost (data obtained through national medication registers from the Social Insurance Institution of Finland). The prevalence of previously diagnosed type 2 diabetes was 11%, 6% and 3% among those with atypical, non-atypical and no depressive symptoms, respectively.

Differences in the distribution of glucose tolerance status between depressive symptoms profile groups were statistically significant (Pearson's chi-square test: $F/\chi^2=40.26$, df=10, p=0.00002). Mean body mass index was 30.8 ± 7.5 kg/m^2, 28.0 ± 5.7 kg/m^2 and 26.7 ± 4.7 kg/m^2 among those with atypical depressive symptoms, non-atypical depressive symptoms and no depressive symptoms, respectively (p=0.002, Kruskal-Wallis test, pairwise; atypical vs. non-atypical). The participants self-reported their physical activity, education level, smoking status, alcohol and antidepressant medication use; of these, when tested pairwise, only use of selective serotonin reuptake inhibitors was different among the subtypes (30% for atypical vs. 11% for non-atypical, p=0.0001, Fisher's exact test).

Taken together with previous findings[5,7], our results support the importance of subtyping depression in people with type 2 diabetes, as recently postulated in this journal[5]. The current results also highlight the phenomenon already in pre-diabetic states. We speculate that the results of previous studies on the association between depression and type 2 diabetes might have been different if depression subtypes had been analyzed.

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WPA Position Statement on Recruitment in Psychiatry

The problem of recruitment in psychiatry is universal. There are very few countries where this problem does not exist. Variations have to be seen in the context of health care systems, training options and educational systems.

The World Health Organization has set a target of one psychiatrist per 10,000 population globally. While this target is met in most European countries, North America and Japan, just under half of the world population live in countries with less than one psychiatrist/100,000 population. The rates are extremely low throughout Africa, and low in South America, Southeast Asia and Subcontinental Asia, with high urban-rural disparity.

Despite the relatively high numbers of psychiatrists, many high-income countries are suffering from a perceived "recruitment crisis". In many countries vacancy rates in training posts remain over 10%. To complicate matters further, often international medical graduates who may see psychiatry as popular take up much of the slack, contributing to "brain drain" from their countries of origin.

Who chooses psychiatry, and what influences their choice? Many students choose medicine for the specific purpose of doing psychiatry, but some change their mind during their training. Others see the process through. Some students fall into psychiatry either passively or choose it actively. The reasons are often complex[1-11].

Most of the studies have focused on understanding issues in Europe and the US. As duration of undergraduate training in psychiatry varies from 2 to 8 weeks, it is important to explore and understand these variations. WPA studies have shown that female doctors are slightly more likely to choose psychiatry. A personal or family history of mental illness increases the likelihood of choosing psychiatry.

Medical students with undergraduate exposure to psychology or social sciences are more likely to choose psychiatry. Having a positive experience of psychiatry teaching and placement with clinical activities and exposure to psychotherapy during medical school, and/or additional exposure through clinical electives, also influence the choice of psychiatry.

What factors negatively influence recruitment? A fall in levels of interest in psychiatry during undergraduate training can be attributed to poor exposure to teaching, a lack of psychiatric facilities and limited clinical exposure.

Furthermore, the quality of mental healthcare in many parts of the world is extremely poor, and largely inpatient, with little opportunity for exposure to community-based psychiatry or other specialities. As such, students may be turned off psychiatry by what they witness during placements.

The relative lack of financial reward can also affect career choice. Other factors are stigma against the psychiatric profession and against mental illness in general, resulting in perception of psychiatry as unscientific, ineffective, or apart from mainstream medicine. There is a perceived lack of respect from colleagues in other specialities and a poor public image.

Furthermore, misconceptions and prejudices against the mentally ill themselves may make psychiatry an undesirable proposition. The stereotypes of psychiatric patients being dangerous or unpredictable and chronicity of psychiatric disorders can also put medical students off psychiatry.

How can recruitment be improved?

- By increasing the availability and quality of psychiatric care, especially in low- and middle-income countries (LMICs), with a focus on training in community-based structures.
- By increasing the quantity and quality of psychiatric teaching and clinical attachments within medical schools, especially in LMICs, and making psychiatry an examinable part of the curriculum at par with other specialities. Psychiatry should be an inherent part of medical school curriculum from day one. Integrating physical and mental health teaching with better focus on public mental health is important.
- By reducing stigma against mental illness through public education campaigns and educational projects aimed at school-age students, and by challenging media representation of mental illness and focusing on eliminating discrimination against individuals with mental illness.
- By increasing representation of mental health professionals on medical school interview panels where possible and selecting candidates with attributes likely to guide them towards psychiatry.
- By an increased and better involvement of psychiatrists in medical school curriculum development, healthcare policy development, healthcare lobby groups, and medical accreditation bodies.
- By encouraging and supporting the development of extra-curricular "enrichment" opportunities that give medical students additional teaching and clinical exposure during their training. These may include a psychiatry society or special interest group, elective and residency programmes, early experience programmes, special study modules, using medical humanities in the curriculum and developing local solutions.

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The WPA website: newly designed with state-of-the-art features, carrying out the mission of WPA

Electronic communication is paramount in today's world, its importance rising day by day. The WPA website (www.wpanet.org) has now been thoroughly re-designed with state-of-the-art features and with useful, attractive and up-to-date content, utilizing the latest technology.

The website currently has a responsive design, which means that the size and dimensions of its pages now get automatically modified so as to make them properly fit the screens of various devices like smart phones and tablets[1]. The website is also integrated with Google Translate, which can automatically translate its content to 103 different languages[2]. The site is also integrated with popular social media sites.

The home page prominently displays the latest news from WPA Member Societies, Scientific Sections, Zonal Representatives, and Affiliated Associations. WPA position papers on various issues can be downloaded from the site. Their translations in several languages are also available. Past issues of the WPA Newsletter, from way back in 1997, are available for download. The E-Learning section features more than 30 educational videos of clinically relevant presentations by some of the leaders in psychiatry today. The Public Education Gallery has articles on the most common mental disorders. The Education section features downloadable materials such as the WPA Template for Undergraduate and Graduate Psychiatric Education and the Essentials of the WPA International Guidelines for Diagnostic Assessment.

One of the most popular sections of the website is that including *World Psychiatry*, the WPA official journal. The new impact factor of the journal is 20.205. It ranks now no. 1 among psychiatry journals worldwide! Issues of the journal, from way back in 2002, are provided for free download, along with translations in Spanish, Russian, Japanese, Romanian, French, Polish, Chinese, Turkish and Arabic.

Recent additions to the website include the WPA Position Statements on Spirituality and Religion in Psychiatry[3], on Gender Identity and Same-Sex Orientation, Attraction and Behaviours[4], on Europe Migrant and Refugee Crisis, and on Intimate Partner Violence and Sexual Violence Against Women; as well as the WPA Curriculum on Intimate Partner Violence and Sexual Violence Against Women, and updates on WPA Scientific Sections[5,6] and publications[7,8].

The relevance and attractiveness of the site's contents are proven by the fact that it now has a Google Page Rank of 6, a measure of how many other important websites have provided links to its pages[9].

The usage data from January 1 to October 24, 2016 reveal that the site has been visited from 199 countries and 7023 cities across the world. The total number of visitors has been 67,947, and the total number of page views has been 263,742.

In tune with the changing times, more exposure will be given in the future to the site's content, for both the professional and lay audiences, in the social media[10]. Provision will be developed for live streaming of various WPA programs, so that our activities can reach a much larger audience without delay, and with minimal additional expenses. The WPA Secretary General as the Editor of the website, with the collaboration and help of the WPA Executive Committee and with the assistance of the WPA Secretariat[11], remain committed to this goal.

The future may also involve conducting WPA sponsored self-paced (on-demand) or timed classes on the website. Webinars might also be one area for the WPA to tap into. A low bandwidth live streaming webinar could provide an array of discussions on a topic of relevance from experts in that area. Of potential interest is also the development of a WPA app, which would definitely add to the ease of accessing the contents on the website and also keep the user up to date with the events and news from the world of psychiatry. These are some of our plans for the future!

Roy Abraham Kallivayalil
WPA Secretary General

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Update on WPA Operational Committee on Scientific Publications

The WPA Operational Committee on Scientific Publications has been quite active in the last year, meeting several times via conference call and at various WPA meetings. The WPA has the aim to provide easy access to up-to-date psychiatric information and research for clinicians and researchers from all over the world[1,2]. To achieve this, under the leader-

ship of R. Heun (Royal Derby Hospital, UK), one of the main goals has been to update the WPA website (www.wpanet.org) by providing a list of links to online journals that include peer-reviewed open-access papers. The quality of the content is the responsibility of the authors and the individual journals. The provision of the links is supported by the national psychiatric associations, but it is not an endorsement of the content of the papers and journals. R. Heun and WPA Secretary General R. Kallivayalil have been determining how best to improve the website and make it user-friendly[3]. Thanks to the generosity of P. Chandra (National Institute of Mental Health and Neurosciences, Bangalore, India), a research assistant has been tasked to help with this project.

P. Tyrer (Imperial College London, UK) has had discussions with the UK Royal College of Psychiatrists about making papers from the journals *International Psychiatry, BJP Open* and *Psychiatric Bulletin* linked to the WPA website, and these have been concluded satisfactorily. Discussions are also taking place with the Wiley journal *Personality and Mental Health* over its articles being available as the journal is linked to the Section of Personality Disorders at the WPA[4,5].

C. Szabo (University of Witwatersrand, South Africa) has been involved in coordinating symposia at various WPA meetings (Tbilisi, Georgia; Cape Town, South Africa) related to publishing and publications, with an emphasis on Operational Committee activities in this regard and a specific focus on developing countries. J.M. Castaldelli-Maia (Medical School of Fundação do ABC, Brazil) has also been quite helpful at developing materials for young psychiatrists regarding how to get published and the process of review and mentorship.

A. Cia (University of Buenos Aires, Argentina) has been very successful at developing and building a library of scholarly work that is translated into Spanish. This has been a very ambitious project, supported by the WPA, and has been tremendously appreciated.

Co-Chair D. Lecic Tosevski (Belgrade University School of Medicine, Serbia), within the very successful 15th Congress of Serbian Psychiatric Association (Belgrade, October 12-15, 2016), organized several events targeting young psychiatrists with the aim to discuss how to prepare and publish scientific papers.

We have appreciated the support of WPA President D. Bhugra[6], President-Elect H. Herrman[7], Secretary General R. Kallivayalil, and administrative support from F. Sotgiu and P. Atiase. We appreciate the ongoing support of WPA Past President M. Maj, under whose leadership *World Psychiatry* has become no. 1 among psychiatric journals in terms of impact factor (new value: 20.205), also entering the top 50 of all scientific journals indexed by Thomson Reuters.

Michelle Riba
WPA Secretary for Scientific Publications

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ICD-11 draft diagnostic guidelines open to input by mental health professionals

The World Health Organization (WHO) Department of Mental Health and Substance Abuse has recently created a new Internet platform (http://gcp.network) for members of its Global Clinical Practice Network (GCPN). On this platform, it is possible to find the draft ICD-11 diagnostic guidelines for several mental disorders, which are being used for ICD-11 field trials[1]. These draft guidelines are open to comments by mental health or primary care professionals who have joined the Network.

Several innovations to be introduced in the ICD-11, part of which have been discussed[2-9] or are related to concerns voiced[10-15] in this journal, are visible in these draft guidelines.

Of particular interest is the section "Boundary with other disorders and normality", provided for each grouping of disorders and not present in the ICD-10, which delineates the differential diagnosis between, for instance, schizophrenia and acute and transient psychotic disorder, schizophrenia and psychotic-like symptoms occurring in the general population, delusional disorder and schizophrenia, schizoaffective disorder and mood disorders with psychotic symptoms, depression and normal grief, depression and prolonged grief disorder, bipolar disorder and primary psychotic disorders.

Also noteworthy are the "Qualifiers" introduced for some disorders. In the case of anorexia nervosa, for instance, since severe underweight status is an important prognostic factor associated with high risk of physical complications and substantially increased mortality, qualifiers "with significantly low body weight" and "with dangerously low body weight", anchored to body mass index values, are provided. In the case of schizophrenia and other primary psychotic disorders, symptom qualifiers are introduced to indicate the degree to which positive, negative, depressive, manic, psychomotor and cognitive symptoms are present in the current clinical presentation. For each symptom domain, four degrees of severity are specified, and anchor points provided.

The new grouping of Disorders Specifically Associated With Stress is introduced, including disorders that are directly related to exposure to a stressful or traumatic event, or a series of such events or adverse experiences. The grouping includes post-traumatic stress disorder, complex post-traumatic stress disorder, prolonged grief disorder, adjustment disorder, and other disorder specifically associated with stress. Acute stress reaction is not considered to

be a mental disorder, but rather appears in the ICD-11 section including reasons for clinical encounters that are not diseases or disorders. The category of complex post-traumatic stress disorder, not present in either ICD-10 or DSM-5, is characterized by the three core elements of post-traumatic stress disorder (i.e., re-experiencing the traumatic event(s) in the present, deliberate avoidance of reminders likely to produce this re-experience, and persistent perceptions of heightened current threat) plus severe and pervasive problems in affect regulation; persistent beliefs about oneself as diminished, defeated or worthless; and persistent difficulties in sustaining relationships and in feeling close to others. The category of prolonged grief disorder, not present in the ICD-10 and corresponding to "persistent complex bereavement disorder" included in the section III of DSM-5, is characterized by a pervasive grief response, persisting for an abnormally long period of time following the loss, clearly exceeding expected social or religious norms for the individual's culture and context, and causing significant social impairment.

The grouping of Feeding and Eating Disorders, involving abnormal eating or feeding behaviours that are not better accounted for by another health condition and are not developmentally appropriate or culturally sanctioned, includes the new category of avoidant-restrictive food intake disorder, whose essential features are avoidance or restriction of food intake, characterized by eating an insufficient quantity or variety of food in order to meet adequate energy or nutritional requirements for the individual, leading to significant weight loss (or failure to gain weight) or other impact on physical health, and not reflecting preoccupation with body weight or shape or a significant body image distortion.

Several expected divergences between the ICD-11 and the DSM-5 already discussed in this journal, such as the different characterization of mixed states and schizoaffective disorder and the retention of the one month duration criterion for the diagnosis of schizophrenia, are confirmed in these draft guidelines.

GCPN members are welcome to provide their input on how the draft guidelines can be improved, especially in terms of their clarity and applicability in clinical, research, educational and administrative settings. Comments will be submitted to the ICD-11 Working Groups responsible for the specific areas and to the WHO Secretariat, so that they can be taken into account before the guidelines are finalized.

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