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World Psychiatry

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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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Addressing mental health needs: an integral part of COVID-19 response

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While governments around the world are acting to contain and end this pandemic, the strain on health, social and economic systems in all countries is unprecedented.

Not only is the COVID-19 pandemic a threat to physical health; it also affects mental health. During a crisis it is natural for individuals to feel fear, sadness and anxiety. Indeed, fear from the virus is spreading even faster than the virus itself. In the current crisis, people can be fearful about becoming ill and dying, losing livelihoods and loved ones, and being socially excluded and separated from families and caregivers. People who test positive for COVID-19 have to cope with anxiety about their condition, physical discomfort, separation from loved ones, isolation, and possibly stigma.

Many people in the world are suffering from loss of livelihoods and opportunities. Those who have loved ones affected by COVID-19 are facing worry and separation. Some people turn to alcohol, drugs or potentially addictive behaviours such as gaming and gambling. Domestic violence has increased. Finally, people experiencing the death of a family member due to COVID-19 may not have the opportunity to be physically present in their last moments, or to hold funerals according to their cultural tradition, which may disrupt the grieving process[1].

Frontline workers, particularly health staff, are playing a crucial role in fighting the pandemic and saving lives. They are under exceptional stress, facing increased workloads, and are being confronted with great suffering and high mortality rates. Some are being forced into triage situations that can cause ethical quandaries with traumatic impact. Their stress is compounded by their risk of being infected, as many facilities lack sufficient personal protective equipment. Sadly, social stigma towards those working with people with COVID-19 has been reported, while what they need is everybody's support[2].

Adversity is not only a potent risk factor for short-term mental health problems as mentioned above, but also for mental and behavioural disorders, such as depression, post-traumatic stress disorder and alcohol use disorder[3]. During the 2003 SARS outbreak in Asia, affected people experienced high levels of traumatic stress. People who had been quarantined, or who worked in high-risk locations such as SARS wards, or who had friends or close relatives who contracted SARS, were much more likely to have mental health problems[4]. It is clear that mental health systems in all countries need to be strengthened to deal with the impact of COVID-19.

There are reports from countries and in the scientific literature that COVID-19 illness is increasingly associated with mental and neurological manifestations, including delirium, as well as anxiety, sleep disorders, and depression[5]. In addition, COVID-19 is likely to exacerbate pre-existing mental health, neurological and substance use disorders, while limiting access for those in need of services. In many countries, community mental health services have stopped functioning. Yet, over 20% of adults over 60 years have underlying mental or neurological conditions, which represent a large proportion of people with severe COVID-19 illness. Long-term care facilities for people with mental health conditions (e.g., mental hospitals and homes for people with dementia) are places where infections can be especially difficult to control. Care and protecting human rights of residents at such facilities must be part of any public health emergency response[6].

Addressing mental health in public health emergencies is vital. Both are critical to the movement for universal health coverage. As expressed through the dictum "No health without mental health", poor mental health is associated with reduced adherence to physical health interventions[7]. A psychosocial lens helps in improving any emergency programming, including public health ones. In such emergencies, psychological factors in the affected population play a key role in their readiness to comply with public health measures. Any success in addressing people's anxiety and distress will make it easier for people to have the will and capacity to follow relevant guidance by public health authorities.

At the World Health Organization (WHO), the Department of Mental Health and Substance Use is working with different pillars of the COVID-19 response within the Organization to develop public messages and promote the integration of mental health and psychosocial support (MHPSS) into the COVID-19 response effort. MHPSS is a cross-cutting area of work across all sectors in all emergencies, and a cross-cutting area of work within health, and within public health emergencies response. The WHO is also the co-chair of the Inter-Agency Standing Committee (IASC) Reference Group for Mental Health and Psychosocial Support in Emergency Settings, a collaboration between WHO, other United Nations agencies, the Red Cross and Red Crescent movement, and international non-governmental organizations working in humanitarian settings.

The WHO, together with partners, has provided MHPSS guidance and awareness-raising messaging, which have been translated into more than 30 languages and are being disseminated widely. This includes, for example, the *IASC Interim Briefing Note Addressing Mental Health and Psychosocial Aspects of COVID-19 Outbreak*[8] and the *WHO Guidance on Mental Health and Psychosocial Considerations during the COVID-19 Outbreak*[1], as part of risk communication and community engagement technical guidance for the COVID-19 response.

Additionally, a wide range of materials are being prepared by the WHO and partners, including specific messages on coping for vulnerable people, including children[9] and older adults, clinical guidance on mental and neurological manifestations of COVID-19, adaptation of existing WHO mental health and psychosocial tools for COVID-19 context, and continuation and adaptation

of essential mental health and psychosocial services in development and humanitarian settings during the COVID-19 pandemic.

Humanitarian emergencies can be an effective impetus to strengthening community mental health care[10], as part of the overarching goal of universal health coverage. Strategies identified by the WHO will guide efforts to strengthen mental health care in countries recovering from COVID-19. These include: a) planning for long-term sustainability from the outset; b) addressing the population's broad mental health needs; c) respecting the central role of government; d) engaging national professional organizations; e) ensuring effective coordination across agencies; f) reviewing mental health plans and policies as part of reform; g) strengthening the mental health system as a whole; h) investing in health workers; i) using demonstration projects to raise funds for wider reform; and j) investing in advocacy to maintain momentum for change. This approach also links to the *WHO Special Initiative for Mental Health: Universal Health Coverage for Mental Health*[11], which will help improve access to mental health services.

Our approach to mental health is comprehensive – not only focusing on responding to the current crisis and recovery after the crisis, but also on preparedness and getting services ready in countries before the next emergency through supporting countries in establishing community based mental health services for everyone everywhere. Health for All means having strong health systems, and strong health systems are resilient health systems.

Tedros Adhanom Ghebreyesus
Director-General, World Health Organization

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Psychiatry in the age of COVID-19

Within a few months, COVID-19 has sickened millions, killed more than 200,000, disrupted the lives of virtually everyone, and caused tremendous anxiety, trauma and grief. As psychiatrists, we are used to helping people who have suffered trauma and loss. Some of us have cared for survivors of disasters, but few have experienced a global pandemic that threatens all of our lives. None of us was prepared for this crisis, and we acknowledge that the observations and adaptations we are writing about here may not stand the test of time.

What do we know about the effects of pandemics on mental health and what can psychiatrists do to help? Studies from earlier outbreaks[1] suggest high rates of acute stress and anxiety among the public, patients and health care workers. A recent study of health care personnel in China found high rates of depression and anxiety, especially among those on the front lines[2]. In our own experience, we have seen increased stress in individuals with preexisting mental health or substance use disorders, who may be socially isolated and have reduced access to their usual treatment programs or support systems.

We have also noted new psychiatric symptoms in individuals experiencing stress, anxiety or grief as a result of the pandemic. Some are experiencing losses under traumatic circumstances, such as not being able to say goodbye to dying loved ones or the inability to offer proper burials. Physical distancing can help slow the spread of the virus, but we know the risks associated with social isolation. This can be particularly challenging for those who are elderly, poor, or without access to telephones or the Internet. Along with isolation, we may experience a loss of structure, increased time for anxious rumination, and limited opportunities for active coping.

Front-line health workers are experiencing severe stress and anxiety while caring for patients under difficult circumstances, battling a disease for which we have no cure, often with limited equipment. They are exhausted and doing their best, but patients keep dying. Clinicians also have to worry about their own health and the risk of bringing a deadly illness home to their families. These experiences may have long-lasting emotional and functional consequences[3].

Every one of us is at some risk for contracting this deadly virus, but there are those who are more vulnerable, and traditional social determinants of health still apply. Historic inequities driving chronic disease rates in people of color, poverty, and health literacy may play a role in differential rates of infection and death. Individuals whose livelihood and ability to obtain food and shelter have been diminished may suffer long-term consequences of this pandemic[4], and those with pre-existing mental health disorders may be at increased risk for developing post-traumatic stress disorder or suicidal ideation[5,6].

Our hospitals were among the first in the US to see patients with COVID-19. We have made a series of changes to our clinical programs and we are talking to our colleagues around the world to learn from each other and to support each other. We have rap-

idly moved our scheduled outpatient visits to telehealth care, going from doing almost no into-the-home telehealth to doing 90% of our visits in this manner. Telehealth allows our clinicians to safely work from home, where they can also care for family members such as children who are out of school.

Inpatient psychiatry is fundamentally different from inpatient medicine in that the care on psychiatry units takes place outside the room in a group and milieu setting, whereas the care on medical floors takes place inside the patient's room. This greatly increases the risk of COVID-19 spread between psychiatric patients and staff. We have developed protocols to screen all existing and new patients to our inpatient units for COVID-19 and we are conducting surveillance testing of staff who have been exposed.

Initial protocols called for movement of all COVID positive patients to designated medical units. However, the behavioral symptom severity of some geriatric patients and agitated younger patients required us to develop protocols for treating these patients on our psychiatry units, in sections designated as COVID hot zones, where we can maintain safe environments through the careful use of barriers and personal protective equipment. Because some freestanding psychiatric facilities struggle with caring for COVID patients, we plan to increase our inpatient bed capacity and we have streamlined the process for moving psychiatric patients out of the emergency room to make space for the anticipated surge in COVID patients. On our consultation-liaison services, we have sought to preserve personal protective equipment and limit staff exposure by employing modalities such as tele-video consultation.

In our organization, psychiatrists have not been asked to redeploy outside of behavioral health care settings thus far. Instead, we have focused on expanding our services to better assist our health care colleagues. Nearly 100 of our psychiatry faculty members are volunteering to provide mental health support to some 20,000 health care workers in our organization. We have also developed a psychiatric consultation service in which psychiatrists provide consultation to primary care providers and other health care professionals caring for patients with mental health or substance use problems anywhere in Washington State, an area that is four times the size of the Netherlands or roughly half of the size of Italy. Our calls come from primary care and community health clinics, jails, temporary field hospitals, recovery centers, and shelters.

Taking a moment to reflect on these changes, we are humbled and impressed by how all people have come together to rise to this challenge. After getting over the initial shock and fear, we have learned that as psychiatrists we can take care of our patients who are tremendously vulnerable right now, take on the care of new patients who are severely stressed and traumatized by this crisis, and provide important support to our health care colleagues on the front lines. We don't know yet what will come next and how long we will have to endure this crisis, but we are preparing for what will likely be a marathon rather than a sprint.

We are all learning a lot. We are learning about our tremendous interconnectedness on a local and even global level. We are seeing people being more tolerant with each other, more forgiving, and giving each other more latitude. We see people spending more time with their families, which can be good for some and stressful for others. We are learning what is truly essential and that a remarkable amount of work can be done from home, although this may not be as true for those who are poor or otherwise disadvantaged. We are finally learning the value of handwashing, even on mental health services where we have traditionally been poor at adopting this vital health practice. And we are noting that the planet must be smiling as we commute and pollute less. We hope that each of you is well and we invite you to share your lessons and your hopes with us as we look ahead together.

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What is resilience: an affiliative neuroscience approach

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Resilience – a key topic in clinical science and practice – still lacks a clear conceptualization that integrates its evolutionary and human-specific features, refrains from exclusive focus on fear physiology, incorporates a developmental approach, and, most importantly, is not based on the negation (i.e., absence of symptoms following trauma). Building on the initial condition of mammals, whose brain matures in the context of the mother's body and caregiving behavior, we argue that systems and processes that participate in tuning the brain to the social ecology and adapting to its hardships mark the construct of resilience. These include the oxytocin system, the affiliative brain, and biobehavioral synchrony, all characterized by great flexibility across phylogenesis and ontogenesis. Three core features of resilience are outlined: plasticity, sociality and meaning. Mechanisms of sociality by which coordinated action supports diversity, endurance and adaptation are described across animal evolution. Humans' biobehavioral synchrony matures from maternal attuned behavior in the postpartum to adult-adult relationships of empathy, perspective-taking and intimacy, and extends from the mother-child relationship to other affiliative bonds throughout life, charting a fundamental trajectory in the development of resilience. Findings from three high-risk cohorts, each tapping a distinct disruption to maternal-infant bonding (prematurity, maternal depression, and early life stress/trauma), and followed from birth to adolescence/young adulthood, demonstrate how components of the neurobiology of affiliation confer resilience and uniquely shape the social brain.

Key words: Resilience, oxytocin system, affiliative brain, biobehavioral synchrony, mother-child relationship, neurobiology of affiliation, sociality, plasticity, meaning

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Resilience, usually defined as positive outcome despite adversity[1-3], is likely the ultimate goal of human maturity and the single most important target of prevention and intervention science. Individuals who are able to face life's hardships with courage and perseverance, maintain positive outlook under difficult circumstances, enjoy both intimate bonds and a wider social circle, express empathy and compassion to others' misfortune, foster industry and a sense of agency toward long-term autonomous goals, live a life of creativity, vitality and meaning, and are free of debilitating symptoms despite early adversity or current trauma, define the hallmark of human achievement and the main goal of clinical effort since Freud. It is thus surprising that, despite decades of research, a comprehensive biobehavioral perspective on resilience has not yet been formulated.

Current empirical work on resilience typically focuses on the neurobiology of stress and fear regulation, or employs epidemiological/clinical research in the aftermath of trauma. In both lines, resilience is conceptualized as the "absence of symptoms" or the "maintenance of mental health" following adversity or trauma[4]. A recent interdisciplinary panel[5], while emphasizing the urgent need to shift the focus from psychopathology to resilience in the field of mental health, and highlighting the immense economic burden and personal suffering caused by stress-related disorders, concluded that resilience can only be defined *ex post facto* after the trauma has passed and some individuals do not succumb and remain symptom-free.

From a scientific standpoint, such position is problematic. Without a clear definition of a construct, empirical evidence cannot accumulate nor can it guide intervention effort. In particular, it is critical to identify whether resilience involves processes that gate deterioration following physical or mental insult, or those that uniquely foster strength and stamina[6,7].

Positive psychology focused on resilience as a key component of well-being[8] and launched the well-known resiliency training in the US army[9]. Some aspects of resilience are also echoed in the writing of post-Freudian psychoanalysts who emphasized the functioning, growing and relating aspects of the self and its embeddedness in the social milieu, such as Sullivan[10], Fromm[11] and Erickson[12]; in the work of Maslow[13] on self-actualization; and in the formulations of humanistic psychology[14]. Yet, these authors did not focus on resilience *per se* but on personal growth, did not integrate systematic research into their models, and did not incorporate neurobiological findings into their conceptualizations, or even negated the relevance of any neuroscientific evidence[15,16]. A human-specific model of resilience, which on the one hand is attentive to internal reality and man's higher faculties, but on the other draws on evolutionary models and incorporates neuroscientific findings into its core concepts, has not been constructed.

Two major issues may further complicate the construction of a comprehensive biobehavioral model of human resilience. First, with most current effort directed toward understanding the neurobiological underpinnings of mental disorders, research in psychiatry has generally focused on features that can be readily tested from a cross-species perspective. This has led to an almost exclusive focus on the neurobiology of fear – the neural, endocrine, genetic and molecular processes that sustain the fear response and enable stress management[4,17-21]. Accordingly, studies often utilize cross-species stress-related paradigms, particularly fear conditioning, and this has resulted in a fear-focused view of resilience[22,23].

Second, a true focus on development as a core component in understanding mental health, particularly resilience, has often been missing, despite the fact that all models of the self are, in essence, developmental (that is, describe stage-like progression from immature to mature states). Resilient individuals are

not only born, but are (critically) raised. It has been advocated[24] that, in order to study resilience, we must follow children from infancy and over lengthy periods to detect age-specific biological, behavioral and social markers that tip children toward a resilient pathway. However, such longitudinal effort is extremely rare.

These two issues have led to a rather limited, one-sided view of resilience. When asked, in a discussion on resilience, "what have you changed your mind about…", a panel of leading researchers[25] all pinpointed the narrow focus on fear physiology and stress neurobiology in resilience theory and research as the main issue they had changed their mind about.

A new conceptualization of resilience must be evolutionary-based, enable a thorough cross-species research, and set the stage for meticulous data collection that tests its specific expression across developmental stages, contexts and psychopathological conditions. Most critical for science, it should be verifiable (i.e., open to proof and falsifiability).

In the following, we propose a model of resilience that is based on the neurobiology of affiliation and offers a biobehavioral, evolutionary-based and developmentally-sensitive conceptualization, which is not constructed on the neurobiology of fear on the one hand or on the pursuit of happiness on the other. Our model takes into account the fundamental condition of mammals, whose brain matures in the context of the mother's body and caregiving behavior, and contends that maturation of all neurobiological processes that foster resilience are embedded in the provisions afforded by the mother's body and species-typical caregiving.

Moreover, the model argues that any understanding of resilience must consider the initial dependence of the infant on its mother and the immense impact that this dependence has on brain structure and function. Mammalian young are born with an immature brain, and their brain is shaped by the mature maternal brain through physical proximity, lactation, and the assemblage of species-typical well-adapted caregiving via processes that provide external regulation from mother to young in a system-specific manner[26,27].

Such external regulation of the immature brain by the mature brain charts the core mechanism of brain development in mammals and functions to fine-tune the infant's neurobiological and behavioral systems to life within the social ecology and its unique features[28,29]. We argue that the tuning of the infant's brain to life within the ecological niche and its distinct hardships marks *the very essence of resilience* and that processes that participate in such tuning define what resilience "*is*", and should become the focus in resilience theory and research.

CORE COMPONENTS OF THE NEUROBIOLOGY OF AFFILIATION

Our model draws on three core components of the neurobiology of affiliation: the oxytocin system, the affiliative brain, and biobehavioral synchrony.

Oxytocin

The ancient oxytocin system, evolving approximately 500 million years ago, functioned to mediate organisms' response to environmental challenges by supporting the regulation of basic life functions, such as water conservation, thermoregulation and energy balance across the phylogenetic scale[31,32]. Hence, its initial involvement in endurance, organism-ecology adaptation, and resilience.

With the evolution of mammals, oxytocin has been incorporated into labor and lactation. For mammalian young, then, the mother-infant bond has become the key context for the maturation of systems that support stress reduction[32]. Life-sustaining functions no longer develop in the context of the group, like in fish or ants, but within the intimacy of the "nursing dyad", via provisions embedded in the mother's body.

In mammals, the oxytocin system became the key one supporting the resilience-by-affiliation mechanisms, where robustness, plasticity and tolerance of ecological hardship is achieved by social contact in processes that span a single cell to human cultural communities[29,33]. Overall, the role of oxytocin in resilience stems from three sources, associated with its involvement in neural plasticity, sociality and immunity.

Oxytocin is implicated in *neural plasticity* at the molecular, cellular and network-assembly levels[34-36]. Oxytocin neurons can co-express with various neurotransmitters, including dopamine, serotonin and opioids. Oxytocin-expressing neurons include a wide variety of cell types, such as GABAergic interneurons, glutamatergic pyramidal cells, and other peptidergic cells[34,37,38]. Oxytocin integrates brain and periphery, incorporates massive epigenetic inputs, and is particularly related to attachment experiences[39,40]. It increases plasticity in the hippocampal network to increase salience of the attachment target[41], and attachment experiences shape oxytocin receptors availability[42].

Oxytocin's pulsatile mode of release is particularly important for neural plasticity, by which it shapes environment-dependent neurobiological systems[43]. Its pulsatile release coordinates birth according to favorable environmental conditions, charting the first integration of brain and environment in human life[44]. Its surge during birth causes gamma-aminobutyric acid (GABA) signaling to change from excitatory to inhibitory, synchronizing the fetus' hippocampal neurons with the transition from prenatal to postnatal life[45,46], setting the lifelong excitation-to-inhibition balance. Optimal balance of excitation and inhibition is critical for adaptive functioning and buttresses the "sensitive period" effect, which is critical to the robustness of all living organisms[47].

Oxytocin plays a key role in *sociality*. The neural systems that enable attachment and bonding evolved through oxytocin's sensitivity to the recurring elements in the environment, imbuing mother and surrounding with incentive value[48-50]. Oxytocin availability at core limbic sites guides infants to prefer cues associated with their mother, leading to the formation of dyad-specific attachments[51,52]. During first post-birth days, oxytocin receptors become connected to specific social cues via oxytocin's links with the brain dopamine reward system[53-55], olfactory-amygdala pathways[56,57], innervation of sensory cortices[54], and sharp-

ening signal-to-noise ratio in hippocampal pyramidal cells[58]. These program the brain's social perception, preferences and memory, and connect them to the attachment target.

Oxytocin supports the integration of individuals into social groups[59,60]. Across evolution, it has been implicated in social functions: in courting rhythmic movement in nematodes[61], social processes in worms[62], mate selection and flocking in birds[63], exclusive bonding in herding animals[64], and social affiliation in rodents[65], primates[66] and humans[29,67]. Evolutionary constraints led this flexible environment-dependent system to direct young to bond with their parents, function within their social ecology, and engage in the social structure of their species[64]. Notably, greater social support and a sense of belonging to the social group have been repeatedly associated with greater resilience[68-70].

The infant's oxytocin system is shaped by caregiving. Animal studies indicate that maternal behavior programs oxytocin receptor availability in the brain[71], and longitudinal human studies show that peripheral oxytocin is programmed by sensitive parenting repeatedly experienced throughout childhood[72-74]. Oxytocin induces a physiological state of quiescence that affords participation in the world without fear and stimulates the desire for social contact through its links with dopamine in striatal neurons[75-77]. This unique state provides the basis for the individual's sense of security upon which resilience can develop.

Finally, oxytocin plays an important role in functionality of the *immune system*. Human studies show associations between oxytocin and immune biomarkers[78,79]. In cell culture, oxytocin reduces oxidative stress and interleukin-6 (IL-6) secretion from stimulated macrophages[80]. In vivo, it decreases inflammatory cytokines, IL-6 and tumor necrosis factor (TNF)-α[81]. During periods of bond formation, including the period of becoming a parent and falling in love, both oxytocin and IL-6, an immune biomarker, increase their activity[82], and oxytocin is implicated in quicker wound healing[83]. Recently, an oxytocin-producing gut bacterium (*Lactobacillus reuteri)* was found to play a role in resilience, stress management, and quicker wound healing in the host, suggesting not only an additional gut-brain axis of oxytocin production, but also a microbiome-host link that promotes resilience[84].

The affiliative brain

The "affiliative brain" charts the network of inter-connected structures that enable humans to form and maintain close relationships[85].

The human affiliative brain, which evolved from the rodent maternal brain, expanded to include several higher-order cortical networks that integrate the immediacy and subconscious motivation with the cognitive aspects of human parenting[30,86]. This global human caregiving network has been further repurposed to sustain human social affiliations with lovers, close friends, and fellow humans, all shaped in the infant's brain by maternal provisions during early sensitive periods[30,85].

Studies of the maternal brain in animal models date back to the 1950s, and describe the critical role of the medial pre-optic area of the hypothalamus in initiating the subcortical network that enables mammalian mothers (and fathers in bi-parental species) to care for their infants[87]. Primed by oxytocin release during pregnancy and labor, the medial pre-optic area sends projections to the amygdala, to increase maternal vigilance for infant safety, and to the ventral tegmental area, to increase maternal reward from infant stimuli, sensitizing a limbic network underpinning maternal care (also including the nucleus accumbens, lateral septum, ventral pallidum, bed nucleus of stria terminalis, and globus pallidus).

In humans, this subcortical network expanded to include higher-order networks that enable empathy, simulation, mentalization, and emotion regulation, forming a global network that supports attachments[30]. In the 3-5% of mammalian species that show bi-parental care, the same system underpins father care. However, recent molecular and system-level findings show that different neuronal populations underpin maternal and paternal caregiving[88], and, while the same network supports human mothering and fathering, the pathway to fatherhood is more cognitive and relies on concrete paternal childcare activities[87,89].

Oxytocin plays an important role in tuning and function of the affiliative brain. Humans are wired for social behavior via activity of the mammalian caregiving network, which contains abundant oxytocin receptors[90]. Oxytocin causes long-term depression in the amygdala[91] to attenuate amygdalar response to aversive social stimuli, increasing network connectivity and enabling response specificity to social targets[92,93].

Following the attenuation of social avoidance, oxytocin enhances motivation for social bonding through its crosstalk with dopamine receptors in striatum, particularly nucleus accumbens. Dopamine acts in nucleus accumbens to organize goal-directed reward-related behavior by inhibiting the output of GABAergic (inhibitory) neurons[94-97], which enables activation of glutamate (excitatory) inputs, leading to energetic, vigorous, goal-directed action[98,99].

Nucleus accumbens shell contains oxytocin receptors that form heteromers (neurons expressing for both oxytocin and dopamine[100]) and this enables dopamine neurons specifically suited to identify sensory-motor reward to encode the temporal patterns of social action[49,101]. This allows the brain to internalize the social partner, encode bond-specific patterns, and draw reward from social synchrony[96,101].

The tighter oxytocin-dopamine crosstalk during bond formation enables the flexible incorporation of the new bond into the self[102] and the formation of sensory-motor memories of attachment experiences[103]. Thus, while dopamine affords motivation and vigor, oxytocin provides the tranquility necessary for bond formation.

While this brain network sustains human parenting, it also provides the neural support for the formation of other affiliative bonds throughout life; hence the term "affiliative brain". Animal[104] and human[85] studies indicate that the mammalian paren-

tal brain also sustains pair-bonds in monogamous mammals[77], and romantic attachment and close friendships in humans[85]. This affiliative network develops in the infant's brain during early sensitive periods through attuned caregiving, and enables the child to form close relationships, fall in love, become a member in social groups from sports team to nations, and eventually nurture his/her own children.

It has long been noted by Darwin[105] that evolutionary adaptations take place at the parent-infant interface and its inherent plasticity enables the emergence of new behaviors which, over time, alter gene expression. Consistently, our model – which places the parent-child interface at its core – highlights how the affiliative brain utilizes its inherent plasticity for resilience, endurance and recalibration.

The affiliative brain confers resilience in multiple ways. Optimal activation of this network enables individuals to form and maintain social bonds throughout life, manage stress by relationships, and, through the crosstalk of oxytocin and dopamine, draw their deepest reward from affiliations, rather than non-social sources (e.g., drugs of abuse). Indeed, disruptions in the integration of oxytocin and dopamine is found in addiction, when reward disconnects from its social targets and disruptions are found in both oxytocin[106] and neural plasticity[107,108].

The parental brain shapes the child's social abilities. We found that parental brain activations in infancy predicted the child's emotion regulation, stress management, and symptom formation across the first seven years of life[109-111]. In parallel, sensitive and synchronous parenting longitudinally shaped the child's affiliative brain in adolescence[112,113]. Finally, humans' large associative cortex enables humans to find meaning through love to abstract ideas, such as homeland or God, and extend affiliations to fellow-humans, pets, or the Earth's flora and fauna, all supported by the same network[85].

Biobehavioral synchrony

Biobehavioral synchrony is the core mechanism sustaining human sociality and affiliation. It is defined as "the coordination of biological and behavioral signals between social partners during moments of social contact", and it describes the mechanism by which the parent's mature brain externally regulates the infant's immature brain and tunes it to social life[29,114,115].

Biobehavioral synchrony creates a template for the coordination of the biological with the social and mental; the merging of autonomous self with autonomous other; and the integration of moments of interpersonal match with moments of mismatch, alone states, and reparation, all within a secure dialogue.

In multiple studies spanning infancy to adulthood, and across a wide range of healthy and high-risk populations in various cultures, we showed that these "precious social moments", when parent and child coordinate their non-verbal behavior, frame moments of biological coordination. For instance, only during these episodes there was synchrony between mother and infant's heart rhythms[116], coordinated release of oxytocin[117], and brain-to-brain synchrony in the social brain[118].

Synchrony links with better stress management[73], higher respiratory sinus arrhythmia[119], and better immune functions[120], depicting a mechanism by which coordinated social behaviors reduce stress and enhance resilience.

The linkage of behavioral and biological synchrony originates *in utero*[121], incorporating the infant's biological rhythms into a social dialogue that transforms the biological into relational and the intra-individual into interpersonal. Patterns of non-verbal synchrony reverberate in the dyadic relationship across time, while expanding in symbolic and interpersonal complexity[122], and such increased diversity of repertoire amidst a core order charts a mechanism of resilience, as suggested by dynamic systems' theory[123]. Notably, all forms of physiological synchrony (neural, endocrine and autonomic) are embedded within behavioral coordination, supporting our main hypothesis that behavioral synchrony frames physiological connection and that resilience is behavior-based[29,124,125].

Biobehavioral synchrony experienced in the first months of life marks a critical experience during a sensitive period that predicts a host of resilience-related outcomes from birth to young adulthood, including emotion regulation, symbolic competence, stress management, lower externalizing and internalizing symptoms, and social brain development[30,114,126,127].

Across development, the non-verbal affect matching of infancy morphs into reciprocal exchanges that incorporate, like expanding ripples, the child's growing symbolic, linguistic and social competencies and evolves to include empathy, perspective taking, and intimacy, all built upon the rhythmic non-verbal core in the service of resilience (see below). This echoes Maslow's notions[13] that the "self" includes both what the person is and what the person can become. Furthermore, while charting a human-specific mechanism that develops across human life, biobehavioral synchrony draws on a long evolutionary line of socially-based survival-related mechanisms in mammals and other eusocial (hyper-social) species that sustain endurance and resilience.

Across evolution, from bacteria to human, synchrony builds on processes that bind two organisms (or entities) into a coupled biology. Recent advances in quantum physics suggest that such coupling began even before the emergence of life, as seen in the phenomenon of "quantum entanglement", the connection of particles across time and space that locks two units together, giving their union immeasurable strength and endurance.

THE THREE TENETS OF RESILIENCE

Taking into consideration the aforementioned foundations of affiliative neuroscience (oxytocin, the affiliative brain, and biobehavioral synchrony), our model highlights three tenets that define what resilience *is*. While all three are required for the making of the resilient individual, they come in different combinations across individuals and cultures, and express differently across ages and stages (Figure 1).

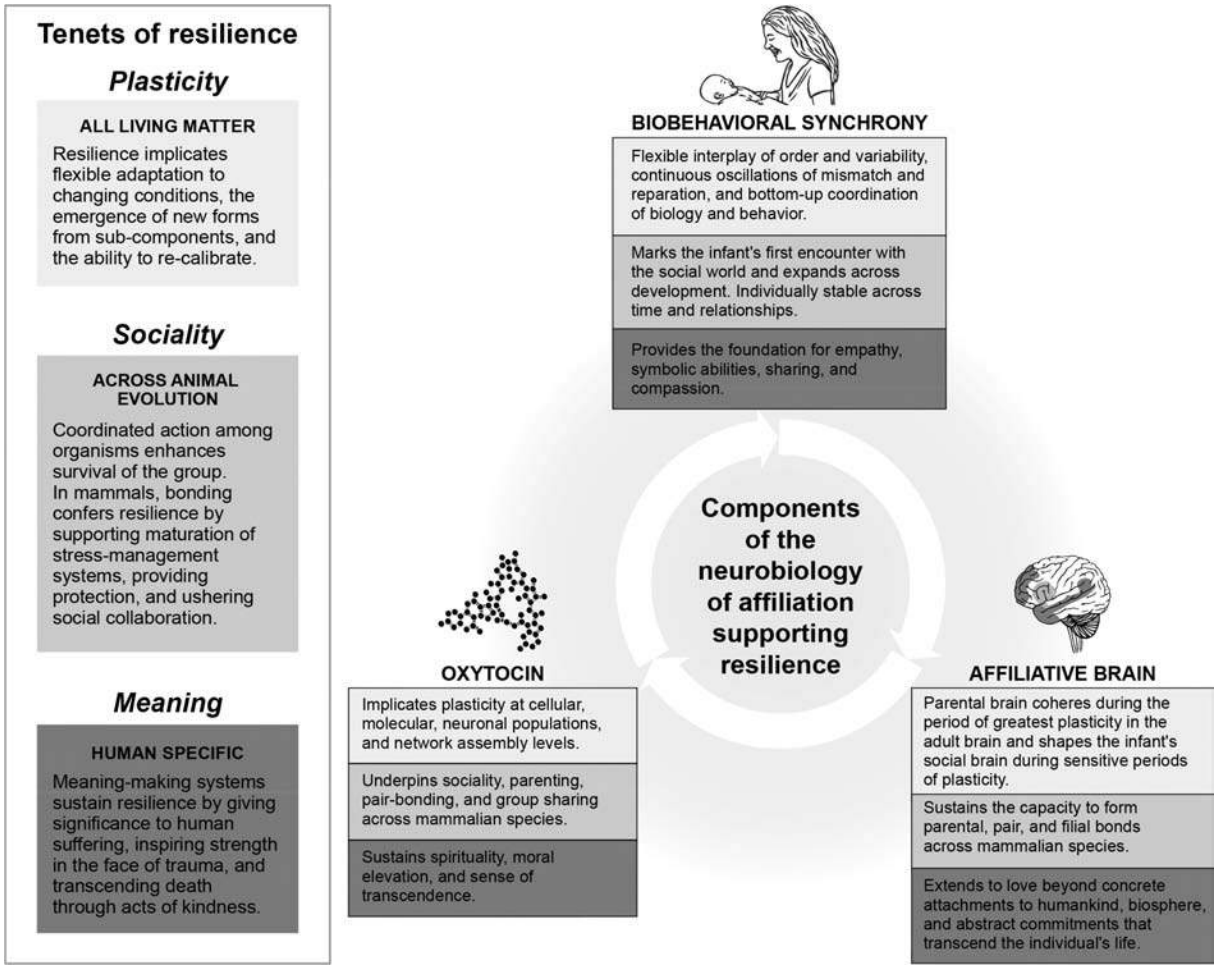

Figure 1 The three tenets of resilience as integrated into the core components of the neurobiology of affiliation

Resilience implicates plasticity

At the outset, resilience involves mechanisms that promote flexible adaptation to changing conditions, resourceful use of contextual provisions in the service of personal growth, and the capacity to persist toward long-term goals tempered by the ability to modify and recalibrate. That is, resilience implies plasticity.

Plasticity relies on neurobiological systems that underpin social fittedness, physical stamina and endurance as they flexibly adapt to diverse conditions[128,129]. Bonding is likely the process exuding the greatest plasticity in mammals. Great neural plasticity has led to the evolution of viviparity (internal gestation) and to physiological reorganization in mother and young that enabled the maturation of the fetus within the maternal body[130]. Immense neural plasticity is also required to make that newborn the most salient object to its mother to the exclusion of all other focus[131].

As noted, the oxytocin system plays a key role in neural plasticity, which is critical to the formation of attachments, and the period after childbirth marks the time of greatest plasticity in the adult brain[132].

The "plasticity" component of resilience comprises two features: a) resilience is integrative and regulatory; b) resilience is time-based.

Resilience is integrative and regulatory

Regulation promotes flexible integration of system components into a functional whole, shaping self, individuality, agency and well-being through the formation of new, person-specific, dyad-specific and culture-specific configurations. Much developmental research has been directed to the construct of "regulation", with some suggesting that this is the single most important concept in understanding developmental disruptions[133,134].

Across multiple fields, "regulation" adopts a system perspective. It describes how various components of the system dynamically coalesce into a functional whole; how higher and lower elements hierarchically organize over time; and how components from within the system integrate online with those in the

immediate environment[123,135-137]. Conceptual models suggest that regulatory processes mature on top of each other from biological to emotional to attentional to self-regulatory processes[138], and parent-child co-regulation (synchrony) supports maturation of higher-order regulatory skills, such as attention modulation and self-control[139-141].

Resilience is time-based

Resilience is time-bound and process-based, and develops from simple to complex and from biological to mental. The "timeness" component of resilience is critical not only across evolution (phylogenesis) and from infancy to adulthood (ontogenesis), but also at the level of concrete social experiences.

Social moments always unfold in time when two or more participants create a novel "dance" of matched and mismatched moments that coordinate behavior, physiology and mental states. The timeness of these encounters enables the formation of new forms from existing units. Time, therefore, is an indispensable component of resilience (the ability to re-calibrate) and this is captured by "synchrony", a time-based construct.

Resilience is social

Sociality underpins survival and adaptation, and species that can better utilize social mechanisms of coordinated action have a significant survival advantage. This is elegantly described by the entomologist E. Wilson[142] in *The social conquest of earth*, where he argues that humans achieved supremacy among vertebrates and ants among invertebrates, in terms of population size, spread across earth, and durability, due to their eusociality (hyper-sociality), which involves the capacity for collaborated action among group members and social organization across generations.

Primitive mechanisms of synchrony are found in ants, fish and birds, and are underpinned by the coordination of biology and behavior through vasotocin, the parent molecule of the mammalian oxytocin and vasopressin[32,62,143]. Humans' biobehavioral synchrony, therefore, relies on a long history of social mechanisms that promoted resilience via action coordination. Consistent with the behavior-based principle of affiliative neuroscience, these mechanisms were selected with a focus on behavior: social behavior in the group in non-mammalian species and affiliative bonds in mammals. Notably, however, while loneliness is hazardous to the well-being of any living organism[144], the "social" component of resilience is highly variable, and wide variability is observed across the animal kingdom, paralleled by great variability in the density and localization of oxytocin receptors[145,146].

Social monogamy

Social monogamy marks the first extension of the mother-infant bond to other attachments within the family, specifically mating and fathering. Studies on social monogamy utilized several primate species (cotton-top tamarins, marmosets and lamurs)[147], and five rodent species, all originating from a single rodent lineage (prairie voles, mandarin voles, California mice, Campbell's dwarf hamsters, and Mongolian gerbils)[148].

Monogamy provides the basis for fatherhood. Direct paternal care is found mainly in socially monogamous species[149], where fathering occurs in the context of maternal care and parents coordinate their caregiving in relation to each other[150]. Paternal care contributes to confer resilience to mammalian young, increasing offspring survival, litter size, and growth rates[151-156].

While the specific ecological pressures that led to bi-parental caregiving and to humans' cooperative breeding are unknown, paternal caregiving stabilized monogamous mating systems. Once social monogamy has been established in a species, it fosters the emergence of complex social behaviors, that foster resilience[154,157].

Both father care and pair bonds involve the extension of the mother-infant bond, repurposing the same neural networks and molecular processes and providing the first expression of both consistency and diversity in the neurobiology of affiliation. Monogamy also necessitates coordination of the three intra-family attachments (mothering, fathering, and the pair-bond) in the formation of a family unit, and such coordination paved the way for the evolution of the human family and, eventually, of complex socio-cultural organizations, leading to humans' supreme resilience in the animal kingdom.

In humans, involved fatherhood confers substantial resilience. Throughout human history, fathers have been the main source of indirect care, controlling the material resources, physical conditions, and social status with which infants develop[158,159]. Historical accounts point to close associations between paternal provisioning and child mortality in pre-industrial US and Europe[160], and anthropological studies indicate that men with more land or higher social status show greater reproductive success[161,162].

In modern societies, greater father involvement enhances child resilience, in terms of better mental health, higher academic achievement and professional attainment, and better self-regulatory abilities[163,164]. Children of involved fathers are less aggressive and resolve conflicts with more respect and dialogue[165], and epidemiological studies show that fatherless children are more prone to aggression, law-breaking, and conduct problems[166,167].

Complex social organizations

While social monogamy marks the first extension of the mother-infant bond to the family unit, complex and hierarchical social organization was thought to evolve only in hominins and expand in parallel to the increase in brain size[168]. Recent research in Western gorillas discovered hierarchical social modularity, defining not only complex affiliative behavior within extended groups of kin, but also reciprocity and cooperation among non-

kin groups toward goal-directed seasonal coalitions, in ways that mirror the social structure of a small human village[169].

Such behavior-based organizations enable the joint gathering of widely-dispersed foods and protection from predators, enhancing resilience through collaborated actions outside the family. Among primates living in groups, such as chimpanzees, post-conflict reconciliation behaviors were observed, which enable group members to amicably resolve conflict and maintain social ties, and these affiliative post-aggression acts involve increase in urinary oxytocin[170].

A study in marmosets showed that the greater the bonding among an affiliative pair (of same or opposite sex), measured in terms of relationship duration, time spent together, and amount of affiliative behavior, the greater the endocrine synchrony of urinary oxytocin fluctuation[171], pointing to biobehavioral links in non-human primates that preceded humans' biobehavioral synchrony.

Biobehavioral synchrony – a human-specific mechanism

Building on these mechanisms of sociality that sustain stress management, group cohesion, and sensory-motor coordination, biobehavioral synchrony is a human-specific mechanism through which two individuals can mutually impact each other's physiology without physical contact, but via the coordination of facial socio-affective signals, which is not found in non-human primates and rodents[29].

Human synchrony develops throughout life into an increasingly complex human social exchange that involves the co-construction of a joint narrative, the capacity to assume multiple perspectives, and the ability to empathize with others' pain, actions, emotions, and mental states. The development of synchrony begins with the mother's recognition of the infant's biological rhythms *in utero* and culminates in adult-adult relationship of mutual care and intimacy.

Resilience involves meaning

While the first two tenets of resilience build on species-general foundations and add a human dimension, the meaning-making element is exclusively human. For a conceptualization of human resilience, we must integrate the species-general foundations of endurance, diversity, adaptation and stress-management with the human ability to give meaning to hardship, adversity and trauma.

Humans' ability to give meaning to trauma often utilizes collective cultural or religious myths and, at other times, builds on forming personal meaning through actions, typically those that involve the strengthening of affiliative bonds or acts of altruism that extend beyond the individual.

Much research has underscored the role of spirituality in the capacity to bounce back from trouble or in the ability to use trauma for growth[172-174]. Studies have also pointed to the importance of generosity in resilience[175], and to the consoling function of religious affiliations that give collective meanings but also generate community support[176,177]. W. James, in *The will to believe*[178], considered belief as an intentional choice that confers resilience and enables the individual to create a personally-meaningful view of reality that gives significance to trauma and hardship. His famous metaphor of turning discrete experiences into a meaningful whole as resembling "alive electrical wires" that light and shine versus "dead wires" that remain diffuse and unlit, elegantly describes this resilience-promoting function of belief.

Meaning-making introduces a future dimension into the concept of resilience, adding a temporal horizon beyond the "remembered presence"[179] of other primates. This underscores the goal-directed function by which humans create cultural myths that transcend the individual's life and fuel internal reserves of resilience in the face of hardship.

The attribution of meaning that transcends the individual's life is not only a core feature of resilience, but also relies on the two systems of the neurobiology of affiliation. Carter[76] suggested that the oxytocin system provides the neurobiological substrate for spirituality, via its role in sustaining love, caring, empathy, and moral elevation, and, specifically, as the oxytocin system enables mammals to experience "a state of vigilance without fear", that is, to be fully aware of the present moment without vigilance of potential danger. Similarly, the neural structures that cohere into the "affiliative brain" and are formed during early sensitive periods enable humans to extend love to unfamiliar strangers, social groups, and abstract ideas, bestowing generosity beyond the individual's immediate bonds.

However, intense cross-generational cultural myths, meaning systems, and religious beliefs run the risk of overlooking the first tenet of resilience – flexibility – by tightening habits, obligations, and submissive attitudes and increasing surveillance and rigidity. Such close-knit groups often function through tight in-group cohesion, achieved by tightening the neural and behavioral synchrony among in-group members to a hyper-social level in the face of real or perceived danger. For instance, throughout human history, soldiers receive intense training for coordinated action, and this motor synchrony enables the removal of cognitive empathy during battle in order to fight and destroy out-group members. The social component of resilience becomes significantly tighter for the in-group and is abolished for the out-group.

Notably, both oxytocin and neural synchrony participate in such in-group/out-group division, built on ancient mechanisms that immediately distinguish friend from foe to protect loved ones. For instance, we studied the neural response of Israeli and Palestinian youth using magnetoencephalography (MEG) while viewing in-group and out-group protagonists in pain. For the first 500 ms, representing the brain's automatic response to vicarious pain, youth responded to the pain of both in-group and out-group members. However, after this half-second of grace, top-down processes blocked the brain's natural empathic response to the out-group, displaying only response to the pain of in-group[180].

Two processes assisted in shutting down the evolutionary-ancient empathic response to a conspecific in distress: increase in

oxytocin levels and tightening brain-to-brain synchrony among group members. Thus, oxytocin and neural synchrony functioned in the service of a superordinate meaning system not supporting empathy, but out-group derogation.

Studies on the involvement of oxytocin in out-group derogation[181] open the question of how to integrate the role of meaning systems which, on the one hand, can increase resilience by building communities and giving cross-generational meaning to trauma, while, on the other, induce out-group aggression and prejudice. Perhaps one solution should focus on directing constant effort to imbue ancient meaning systems with flexibility and humanity, so that old rituals do not become rigid and extend to all fellow humans.

SYNCHRONY FROM INFANCY TO ADULTHOOD: THE UNFOLDING OF RESILIENCE

Synchrony does not only mature across animal evolution, but also throughout the lives of individuals. Synchrony's main development occurs within the mother-child relationship, the primary mammalian bond, and from there it expands to other social bonds, including fathers, mentors, close friends, and romantic partners, to humankind, and to a sense of synchrony with nature, art, and sacred experiences.

These notions provide biological and scientific evidence to Winnicott's conceptualization in *Playing and Reality*[182] on the mother's non-impinging presence as the basis for symbol formation, play, creativity, and spiritual experiences. Synchrony increases in complexity, diversity of repertoire, symbolic level, and degree of mutuality across childhood and adolescence, tuning the experience-dependent social brain to understanding others' mind, showing empathy to others' distress, and participating in relationships[183]. The rootedness of synchrony in evolutionary-ancient patterns and in the fetus' biological rhythms grounds this experience in the physical and the concrete and enables the entire history of the relationship to resonate within a human moment of meeting.

While philosophical perspectives on "embodiment" suggest that the "self" constructs from micro-identities that unfold during concrete daily experiences, synchrony adds the element that the self assembles from concrete patterns *with a significant human*. Our model details the maturation of this phenomenon across both evolution and human life, and charts its contribution to resilience in the face of condition-specific adversity.

Mother-infant synchrony originates from the mother's recognition of the infant's first biological rhythms *in utero*, such as heart rhythms and sleep-wake cycles, which send signals to the placenta and the maternal brain[184-186]. Following birth, mothers entrain these familiar rhythms into the dyadic exchange.

Studies from the 1970s described how mother-infant face-to-face interactions build on the "burst-pause" pattern of biological periodicities, such as sucking or crying[187,188]. From the entrainment of these biological rhythms, synchrony progresses through distinct stages into an empathic, adult-adult relationship that is dialogical and empathic.

We followed mother-child synchrony from birth up to age 25 and observed how interactions maintained the same non-verbal rhythmic patterns, arousal fluctuations, and positive peaks across a quarter of a century. For instance, some dyads cycle steadily between low and medium arousal, while others engage in quick peaks of positive arousal. Such stability gives order while complex and creative patterns are incorporated into the dialogue and form a familiar and unified event.

Apart from providing the "rhythm of safety", two additional features of synchrony are particularly important in fostering resilience. First, the micro-structure of the synchronous experiences is that of a constant shift between rupture and repair. According to Tronick[189], mothers synchronize with the infant only about 30% of the time; thus, dyads spend more time in mis-coordinated states that are framed by precious moments of synchrony. Psychoanalytic and developmental authors[189,190] emphasize the importance of such match-mismatch cycles for teaching infants how to tolerate moments of non-attunement and how to repair the misunderstanding inherent in human dialogue.

Two types of deviations from the long-mismatch-shorter-match pattern are described. The first, hypersynchrony, is found in anxious mothers and expresses in heightened episodes of matching (above 45% of the time); the second, withdrawal, observed in depressed mothers, involves a near total lack of attunement. Both result in regulatory difficulties in infants[191,192]. Synchrony, therefore, creates a series of micro-events consisting of constant rupture and repair, training infants for social frustrations within a safe context. At around 9 months of age, infants begin to assume responsibility for interactive "repair"[193], which prepares them for the equal relationships with friends and partners.

A second resilience-promoting feature of synchrony is its role as the first context for the development of predictions in the brain. Recent models on "predictive coding"[194,195] view the brain as a computational device whose main role is to increase adaptation by minimizing entropy and augmenting certainty. Neural oscillations play an important role in predictive coding: alpha oscillations participate in building predictions, beta oscillations in assessing the accuracy of these predictions, and gamma oscillations in prediction error, the constant pitting of the brain's predictions with incoming information[196,197]. Synchronous experiences provide a template for polyrhythmic coherence that enables multisensory representation of the body in the world[197] and involves the integration of alpha, beta and gamma rhythms in formation of social predictions during real-life events[112].

Using ecological paradigm and hyperscanning techniques, we found brain-to-brain coupling of gamma rhythms between both mothers and children[118] and romantic partners[198] during moments of behavioral synchrony. Gamma rhythms have been shown in both animal[199,200] and human[201,202] studies to index brain maturity, highlighting the role of synchrony in fine-tuning this maturity. Gamma rhythms and prediction error in visceromotor cortex and motivation areas amplify feelings but blur the distinction of self and other, due to the agranularity of these re-

gions[203]. Thus, the experience of synchrony can provide a new vantage point on social brain maturation in real-life contexts.

Developmental stages of synchrony

In multiple longitudinal and cross-sectional studies, we detected five distinct stages in the development of synchrony from pregnancy to young adulthood, and showed individual stability among these stages and sensitivity to specific adverse conditions.

Preparation for synchrony relates to the mother's increasing familiarity with the fetus' biological rhythms: the sleep-wake cycle, consolidating at around 31-32 weeks of gestation[204,205], followed by the organization of heart rhythms at around 33 weeks of gestation[206,207]. These cycles coordinate with placenta response[208], and better organization of these biological rhythms predicted greater mother-infant synchrony at 3 months[121].

Neonatal period: maternal postpartum behavior

Immediately after birth and across the first 6 weeks of life, human mothers – like any mammalian mothers – express the species-specific repertoire of maternal behavior, which in humans involve gaze at the infant's face and body, expression of positive affect, "motherese" high-pitched vocalizations, and affectionate touch. However, unlike other mammals, human mothers coordinate their behavior with the neonate's scant moments of alertness. Thus, in health, the human infant experiences at birth a coordination between his/her inner state and the response of the social world.

The expression of maternal postpartum behavior in the neonatal period provides the foundation for the development of symbolic competence in the toddler years[209], and better cognitive development and less externalizing and internalizing symptoms across early childhood[210], and correlates with parental oxytocin[211].

Infancy: affect synchrony

During the third month of life, mothers and infants begin to engage in an interactive "dance", where they coordinate their gaze, affective expressions, co-vocalizations, and touch patterns into a dyad-specific rhythmic dialogue. This non-verbal experience plays a key role in social, emotional, cognitive, and brain development[114]. Mothers and fathers engage in parent-specific forms of synchrony, more rhythmic in mothers and object-focused in fathers[212].

Parent-child affect synchrony is associated with multiple hormones that support bonding, such as oxytocin, vasopressin, beta-endorphin, prolactin, cortisol and salivary alpha amylase, as well as immune biomarkers, including salivary IgA and IL-6[213]. Similarly, it is linked with activation of the affiliative brain in both mothers[214] and fathers[89]. Non-verbal synchrony is also found during triadic mother-father-infant interaction[215], setting the stage for children's social participation in cultural and group activities.

Toddler/preschool: symbolic play sequences and co-construction of imaginary narratives

At the second and third years of life, toddlers begin to engage in symbolic play and start to imbue objects with symbolic meaning and "story-like" symbolic sequences. Children's symbolic complexity is not only predicted by synchrony with mother and father in infancy[216], but the temporal contour of the infant's rhythmic exchange with mother and father predicts the organization of symbolic play sequences – brief, random and numerous with father, and longer, slower-to-build and fewer with mother[126].

During the preschool years, children begin to co-construct a dialogue that contain future and past events, imaginary scenarios, and alternate reality, in which they can immerse themselves. These playful creative abilities draw on the non-verbal synchrony of the first months of life[210] and transform the synchronous dialogue into a social event involving creativity, language and emerging theory-of-mind skills, that express inner reality. Preschoolers' reciprocal interactions with mother and father predict children's theory-of-mind abilities and the development of a moral stance across childhood and adolescence[114].

At this stage, children begin to have "best friends" and enter into social institutions built by the culture. The experience of affect synchrony shapes the child's social competencies with peers in culture-specific ways[217]. Parental oxytocin levels, OXTR genes, and early synchrony predict children's synchrony with their first best friend[72].

Later-childhood/adolescence: empathic dialogue

Beginning at around 9-10 years, and continuing into adolescence, children markedly reduce the amount of "play" interactions with their parents, and the dialogue becomes a verbal one: interactions that require the resolution of conflicts, exchange of information, and, in health, parent-child discussion of experiences, ideas, feelings, opinions, and plans for the future.

The synchronous dialogue at this stage incorporates the child's emerging capacity for behavioral, emotional and cognitive empathy; the ability to plan ahead, elaborate, cooperate, and show motivation; and the capacity to see the other person's point of view. Such social abilities, particularly at this stage when the attachment focus shifts from parents to friends, are crucial for children's well-being, and are associated with resilience in the face of adversity and with maturation of the social brain[113,218-220].

Adulthood: mutuality, intimacy and perspective-taking

When the mother-child bond was "good enough" and synchrony progressed along developmental lines, creating space for

both resonance and reparation, mother and young adult are able to face each other as two adults who still maintain their roles, but are able to incorporate them into a dialogue that respect their maturity yet reverberates their entire relationship. It rests on the early familiar rhythms and echoes all developmental stages, but it is a dialogue that is mutual and respectful, intimate and autonomous, familiar and secure, and still differs from a couple.

Such dependable synchrony enables individuals to enter with trust and mutuality other relationships and build the bridge to the next generation, that can transcend the parent's life through the adult child's ability to evoke the dyadic experiences with the parent in his/her own brain in the parent's absence.

Overall, synchrony, which gradually enriches the infant's social repertoire with the maturation of more complex mental abilities, enables variability within order, diversity within familiarity, and creativity within stability. Synchrony bears on the "stuff" of life, where the biological integrates with the social to give meaning, form bonds, and withstand hardship.

THE MAKING OF THE RESILIENT CHILD: THREE LONGITUDINAL HIGH-RISK COHORTS

Our model suggests that biological and social provisions embedded in the mother-infant bond provide the foundation for life-long resilience. For many children across the globe, however, these provisions are compromised. To make progress in understanding resilience, we must tease apart one adverse condition from the next, examine the specific provisions impaired by each, and test how these omissions affect outcome.

We have suggested that human studies must begin at birth or as close to it as possible, employ longitudinal designs, and examine the "missing component" in the maternal provisions on the basis of specific research programs in animal models, that manipulate these provisions and test their sequalae on offspring brain and behavior[30].

There are three main sources of disruptions to maternal-infant bonding, stemming from mother, child and context, each affecting millions of children worldwide.

Maternal postpartum depression impacts 15-18% of parturient mothers in industrial societies, and up to 30% in the developing world[221]. We have suggested that Meaney's work[222] on the long-term effects of low maternal licking-and-grooming on the brain oxytocin and stress response in rat pups may provide insights into the long-term consequences of maternal depression.

Premature birth occurs in 10.5% of live birth in industrial societies[223], and its well-known negative impact relates, in part, to maternal separation following incubation, and its effects on environment-dependent life-sustaining systems, resonating Hofer's "maternal proximity" model[27].

Early life stress bears long-term negative consequences on development. One in five children worldwide are growing up in the context of chaos, immigration, food or shelter insecurity, tribal or ethnic war, poverty, and violence. The animal model that may parallel these disruptions is the "varying foraging demands"[224,225], in which bonnet macaque mothers are exposed to episodes of available food versus unavailable and difficult to find food, alternating unpredictably between times when mother is available and periods of minimal caregiving. Such conditions were found to carry the worst effect on offspring – in terms of brain growth, stress response, and behavior – compared to the high or low conditions, suggesting that the inconsistency embedded in early life stress is the most detrimental to children's resilience.

To understand resilience from a developmental neuroscience perspective, we followed three cohorts of mothers and infants from birth (or infancy) up to adolescence/young adulthood, focusing on how the components of the neurobiology of affiliation differentiated children on a risk versus resilient trajectory. Each cohort tapped one of the aforementioned disruptions to maternal-infant bonding, and hypotheses were based on the parallel animal models.

The *postpartum depression* cohort utilized a community birth-cohort to tease out mothers who were chronically depressed across the child's first years. The *war-exposed* cohort involved mothers and children living in a zone of continuous war-related trauma, and the *premature cohort* included low-birthweight but neurologically intact premature infants, half of whom received maternal-infant skin-to-skin contact ("kangaroo care") in the neonatal period. Repeated assessments of synchrony, regulatory skills, oxytocin, stress hormones, and psychopathology were conducted across childhood, and at the final time-point we imaged the social brain.

Maternal postpartum depression

Our birth cohort included only physically healthy, cohabitating mothers who were above 21 years and above poverty line, to tease apart the effects of depression *per se* from frequently co-occurring conditions (single parenthood, teenage mothers, poverty). Women were assessed for depression repeatedly across the first year, and again at 6 and 10 years. We formed two cohorts: children growing up in the context of chronic maternal depression from birth to 6 years, and healthy controls.

Maternal depression increases psychopathology

Exposure to early and chronic maternal depression markedly increased child propensity for psychopathology, even when families were at low risk. At six years, 60% of children to mothers who were diagnosed with major depression at both 9 months and 6 years, and reported being generally depressed throughout the child's early years, received a full-blown Axis I psychiatric diagnosis (compared with 15% of controls), with the most prevalent disorders being anxiety and conduct disorders[226]. At 10 years and pre-adolescence, more than 50% of these children still received a psychiatric diagnosis, even when mothers remitted, highlighting the long-term effect of early exposure. Higher externalizing and internalizing symptoms were also reported in children of de-

pressed mothers[227].

Synchrony fosters resilience

Depressed mothers failed to provide the age-appropriate co-regulatory caregiving required to support development. At 9 months, micro-analysis of non-verbal behavior indicated that depressed mothers showed minimal social gaze, positive affect, and affectionate touch, and engaged in minimal synchrony with their infant[191]. As synchrony extended over time, depressed mothers were unable to develop more mature forms of reciprocal dialogue.

Synchrony was individually stable from birth to adolescence, and the lower synchrony in children of depressed mothers predicted increased psychopathology and greater social withdrawal. At 6 years, children of depressed mothers showed little behavioral empathy[228]. At 10 years, they showed lower executive functions and reduced emotion understanding. These aberrant socio-emotional outcomes were predicted by the lower synchrony.

At the same time, synchrony functioned as a resilience component. Among children of depressed mothers who still received more synchrony (either from their fathers, due to greater functionality of the oxytocin system, or because of the child's inborn sociability), it served as a protective factor.

Children's ability to function more adequately in the social world, form friendships, and engage in peer activity, all triggered by synchrony, markedly reduced the effects of early maternal depression on the propensity for mental disorders, executive abilities, and emotion knowledge. This effect was particularly salient in late childhood, a period when peer relationships begin to assume a greater impact on children's lives, lending support to our argument that resilience components function differently at various stages and that development should become a focus in the conceptualization and research of resilience.

Altered stress response is mediated by mothers' negative parenting

Effects of maternal depression on children's stress response were complex, depending on developmental stage, type of measurement, and resilience indicators. At 9 months, infants of depressed mothers showed greater cortisol reactivity to a social stressor and diminished recovery[229]. At 6 years, maternal depression impacted cortisol variability, but this was found only among children who received tense, critical and negative parenting[228]. These findings highlight the importance of the plasticity/flexibility component of resilience for stress reactivity. At 10 years, only children of depressed mothers who received more negative parenting exhibited higher cortisol, and such over-activation of the hypothalamic-pituitary-adrenal (HPA) axis mediated the effects of depression on psychopathology[221].

We also measured salivary IgA, a biomarker of the immune system, and found higher levels in children of depressed mothers in late childhood, indicating greater stress, but this was found only among children receiving minimal synchrony, attesting to the resilience role of synchrony on the stress and immune systems.

Fathers enhance resilience

In the context of the minimal synchrony provided by the depressed mother, a synchronous father-child relationship served an important resilience function. When fathers showed sensitive and reciprocal parenting, the propensity for psychopathology among children of depressed mothers markedly decreased[230]. It appears that one mechanism by which sensitive fathering promotes resilience is by altering the family atmosphere, making family interactions more cohesive, harmonious and involved even when mothers are depressed[231]. These findings echo the "social monogamy" mechanism described above, and suggest that opening the maternal-infant bond to other affiliative bonds within the family confers resilience.

In another study, we followed parents and their first-born child in the Israeli and Palestinian societies from infancy to preschool. We found that maternal depression carried a less toxic effect on child psychopathology and symbolic competencies in the Palestinian society, and this was related to the extended-family living arrangements in this culture, which enabled children ample opportunities for synchronous interactions with other adults of kin relationship[232].

Oxytocin promotes resilience

At both 6 and 10 years, depressed mothers and their children had lower oxytocin production, as measured in both saliva[226] and urine[233]. Both mothers and children had greater prevalence of the GG genotype on the OXTR gene (rs2254298), associated with greater vulnerability for mental disorders[234]. When mothers had the A allele on the OXTR gene, the child's propensity to receive an Axis I diagnosis at 6 years was reduced by half[226]. At 10 years, when children's salivary oxytocin was high, this attenuated the effects of maternal depression on child externalizing and internalizing symptoms[227].

Adolescents' affiliative brain

In early adolescence, we measured children's neural empathic response to others' pain and the brain basis of attachment using MEG. Among children of depressed mothers, we found disruptions to the neural empathic response in the superior temporal sulcus, a hub of the social brain, which showed diminished alpha activation and quicker abortion of neural response at around 900-1100 ms post-stimulus. Such aborted response was predicted by the augmented intrusive and negative parenting and diminished synchrony that these adolescents experienced in infancy, highlighting the detrimental effects of the depressed

mother's style on brain development over time[219].

To assess the brain basis of attachment, we employed the typical paradigm of exposing children to videos of their own interaction with their mother at an earlier stage as compared to unfamiliar interaction. The typical neural activation to attachment cues involved a multi-rhythmic response of alpha, beta and gamma, including alpha suppression in posterior region, and beta and gamma activations in a large right cluster including the superior temporal sulcus, fusiform gyrus, and insula. However, children of depressed mothers, but *only* those who developed an affective disorder themselves, showed an aberrant response involving both reduced response to social cues and attenuation of the differentiation between attachment and non-attachment stimuli. These disruptions were predicted by the lower functionality of the oxytocin system and the reduced mother-child synchrony across childhood.

While these findings specify the risk for later attachments in children of depressed mothers, they also show that some children growing up in the context of chronic maternal depression are more resilient, and that components of the neurobiology of affiliation are markers of resilience.

Early life stress and trauma

Our early life stress and trauma cohort included children and their mothers living in a zone of continuous war who were exposed to repeated and unpredictable missile and rocket attacks for nearly 20 years. We assessed children in infancy, middle childhood (5-7 years) and late childhood (10 years), and imaged the social brain in early adolescence.

Comorbid mental disorders following chronic early trauma

Children growing in such a traumatic and chaotic environment exhibited a 3 to 4-fold increase in the prevalence of Axis I mental disorders and a marked increase in internalizing and externalizing symptoms. In comparison with the depressed mothers cohort, a special feature of this cohort was that two thirds of the diagnosed children showed more than one diagnosis, with some presenting three or even four mental disorders, suggesting that trauma expresses in multiple dysfunctions across the entire psychopathological spectrum[235].

Assessing the trajectories of risk and resilience across the first decade of life in trauma-exposed children, we found that children who never exhibited mental disorders or remitted after early psychopathology had mothers who were less symptomatic, experienced more synchrony, and showed greater social competence at late childhood (10 years)[236].

Oxytocin buffers stress

In this cohort, oxytocin functionality was associated with resilience in the face of trauma. Greater functionality in the oxytocin receptor gene in child, mother and father differentiated children who developed chronic post-traumatic stress disorder (PTSD) from those who remitted by middle childhood[235].

At 10 years, unlike the children of depressed mothers, we found no group differences in children's oxytocin levels, indicating that not all children growing up within a war zone show fundamental disruptions to the biological basis of affiliation, and that some mothers are able, by recruiting significant effort, to buffer the hazardous effects of war on their child. Oxytocin levels in war-exposed mothers, however, were lower, attesting to the immense burden of raising a child in the context of unpredictability and trauma, and such burden was found across multiple maternal hormonal and neural systems.

Endocrine synchrony was found between mother and child. When maternal oxytocin was low and synchronous parenting reduced, children exhibited significantly more symptoms. But this was not the case when mothers maintained high oxytocin levels and exhibited sensitive, non-intrusive parenting[120].

The stress response

We measured mothers' and children's chronic and phasic cortisol in early childhood, late childhood, and early adolescence, by assessing both hair and salivary levels of the hormone. In early childhood, cortisol and salivary alpha amylase, a marker of the sympathetic arm of the stress response, differentiated exposed children with and without PTSD. The exposed no-PTSD children had significantly higher levels, while the PTSD children had low and flat levels[236]. These findings suggest that, in the context of chronic trauma and during early childhood, greater activation of the HPA axis marks resilience, not risk.

At 10 years, again, both chronic and phasic markers of the HPA axis were elevated only in war-exposed children who developed psychopathology, and those were children of mothers with higher HPA axis activation and lower synchrony[73]. We suggest that "mothers stand between war and the child" and that, when mothers are able to contain their own stress and protect the child from the external trauma, they are capable to buffer the child's stress response.

In early adolescence, however, exposed children as a group, as well as their mothers, showed higher and less variable cortisol levels, suggesting that chronic exposure to unpredictable stress marks a risk factor in itself, regardless of the relationship. Possibly, such vulnerability is expressed during key developmental periods, such as the transition to adolescence[237]. Immune biomarkers were higher in war-exposed mothers and children, highlighting the great wear-and-tear on the immune system in the context of chronic adversity and supporting models on allostatic load and the stress response[238].

Children's and mothers' brain

In this cohort, unlike the other two, we imaged both mother's and child's brain in identical paradigms, in an attempt to assess

how chronic stress impacts neural systems in both sides of the caregiving dyad. Across paradigms, we found that alterations in brain functioning were predicted by the history of the relationship, differentiating children on risk or resilience trajectories for maturation of the social brain.

We assessed connectivity and power of the default mode network (DMN), the neural system that sustains the sense of self, switch of internal and external attention, and autobiographical memory[239-241]. In both mothers and children, disruptions were found to DMN connectivity, not power, highlighting again the role of the plasticity component in resilience and the reduced ability of the discrete structures to cohere into a unified system that provides a foundation for the sense of self.

Disruptions to maternal DMN were found in alpha rhythms, the main rhythm of the awake mature brain, whereas disruptions to children's DMN occurred in the theta band, a biomarker of the developing brain[242]. Children with PTSD showed the greatest disruption to theta connectivity. Disruption in theta connectivity patterns were predicted by maternal intrusive, anxiety-provoking parenting across childhood and by higher cortisol production in later childhood, underscoring the long-term effects of unpredictable rearing combined with uncontained parenting on the core system sustaining neural functions[243].

We found no group differences between exposed and non-exposed children in the neural empathic response to others' distress. This response involved alpha activation in a large cluster including the supplementary motor area, part of the embodied-simulation network, and the middle cingulate cortex, a node of the DMN. Synchrony, which was diminished in the war-exposed cohort, mediated the effects of early trauma on the neural empathic response, and children receiving more synchrony across childhood showed greater activation to others' distress[244]. Mothers' neural empathic response similarly showed disruptions, but those were specific to the adult brain[245].

Prematurity

Our "kangaroo care" project is the only existing study testing the effects of maternal separation and structured contact on the maturation of life-sustaining functions over time in human infants. Mothers of low-birthweight premature infants (<1,750 g) were randomized to the experimental intervention (skin-to-skin contact for at least one hour per day for at least 14 consecutive days during the incubation period) or to standard incubation care.

Dyads were followed seven times across the first decade (before the intervention, at discharge, at 3, 6, 12 and 24 months corrected age, and at 5 and 10 years). In young adulthood (18-20 years), we home-visited young adults and observed their relationship with their mothers, assessed hormonal indices and executive functions, and within the next month imaged the social brain using functional magnetic resonance imaging.

We found that provision of maternal bodily contact impacted the same systems in humans as it did in young mammals. Kangaroo care improved autonomic functioning and organized the sleep-wake cycle, and improved newborn orientation and information processing. At the same time, it improved mothering and the provision of maternal behavior in the neonatal period[246].

Consistent with our model of the staged development of regulatory functions[138], these improvements in physiological regulation and mothering enhanced resilience and dynamically impacted development. Neonates showed better arousal modulation in the processing of highly-aroused stimuli at 3 months, better exploratory behavior at 6 months, and better abilities for self-control at 1 and 2 years. Mental, but not motor, abilities were improved in the experimental group at 6, 12 and 24 months[247,248]. At the same time, mother-infant synchrony improved, and mothers also expressed more breast milk, triggering an oxytocin response[249]. Following kangaroo contact, synchrony was greater at any observation across the first years, and the higher social reciprocity linked with better cognitive and regulatory abilities[210].

At 10 years, we found that the improved regulatory capacities of the kangaroo care subjects persisted. We found higher respiratory sinus arrhythmia and better responsivity of this arrhythmia to emotional stress, indicating more adaptive functioning of the autonomic nervous system. Sleep was measured by actigraphy worn across five consecutive nights, and children who received kangaroo care as neonates showed better sleep organization and shorter wake bouts. Furthermore, the kangaroo children's HPA axis response to social stressor exhibited diminished cortisol stress response and quicker recovery[250]. As to cognitive abilities, by 5 years there were no longer differences in general IQ, but kangaroo care subjects had improved executive abilities, working memory, and cognitive flexibility at 5 and 10 years.

Overall, our findings underscore the systems impacted by the resilience components embedded in the maternal body and well-adapted caregiving, as those related to the management of stress, flexible response to environmental conditions, modulation of arousal and attention, and the capacity to engage in reciprocal dialogue.

In young adulthood, we imaged the brain's empathic response to others' emotions in the kangaroo care group and the controls, assessing how the brain sustains "empathic accuracy", an important determinant of the empathic response[251,252], and differentiates response to others' distress, sadness and joy. Using complex analysis, we detected three structures that showed highly dissimilar activations across emotions: the amygdala, anterior insula, and temporal pole. Synchrony measured across development, from infancy to young adulthood, mediated the links between group membership and social brain's flexible empathic response to others' emotions. Thus, the kangaroo care increased synchrony provided a pathway by which early attachment experiences shaped the flexible neural response to others' affective states.

CONCLUSIONS

Resilience is a core construct in clinical theory and research that is yet to receive a comprehensive, biobehavioral conceptualization. Two main lacunas in current models on resilience in-

volve the exclusive focus on the neurobiology of fear and the lack of empirical attention to development. Moreover, most models define resilience on the negation (i.e., absence of symptoms following trauma) rather than addressing what resilience *is*.

We argue that the initial condition of mammals should be taken into consideration in understanding resilience. Mammalian young are born with two important constrains: their brain is immature at birth, and young maintain close proximity to a nursing mother. As such, all systems that support resilience, stress management, adaptation and endurance mature in mammals in relation to the provisions afforded by mother's body and caregiving behavior.

We propose a model of resilience based on the neurobiology of affiliation, the emerging scientific field that describes the neural, endocrine, genetic and molecular processes which underpin our capacity to bond, love, care, empathize and belong to social groups.

Our model highlights three core components of the neurobiology of affiliation that sustain resilience. These include the oxytocin system, the affiliative brain, and biobehavioral synchrony.

The oxytocin system is implicated in plasticity at the cellular, molecular and network assembly levels, wires the brain toward attachments, underpins the mammalian capacity to manage hardships through relationships, and plays a role in the immune system.

The affiliative brain evolved in humans from the rodent maternal brain, expanded to include higher-order structures that enable empathy, simulation and mentalization, and extended to support all other affiliative bonds, including romantic attachment, close friendship and mentorship. It is marked by great plasticity, cross-generationally transmits to infant during early sensitive periods, and shapes socio-emotional competencies.

Biobehavioral synchrony involves the coordination of biological and behavioral processes during social interaction, and it is the mechanism by which the maternal mature brain externally regulates the infant's immature brain and tunes it to social life. Humans' biobehavioral synchrony draws on mechanisms by which coordinated social behavior fosters diversity and adaptation across animal evolution, and develops within the mother-infant bond on the basis of the fetus' biological rhythms *in utero*, upon which the mother builds a social non-verbal "dance" during the first months of life. This synchronous exchange expands across development into a dialogue of mutuality, intimacy, and acknowledgement of multiple perspectives, and transfers from the mother-child relationship to other human affiliation and encounters throughout life, charting a key trajectory in the development of resilience.

Our model proposes three tenets that address what resilience *is*. These include plasticity, sociality and meaning. While the first two are animal-general, the latter is human-specific. All three tenets are supported by oxytocin, the affiliative brain, and biobehavioral synchrony, due to their involvement in neural and behavioral plasticity, their role in attachment and sociality, and their support of the capacity to attribute meaning to trauma through cultural and spiritual systems and affiliative acts that transcend the individual.

This model is supported by evidence from three longitudinal cohorts, each followed from birth/infancy up to adolescence/young adulthood. Each cohort addressed one type of disruption to maternal-infant bonding, originating in mother, child or context (maternal depression, premature birth, and chronic exposure to war-related trauma), which bears long-term impact on the child's brain, behavior and well-being. In each cohort, hypotheses were built on a specific research program in animal models that describes the "missing component" in each condition (liking-and-grooming, variable foraging demands, and maternal proximity). We repeatedly measured psychopathology, parenting, synchrony, oxytocin and stress hormones, cognition and regulatory functions, particularly looking for factors that separate children on risk versus resilient trajectories. In adolescence/young adulthood, we imaged the social brain.

Disruptions to development emerged across conditions; yet, outcomes were condition-specific and mainly expressed in interaction effects, with some children showing significant resilience. Components of the neurobiology of affiliation – synchrony and oxytocin – functioned as resilience factors across development in condition-specific ways. Endocrine synchrony (the hormonal concordance between mother and child oxytocin and stress hormones) functioned to increase risk or resilience, attesting to the mother's continuous biological external-regulatory impact on risk and resilient trajectories. In late childhood, children's social competencies, buttressed by synchrony, functioned as important resilience markers. Regulatory functions matured on top of one another, and greater regulation improved later functioning, particularly alterations during early sensitive periods, as, for instance, resulted from mother-infant skin-to-skin contact to premature infants.

In imaging the social brain, we found alterations pending on risk and resilience status. While children reared by chronically depressed mothers aborted the neural empathic response, not all children growing in traumatic contexts showed disruptions; *only* those who received minimal synchrony. The brain basis of attachment was disrupted in children of depressed mothers, but *only* among those who developed affective disorder. Similarly, when assessing the brain basis of empathic accuracy, premature infants who received synchrony showed an adequate social neural response.

In sum, drawing on 20th century philosophical and neuroscientific models that formulated a concrete, behavior-based approach to cognition and action and blurred the distinction of brain and mind, our model aims to direct attention to systems that sustain our capacity to form affiliative bonds, enter into social groups, and use relationships to manage stress, as core features of the human capacity to withstand, even thrive, in the face of trauma.

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Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): I. Psychosis superspectrum

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The Hierarchical Taxonomy of Psychopathology (HiTOP) is a scientific effort to address shortcomings of traditional mental disorder diagnoses, which suffer from arbitrary boundaries between psychopathology and normality, frequent disorder co-occurrence, heterogeneity within disorders, and diagnostic instability. This paper synthesizes evidence on the validity and utility of the thought disorder and detachment spectra of HiTOP. These spectra are composed of symptoms and maladaptive traits currently subsumed within schizophrenia, other psychotic disorders, and schizotypal, paranoid and schizoid personality disorders. Thought disorder ranges from normal reality testing, to maladaptive trait psychoticism, to hallucinations and delusions. Detachment ranges from introversion, to maladaptive detachment, to blunted affect and avolition. Extensive evidence supports the validity of thought disorder and detachment spectra, as each spectrum reflects common genetics, environmental risk factors, childhood antecedents, cognitive abnormalities, neural alterations, biomarkers, and treatment response. Some of these characteristics are specific to one spectrum and others are shared, suggesting the existence of an overarching psychosis superspectrum. Further research is needed to extend this model, such as clarifying whether mania and dissociation belong to thought disorder, and explicating processes that drive development of the spectra and their subdimensions. Compared to traditional diagnoses, the thought disorder and detachment spectra demonstrated substantially improved utility: greater reliability, larger explanatory and predictive power, and higher acceptability to clinicians. Validated measures are available to implement the system in practice. The more informative, reliable and valid characterization of psychosis-related psychopathology offered by HiTOP can make diagnosis more useful for research and clinical care.

Key words: HiTOP, psychosis, thought disorder, detachment, schizophrenia, psychotic disorders, personality disorders, psychoticism, introversion, clinical utility

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The Hierarchical Taxonomy of Psychopathology (HiTOP) consortium was formed by psychiatric nosologists to integrate evidence from studies on the organization of psychopathology and outline a system based on these data[1]. This effort is motivated by shortcomings of traditional taxonomies: arbitrary boundaries between psychopathology and normality, diagnostic instability, heterogeneity within disorders, frequent disorder co-occurrence, and inability to account for subthreshold cases. The HiTOP system addresses these problems by: a) defining psychopathology in terms of dimensions of psychological function that range from normal to abnormal, b) identifying dimensions based on observed covariation among signs, symptoms and maladaptive behaviors, and c) combining these primary dimensions into larger spectra.

The dimensional approach resolves the issue of arbitrary boundaries and diagnostic instability, as evidenced by the high test-retest reliability of dimensional psychopathology constructs [2-5]. Also, no patients are excluded from the system, because even individuals with subthreshold symptoms or unusual symptom profiles can be characterized on a set of dimensions. The HiTOP model reduces heterogeneity within constructs by grouping related symptoms together and assigning unrelated symptoms to different dimensions[6-9]. Comorbidity is recognized in this system through assignment of related conditions to the same spectrum. The hierarchical organization allows for a flexible description of a patient in terms of broad spectra or narrow subdimensions, depending on the desired degree of specificity.

The HiTOP system currently includes six higher-order spectra: internalizing, somatoform, disinhibited externalizing, antagonistic externalizing, thought disorder, and detachment[1]. These major dimensions of psychopathology reflect individual differences in a given domain across the entire population. Spectra can be combined into larger superspectra: emotional dysfunction (internalizing and somatoform), externalizing (disinhibited and antagonistic), and psychosis (thought disorder and detachment)[10-14]. Above the superspectra sits the general psychopathology or p factor, a dimension that contains features common to all mental disorders[15,16].

The HiTOP system was derived from a large body of structural research[1,17,18], but its external validity and utility are less established, as previous reviews of these topics had limited scope[19-21]. To address this shortcoming, the Utility Workgroup of HiTOP consortium assembled teams of experts to systematically review evidence on validity and utility of the system. Expert reviews were organized according to the three superspectra. The present paper is the first in this series and focuses on the psychosis superspectrum.

This superspectrum encompasses two spectra: thought disorder and detachment. The thought disorder spectrum describes individual differences that range from conventional and uncreative thinking to perception and cognition that are only tenuously based in reality. It includes both positive symptoms and the personality trait of psychoticism, also known as positive schizotypy[22-27]. The label "thought disorder" aims to capture these diverse elements and is distinct from formal thought disorder (i.e., incoherent thought and discourse), which is one of many symptoms in the spectrum. The detachment spectrum describes individual differences in volition (ranging from energetic pursuit of goals to apathy), sociability (ranging from strong social engagement to disinterest in people), and affective expression (ranging from highly expressive to restricted). This spectrum spans from the personality trait of introversion, to negative schizotypy, to negative symptoms[22,28-32].

The spectra include both maladaptive traits and symptoms. These parallel each other but reflect different timescales. Signs and symptoms reflect the current state, problems that may be acute and transient; whereas maladaptive traits capture typical levels of these problems over many years and are fairly chronic[33,34]. For instance, disorganization symptoms indicate current disturbance in organization or expression of thought and odd behavior, whereas trait peculiarity describes very similar problems but assessed over the lifetime. Indeed, disorganization and peculiarity are closely aligned empirically[35,36]. Furthermore, maladaptive traits change over time, but gradually and slower than symptoms[37-39]. Moreover, traits cover a broader range of individual differences, spanning from healthy to vulnerable to symptomatic[40-42], thus providing useful prognostic and etiologic information to complement symptom-based assessment.

The HiTOP follows a long tradition of models that posited a spectrum spanning from normality to personality pathology to schizophrenia[43-45] and elaborates on them using modern statistical modeling techniques and new evidence. It also builds on the idea of an extended psychosis phenotype, a transdiagnostic entity that includes subclinical psychotic experiences as well as frank psychosis[46-49]. The thought disorder spectrum encompasses this phenotype, and extends it to include trait psychoticism, forming a dimension that spans the entire population. The HiTOP conceptualization of psychotic disorders is also consistent with staging models and clinical high risk approaches[50-53], as HiTOP describes spectra along which people may progress from subthreshold vulnerability to symptoms.

In this paper, we examine the evidence on structural coherence and composition of thought disorder and detachment, and consider the validity and utility of these spectra.

STRUCTURAL EVIDENCE

Composition of major dimensions

The psychosis superspectrum emerges in research on the structure of psychiatric diagnoses[11] and of maladaptive personality traits[54]. It is well-documented as a non-affective dimension of psychosis that encompasses positive and negative symptoms[6-8,55]. This union of positive and negative symptoms or corresponding maladaptive traits has long been recognized clinically in diagnoses of schizophrenia and schizotypal personality disorder. Indeed, these diagnoses were found to define a dimension distinct from the emotional dysfunction and externalizing superspectra[56-62], as summarized in Table 1.

The thought disorder spectrum has been observed in many studies, which defined it primarily by positive symptoms or psychotic experiences[26,63-66]. Moreover, studies of personality pathology consistently find the corresponding psychoticism dimension[67-71]. The detachment spectrum has been reported in multiple studies of mental disorders[11,26,62,71-73]. It emerged in research on psychosis as a distinct dimension of negative symptoms[7,8,30,55,74,75]. Furthermore, detachment has been replicated several times in studies of maladaptive traits[67-70], and its healthy range – introversion – is extensively documented[32,71,76-78].

Overall, structural studies suggest that schizophrenia, schizophreniform disorder, schizoaffective disorder, and schizotypal and paranoid personality disorders reflect elevations on both thought disorder and detachment spectra (Table 1). Other psychotic disorders are linked specifically to the thought disorder spectrum, whereas schizoid and avoidant personality disorders are linked solely to detachment.

Several studies considered obsessive-compulsive disorder and, although some linked it to the psychosis superspectrum[60,63], the majority found that it falls within the emotional dysfunction superspectrum[26,57,58,62,66]. Two studies placed dependent personality disorder on detachment[62,73], but meta-analyses of personality disorders and maladaptive traits located dependent personality disorder on internalizing[70,79,80]. One study linked dysthymic disorder to detachment[73], but this is inconsistent with extensive evidence placing depressive disorders on internalizing[1]. Consequently, these three disorders and their symptoms will not be considered here.

Dissociative disorders were linked to the thought disorder spectrum in only one study[63]. However, a substantial literature has documented close ties of dissociative disorders with psychotic disorders and psychoticism[81-83]. These studies provided evidence of comorbidity, symptom overlap, and common risk factors that support the placement of dissociation within the thought disorder spectrum. In research on the structure of personality pathology, dissociation symptoms have been placed on psychoticism[84,85]. Hence, we assigned dissociation to thought disorder on a provisional basis, pending further structural research.

Bipolar I disorder was linked to thought disorder in three studies[56,58,60] and to internalizing in one[61]. Several other studies reported an association between mania and internalizing, but did not examine an association between mania and thought disorder[86-89]. We provisionally included mania in thought disorder, but it remains uncertain whether mania is better placed on internalizing, blends features of both spectra, or forms a dimension distinct from them.

Table 1 Higher-order structures that included psychotic disorders or schizotypal personality disorder in interview-based studies

	Sample size	Sample type	Schizophrenia	Schizotypal PD	Psychosis, psychotic experiences	Bipolar I	Paranoid PD	Schizoid PD	Avoidant PD	Dependent PD	Dysthymic disorder	Dissociative disorder	OCD
Psychosis superspectrum													
Wolf et al[61]	205	Inpatient	+			–							
Markon et al[62]	8,405	Community		+	+		+	+	–				–
Kotov et al[58]	2,900	Outpatient		+	+	+	+	+					–
Kotov et al[57]	469	Inpatient	+	+									–
Keyes et al[56]	34,653	Community		+		+	+	+	+				
Caspi et al[60]	1,000	Community	+			+							+
Shanmugan et al[59]	9,498	Community youth	+		+								
Total	57,130		4/4	4/4	3/3	3/4	3/3	3/3	1/2	0/0	0/0	0/0	1/4
Thought disorder spectrum													
Chmielewski[63]	381	Outpatient		+	+							+	+
Wright et al[66]	8,841	Community			+								–
Wright & Simms[26]	628	Outpatient		+	+		–						–
Schaefer et al[65]	2,232	Community adolescents			+								
de Jonge et al[64]	15,499	Community			+								
Total	27,581		0/0	2/2	5/5	0/0	0/1	0/0	0/0	0/0	0/0	1/1	1/3
Detachment spectrum													
Markon et al[62]	8,405	Community							+	+			
Roysamb et al[73]	2,794	Community						+	+	+	+		
Forbes et al[11]	2,900	Outpatient		+				+	+				
Wright & Simms[26]	628	Outpatient		–				+	–				
Total	14,727		0/0	1/2	0/0	0/0	0/0	3/3	3/4	2/2	1/1	0/0	0/0

PD – personality disorder, OCD – obsessive-compulsive disorder

Role of maladaptive traits

Psychoticism and detachment traits emerged from research on personality pathology, and are included in the DSM-5 alternative model of personality disorders. These dimensions were also found in research on schizotypy, a personality vulnerability to psychotic disorders, which identified distinct positive and negative schizotypy dimensions[90]. Similar dimensions emerged in research on clinical high risk for psychosis, which described positive and negative risk syndromes[91]. Positive schizotypy and positive risk syndrome were found to map onto psychoticism, and negative schizotypy and negative risk syndrome onto detachment[92,93].

Psychoticism shows clear links to schizotypal personality disorder, dissociation, and psychotic disorders[23,26,85,94,95]. Detachment has a specific association with schizoid personality disorder, as well as weaker links to avoidant and schizotypal personality disorders[23,26,80,94,95]. Both traits are tightly linked to schizophrenia[24,96]. Overall, cross-sectional data suggest that these traits underpin thought disorder and detachment spectra.

These relationships are further underscored by evidence that psychoticism and detachment predict first onset of psychosis and negative symptoms[41,97,98], consistent with the view that these traits are precursors to symptoms[43]. Psychosis onset is predicted more by psychoticism than detachment, and detachment can be considered a vulnerability trait for negative symptoms and schizophrenia[98]. These findings are consistent with high rates of future schizophrenia onset in treatment-seeking samples with schizotypal personality disorder[99,100].

Detachment is aligned with introversion and can be considered its more extreme and maladaptive expression[32,78,101]. In psychotic disorders, positive symptoms were found to align with psychoticism, and negative symptoms with detachment and introversion[22,28,29,41,102,103]. Thus, symptoms and traits jointly define HiTOP spectra. Some theories of relations between personality and psychotic disorders hypothesized a latent discontinuity, with risk of psychosis limited to a qualitatively distinct subgroup[43,104]. Studies of this question produced mixed results, and further research is needed to determine whether any discontinuities exist in the psychosis superspectrum[105,106].

Overall model

Subdimensions have been consistently identified within the spectra. Thought disorder symptoms can be decomposed into reality distortion (hallucinations and delusions) and disorganization (formal thought disorder and bizarre behavior) dimensions[107-109]. Dissociation and mania can be added as provisional dimensions[56,58,60,63,83]. The spectrum also includes facets of psychoticism trait: peculiarity (odd appearance, speech and behavior), unusual beliefs (unfounded or magical), unusual experiences (perceptual distortions, depersonalization and derealization), and fantasy proneness (vivid imagination and tendency to become engrossed in inner experiences)[25,68,78,110].

Detachment symptoms include inexpressivity and avolition dimensions[7,111-113]. Trait facets of detachment comprise emotional detachment (difficulties in the experience, description and expression of feelings), anhedonia (deficits in positive emotions and energy), social withdrawal (avoidance of interpersonal interactions due to disinterest), and romantic disinterest (lack of interest in sex and intimacy)[25,68,78]. Further subdivisions are possible[74,114,115], but are not yet established.

The overall model of major dimensions and their components is summarized in Figure 1. It extends the current HiTOP model[1] in several respects based on additional evidence. DSM-5 diagnoses are not included in HiTOP, but they are comprised of the same features (signs, symptoms and traits). Consequently, spectra can be observed in patterns of comorbidity among disorders, thus helping to define these major dimensions of HiTOP. In the present paper, we focus on validity and utility of thought disorder and detachment spectra, although with the understanding that they contain multiple trait and symptom subdimensions.

VALIDITY EVIDENCE

The HiTOP Utility Workgroup examined validity of thought disorder and detachment spectra against nine criteria: behavior genetics, molecular genetics, environmental risk factors, cognitive and emotional processing abnormalities, neural substrates, biomarkers, childhood temperament antecedents, illness course, and treatment response.

These validators are based on the eleven criteria outlined by the American Psychiatric Association's Diagnostic Spectra Study Group for the meta-structure project, the goal of which was to identify coherent clusters of mental disorders[116]. The meta-structure project criteria were an extension of the validators proposed by Robins and Guze[117]. Among the eleven criteria, we did not consider "comorbidity" and "symptom similarity", as these are ensured in derivation of the HiTOP model. Indeed, the spectra are defined by disorder and symptom co-occurrence.

We sought to determine whether thought disorder and detachment spectra are coherent on each validator; that is, if psychopathology included in the spectrum has similar associations with the criterion. We examined literatures on symptom dimensions and traits included in the two spectra. Related disorders were considered also, as existing validity research largely focused on diagnostic groups. We found that data on some conditions (e.g., dissociation) are very limited, and we do not discuss them in this validity section.

Behavior genetic evidence

Evidence for a genetically coherent psychosis superspectrum was originally observed in family studies. This research found that relatives of people with schizophrenia have highly increased rates of non-affective psychoses, schizoaffective disorder, schizotypal and paranoid personality disorders, as well as schizophre-

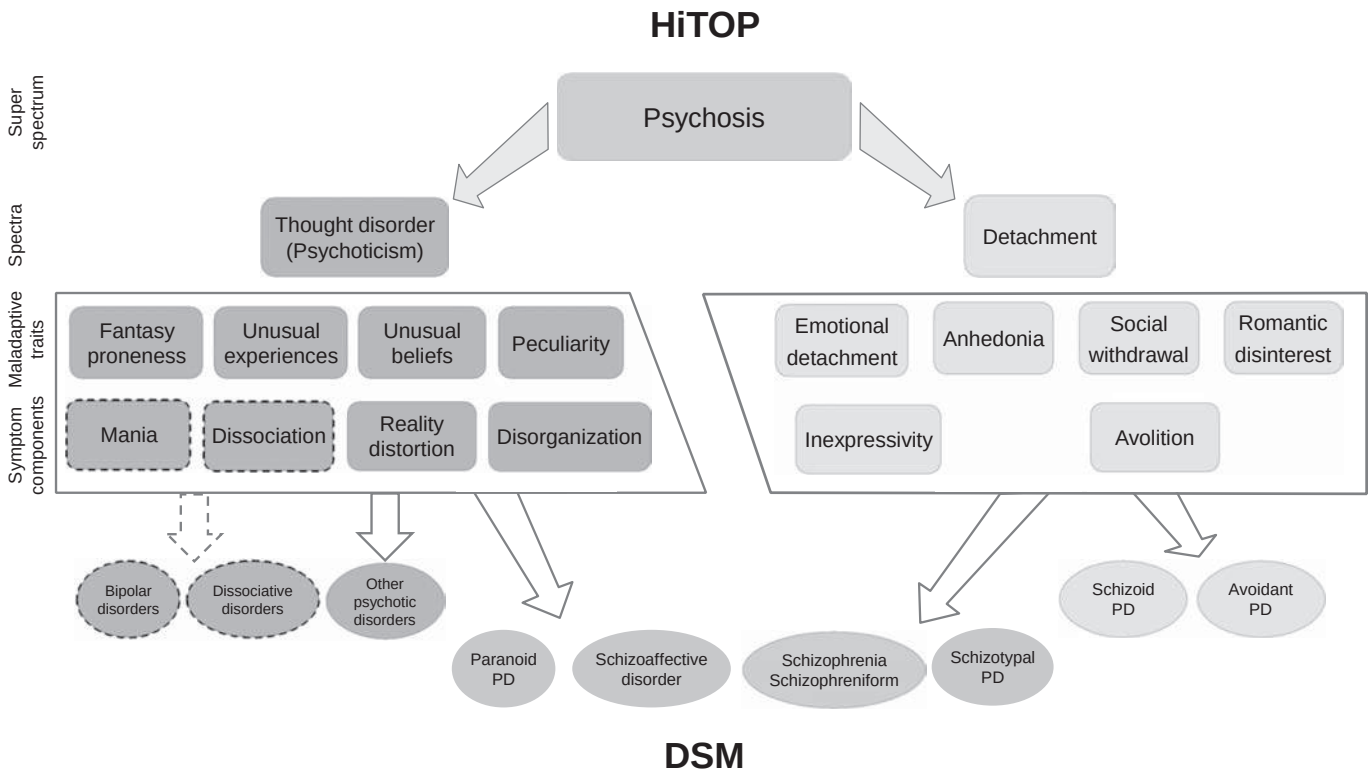

Figure 1 Dimensions within the Hierarchical Taxonomy of Psychopathology (HiTOP) psychosis superspectrum. PD – personality disorder

nia[118]. Twin research identified a similar genetic factor common to schizotypal, schizoid and paranoid personality disorders[119].

Evidence for the thought disorder spectrum is even more compelling. Schizophrenia, bipolar I disorder, and schizoaffective disorder have shown high level of genetic overlap across studies that used family, adoption and twin designs[120-123]. This pattern supports the genetic coherence of the thought disorder spectrum. Moreover, family data suggest that this spectrum is distinct from genetic liabilities to internalizing and externalizing problems[123]. Importantly, twin modeling revealed that genetic risk for thought disorder is continuous, such that clinical and subclinical levels of the spectrum reflect the same genetic liability[124]. Also, directly measured psychoticism was found to be substantially heritable[125,126].

The detachment spectrum has been linked to schizophrenia in family studies. This research established that the detachment trait is elevated in relatives of people with schizophrenia compared to relatives of healthy probands or probands with mood disorders, indicating a specific connection between detachment and schizophrenia[127]. Moreover, schizophrenia showed stronger familial associations with detachment than with psychoticism[127].

Twin studies supported the genetic coherence of the detachment spectrum. They identified a genetic factor common to schizoid and avoidant personality disorders[128,129], and potentially to schizotypal personality disorder and dysthymic disorder as well[128]. The genetic detachment factor also emerged in twin studies of maladaptive traits[129]. Furthermore, a twin study of normal and maladaptive personality found a genetic factor defined by detachment, schizoid and avoidant personality disorders, as well as introversion (and also low openness)[130]. This factor was distinct from genetic liabilities to other forms of personality pathology. Also, directly measured detachment shows considerable heritability[125,126].

Overall, this research provided clear evidence of two coherent and distinct genetic factors – aligned with psychoticism and detachment – that underpin the proposed psychosis superspectrum. Moreover, the superspectrum itself is highly heritable, with 73% of variance due to genetic influences[131].

Molecular genetics

Molecular genetic research strongly supports the genetic coherence of the thought disorder spectrum. Genome-wide association studies (GWAS) of schizophrenia and bipolar disorder found that many common genetic variants, each with a small effect size, contribute to risk for both conditions[132-134]. Indeed, the genetic correlation between schizophrenia and bipolar disorder is very high (rg = .70)[132,135]. This genetic overlap is further confirmed by correlation between their polygenic risk scores[136,137]. Notably, bipolar I disorder relates more strongly to schizophrenia than to depression (rg = .71 vs. .30), whereas the opposite is true for bipolar II disorder (rg = .51 vs. .69)[132]. Overall, molecular genetic evidence indicates a special connection between mania

and thought disorder. Reality distortion – including subthreshold symptoms – and disorganization were associated with the genetic risk for schizophrenia, but these effects were modest and not specific[138-140].

The genetic coherence of the detachment spectrum has not been studied, but genetic links between detachment and thought disorder dimensions have been documented, which supports the psychosis superspectrum. Schizophrenia polygenic risk score was found to predict negative symptoms both in patients and in the general population[140-143]. Also, anhedonia and low sociability demonstrated moderate genetic correlations with schizophrenia[144,145].

Beyond common genetic variants, approximately 2-3% of schizophrenia patients have rare variants with substantial effect on the risk for the disorder, such as copy number variants (CNVs)[146]. CNVs have not been consistently implicated in risk for the psychosis superspectrum aside from schizophrenia. However, one study found elevated burden of CNVs in schizoaffective disorder[147] and another found it in individuals with psychotic experiences[138].

In sum, molecular genetic research supports the coherence of the thought disorder spectrum and the psychosis superspectrum. Bipolar I disorder has been clearly linked to thought disorder on the genetic level. However, the genetic structure of detachment and lower-order dimensions in both spectra remain to be explicated.

Environmental risk factors

A wide range of environmental risk factors have been identified for schizophrenia and the psychosis superspectrum broadly[148]. We focus here on the most replicated effects.

Ethnic minorities and migrants experience high rates of nonaffective and affective psychotic disorders[149-153]. In the general population, ethnic minority status was associated with elevated psychoticism[48,154]. In patients, minority status was correlated with more severe reality distortion, disorganization, and negative symptoms, although this last effect is weaker and less consistent[8,155-157]. Multiple processes may explain effect of minority status, such as high social adversity, but are not yet fully understood[153].

The incidence of psychotic disorders is considerably higher in urban than rural areas[158,159]. In patients with first-episode psychosis, urbanicity was associated with more severe reality distortion and disorganization symptoms[156]. In the general population, it was associated with elevated psychoticism[160-162]. Links between urbanicity and detachment have not been studied. The effect of urbanicity on psychosis is unlikely to be explained by methodologic confounds, such as social drift, but it is uncertain which of the many exposures common in urban environments explain elevated risk[158]. Importantly, the effect appears not to hold in low- and middle-income countries, where urbanicity may index greater access to resources[163].

Childhood adversity and trauma is a potent risk factor for nonaffective and affective psychotic disorders[164,165]. This association was observed at all levels of thought disorder, from psychoticism to symptoms to diagnosis[166]. Childhood adversity is also a risk factor for bipolar I disorder[167]. Childhood adversity is clearly linked to reality distortion symptoms, while its association with negative symptoms is less consistent and understudied, and data on disorganization are lacking[168]. With regard to traits, childhood adversity is consistently associated with psychoticism, and preliminary evidence supports a link to detachment[169,170].

Cannabis use was found to predict onset of psychotic symptoms and psychotic disorders[171]. In the general population, it was associated with both elevated psychoticism and detachment, although the latter effect was weaker[48,172-174]. In patients, cannabis use was associated with more severe reality distortion symptoms and was not consistently linked to other symptoms[175-179].

Overall, these data indicate common risk factors for each spectrum. Ethnic minority status and cannabis use were linked to both detachment and thought disorder spectra, especially to the latter. Urbanicity and childhood adversity were linked more specifically to the thought disorder spectrum.

Cognitive and emotional processing abnormalities

In schizophrenia, schizoaffective disorder, bipolar I disorder, and schizotypal personality disorder, cognitive deficits were documented in all domains: sensorimotor, attention, learning and memory, executive functions, language, and social cognition[180-184]. These deficits were most pronounced in schizophrenia, but the other disorders showed a similar, although less extreme, profile of cognitive impairment[185-188]. With regard to dimensions, negative and disorganized symptoms were linked to all aforementioned deficits, whereas reality distortion was essentially unrelated to cognitive impairment[189-191]. Similarly, among maladaptive traits, detachment showed the strongest association with a range of cognitive deficits[192-194]. The reported effects were weaker for traits than for symptoms, likely because nearly all personality studies were performed in non-clinical populations with a limited range of psychopathology.

Schizophrenia, schizoaffective disorder, and schizotypal personality disorder also showed deficits in ability to anticipate and seek pleasurable experiences[31,182]. Behavioral deficits were documented in reward processing tasks including delay discounting, reinforcement learning, and emotion-based decision making[195-199]. These effects were specific to detachment and largely unrelated to thought disorder[31]. In contrast, mania was associated with hypersensitivity to rewards[200,201].

Overall, research consistently indicates that cognitive deficits are linked to detachment and disorganization, reward processing deficits are specific to detachment, reward hypersensitivity is specific to mania, and none are clearly related to reality distortion. HiTOP conceptualization of psychopathology can help to isolate associations with cognition that are obscured in heterogeneous diagnoses.

Neural substrates: neuroimaging

Neural correlates of the psychosis superspectrum have been identified using various imaging modalities, and the number of

potential substrates is very large. Here we focus on the most robust findings that were examined across multiple conditions. We discuss the thought disorder spectrum and then the detachment spectrum.

The thought disorder spectrum is associated with structural deficits in numerous brain regions[182]. The most replicated finding is smaller hippocampal volume in schizophrenia, schizoaffective disorder, bipolar disorder, and schizotypal personality disorder[202-205]. This was also observed in relatives of people with schizophrenia[206]. Furthermore, smaller hippocampal volume was associated with severity of reality distortion symptoms[205]. Of note, other volumetric differences have been linked to multiple disorders in the spectrum, but research on them is more limited[203,207-210].

Structural connectivity abnormalities were reported throughout the thought disorder spectrum. Small splenium of the corpus callosum was found in patients with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder, as well as in their relatives[211]. This indicates weak connectivity among multiple brain regions, including the hippocampus. Moreover, smaller splenium was associated with worse reality distortion symptoms[211]. Studies using fractional anisotropy found that low white matter integrity in the genu of the corpus callosum and in the posterior cingulum fiber bundle are present in both schizophrenia and bipolar disorder, as further evidence of common abnormalities in structural connectivity[212].

Functional connectivity alterations were observed in thought disorder as well. The most replicated finding is hypoconnectivity of multiple brain networks in schizophrenia, schizoaffective disorder, and bipolar disorder[213-215]. Connectivity patterns differ across conditions, but show substantial overlap, especially hypoconnectivity within the default mode network and cingulo-opercular network. This hypoconnectivity was found across psychotic disorders and in people with psychotic experiences[216-218]. Similarly, poor efficiency in the connectivity of the cingulo-opercular network was observed across psychotic disorders[219] and was associated with psychoticism in the general population[218].

The detachment spectrum has been studied less extensively, but a few promising findings have emerged. A large study not only found a widespread cortical thinning in schizophrenia, but also linked it to negative symptoms, whereas correlations between positive symptoms and cortical thickness were much more limited[208]. Also, negative symptoms were associated with smaller volume of left caudate nucleus, supporting involvement of the ventral striatum dysfunction in detachment[220].

Functional magnetic resonance imaging supported this interpretation, revealing bilateral hypoactivation of the ventral striatum during potential reward anticipation in schizophrenia, other psychotic disorders, and clinical high risk samples[221]. Importantly, this hypoactivation was associated with negative and not positive symptoms. These findings are consistent with the role that the ventral striatum plays in motivation and reward processing[222,223], in line with emotion deficits described earlier.

With regard to connectivity, negative symptoms were associated with low white matter integrity in many brain regions, including the corpus callosum[224], and with hypoconnectivity within the default mode network[216]. However, connectivity research is fairly preliminary, and detachment traits and related personality disorders have not been studied.

In addition, abnormal activation patterns within the dorsolateral prefrontal cortex and connected executive control regions during working memory tasks were consistently found in schizophrenia and clinical high risk states[225,226]. Moreover, these abnormalities were associated with the psychosis superspectrum in the general population[227]. Some evidence suggests that this association is with detachment rather than thought disorder, consistent with behavioral data on working memory performance and negative symptoms[190,227,228]. However, specificity remains uncertain, and abnormal activations during working memory may be a marker of the overarching superspectrum.

Neural substrates: neurophysiology

Neurophysiological measures have provided further understanding of neural processes underpinning the superspectrum. Deficits in basic inhibitory processes have been documented in schizophrenia, schizotypal personality disorder, and bipolar disorder[182,229,230]. These processes include sensory gating (P50 amplitude), prepulse inhibition, and antisaccade eye movement. They suggest poor selective attention and inhibition, resulting in sensory and cognitive overload, which can contribute to psychoticism and positive symptoms[230].

Electroencephalography probes neural dysfunction more directly. Abnormalities in P300 amplitude and latency as well as mismatch negativity have been established in schizophrenia, clinical high risk states, schizotypal personality disorder, and bipolar disorder[182,192,231-234]. This pattern suggests that P300 and mismatch negativity track thought disorder, but direct evidence of specificity is limited, and they may prove to be markers of the general psychosis superspectrum.

A relatively new marker is error-related negativity, a key measure of early performance monitoring associated with function of the anterior cingulate[235]. This measure is blunted across psychotic disorders as well as in schizotypal personality disorder and clinical high risk groups[236]. This blunting appears to be specific to detachment rather than thought disorder[237,238].

Biomarkers

Blood-based measures are emerging as potential biomarkers for the psychosis superspectrum. Metabolic dysregulations – such as high glucose and triglyceride levels – can be found in both schizophrenia and bipolar disorder[239,240], but they are in part related to the impact of some antipsychotic medications. Pro-inflammatory markers – including interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL1-RA, and sIL-2R – were found to be upregulated both in schizophrenia and bipolar disorder[241], but this profile is not specific, as depression and other mental disorders show similar abnormalities[241,242].

Overall, proteomics research identified 77 proteins altered in

both schizophrenia and bipolar disorder, and only 21 of them were also altered in depression[243]. Many of these effects were observed only in a single study. However, alterations in brain-derived neurotrophic factor (BDNF) have been consistently replicated[244,245]. This is a neurotrophin that modulates neuronal development and plasticity, and its blood levels have been found to be decreased in both schizophrenia and bipolar disorder.

Gene expression has been studied in postmortem brains, and transcriptomic profiles of schizophrenia and bipolar disorder have been found to be very similar[246-248]. The largest study to-date reported that cortical transcriptomic profiles of schizophrenia and bipolar disorder are much more similar to each other (rs = .70) than to profiles of major depressive disorder, alcohol use disorder, and autism (rs = –.06 to .43)[249]. The common thought disorder transcriptomic profile includes alterations in multiple pathways, such as genes controlling immune function[247,249,250].

Gene expression in the brain is not a practical biomarker, but expression in the peripheral blood tends to mirror expression in the brain[251]. Indeed, blood transcriptomic profiles of schizophrenia and bipolar disorder were found to be similar and include altered expression of immune system genes[252,253]. Relations between gene expression and symptom dimensions are understudied, but preliminary evidence suggests that altered expression of immune genes is specific to psychoticism, whereas expression of mitochondrial genes is associated with detachment[253]. Analyses of DNA methylation in blood revealed similar profiles in schizophrenia and bipolar disorder[254], but findings differed across studies and were confounded by methodological differences, so should be considered preliminary.

Overall, studies of immune function, proteomics and transcriptomics suggest that schizophrenia and bipolar disorder share a biological signature. This signature may be common across the thought disorder spectrum. However, conclusions have been moderated by methodological limitations of existing studies, and other disorders and dimensions relevant to the psychosis superspectrum are understudied.

Childhood temperament antecedents

Longitudinal data on links between childhood temperament and adult psychosis superspectrum are very limited. A few studies assessed psychoticism in childhood – using informant reports – and found that it predicted self-reported psychoticism in adolescence and adulthood[255-257]. In youths, both psychoticism and detachment were found to predict future onset of psychotic disorders as well as of schizotypal and schizoid personality disorders, with some evidence that psychoticism is a risk factor primarily for psychotic symptoms and detachment for negative symptoms[36,41,97,98,258,259].

This evidence suggests that the psychosis superspectrum has roots in childhood psychoticism and detachment traits, with onset of disorders resulting from progression along the continuum toward greater severity, as has been found for progression from psychotic experiences to disorder[260-262]. However, existing knowledge is limited by reliance on clinical high risk or treatment-seeking samples and lack of data on preschool temperament. Also, the specificity of the observed links is uncertain, as most studies examined only a small set of traits and disorders.

Illness course

Chronic course is a hallmark of schizophrenia, as only a small minority of cases achieve durable recovery[263]. We examined whether chronicity characterizes the entire superspectrum. Recovery is typically defined by both symptom remission and good functioning[264], so we considered both in turn. The rate of symptom remission in schizophrenia following treatment is approximately 37%, largely due to high chronicity of negative symptoms[265]. Likewise, schizotypal and avoidant personality disorders show remission rates of 23-47% two years after diagnosis[266]. In contrast, 84% of first-admission patients with mania achieve remission within a year[267].

Functional outcome follows the same pattern. First-episode schizophrenia results in moderate illness severity at follow-up, with a mean Global Assessment of Functioning (GAF) score of 56 [268]. Schizotypal personality disorder has a similar outcome, with a mean GAF score of 53 at two-year follow-up[269]. In avoidant personality disorder, two-year outcome is somewhat better, with a mean GAF score of 62, indicating mild severity[269]. Bipolar disorder shows the best outcome, with a mean GAF score of 70 two years after first hospitalization[270,271].

Studies that measured the spectra directly found that psychoticism and detachment are impressively stable over time, with 10-year stability correlations of .66 and .82, respectively[272]. Moreover, psychoticism, trait detachment, and especially negative symptoms are associated with poor functioning and predict worse global outcomes even ten years later[41,273-275]. Positive symptoms appear to predict worse functioning in the general population[260], but not in patients with psychotic disorders, where negative symptoms account for impairment[276]. This highlights the greater role of detachment than thought disorder in functioning. Overall, the two spectra show high chronicity and so do many conditions related to them, with the notable exception of mania.

Treatment response

The thought disorder spectrum shows a common response to antipsychotics. These medications are efficacious for reality distortion and disorganization symptoms across psychotic disorders[277-279]. Antipsychotics also treat manic episodes[280]. Moreover, emerging evidence suggests that antipsychotics can reduce psychoticism in patients who do not have frank psychosis[281]. However, antipsychotics are much less efficacious for the detachment spectrum, such as for negative symptoms, and observed benefits may be limited to secondary negative symp-

toms[282]. Tentative evidence suggests that neuromodulation techniques providing stimulation to specific neural networks can improve negative symptoms[283], but this research is still limited.

The thought disorder spectrum shows a common response to psychotherapy. Cognitive behavioral therapy (CBT) was found to improve positive symptoms compared to treatment-as-usual both at the end of treatment and at follow-up, but it does not outperform other therapies or active control[284]. Other emerging treatments may be more efficacious. Acceptance and commitment therapy (ACT) and meta-cognitive therapy both have shown moderate beneficial effects for positive symptoms, although no significant effects for negative symptoms[284]. Functional behavioral assessment-based interventions appear to be effective for disorganization symptoms across disorders[285].

The detachment spectrum shows a common response to social skills training, which reduces negative symptoms[286-289] and detachment traits[290]. These effects persist after the end of treatment[286] and reduce the probability of transitioning from schizotypal personality disorder to psychotic disorder[291]. Cognitive remediation, a behavioral intervention aimed to improve cognitive processes and not targeting symptoms directly, has been nevertheless found to reduce negative symptoms compared to treatment-as-usual, both at the end of treatment and at follow-up[292]. CBT is efficacious for reducing negative symptoms across psychotic disorders when compared to treatment-as-usual, both at the end of treatment and at follow-up[284,287].

Overall, CBT is an efficacious treatment for both spectra and, indeed, many other forms of psychopathology. In contrast, antipsychotics, ACT and meta-cognitive therapy are relatively specific to the thought disorder spectrum, whereas social skills training and cognitive remediation are relatively specific to the detachment spectrum. Social skills training is efficacious for both detachment symptoms and traits, and emerging evidence suggests that antipsychotics may be efficacious for trait psychoticism as well as frank psychosis. Much less is known about treatment for lower-order dimensions, although social skills training may be particularly efficacious for avolition[293], and functional behavioral assessment-based interventions for disorganization[285].

Summary of validity evidence

Our review of validity evidence is summarized in Table 2. It indicates both substantial coherence within each spectrum and overlap between spectra, which supports validity of the superspectrum. However, the two spectra show more differences than similarities, with 15 validators specific to thought disorder, six to detachment, and 12 common to both.

Of note, blank cells in Table 2 indicate lack of robust evidence, but not necessarily lack of an effect. So, similarities within and between the spectra may be stronger than they appear now. In particular, research is very limited on schizoid and avoidant personality disorders.

Importantly, many of the validators examined are not specific to the psychosis superspectrum. For example, childhood adversity, pro-inflammatory markers, and response to CBT have been linked to emotional dysfunction and externalizing superspectra as well[56,241,242,294,295].

Mania stood out on several validators. Unlike other conditions in the superspectrum, bipolar I disorder tends to have episodic course, often shows good functioning between episodes, and manifests hypersensitivity to rewards. On the other hand, bipolar I disorder is similar to other conditions in the spectrum on numerous other validators, consistent with the view that mania belongs on the thought disorder spectrum, albeit with certain distinguishing features.

Overall, validity findings agree with the structural evidence. This suggests that the HiTOP characterization of psychotic disorders and related personality disorders can provide an informative guide to researchers and clinicians.

UTILITY EVIDENCE

The HiTOP has been compared to traditional diagnostic approaches with respect to reliability, explanatory power, prognostic value, and clinical utility.

Reliability is an essential requirement for a nosology, as an unreliable diagnosis cannot convey useful information. The DSM-5 field trials found an inter-rater reliability (kappa coefficient) of .46 for schizophrenia, .50 for schizoaffective disorder, and .56 for bipolar I disorder[296], which indicates only mediocre agreement between diagnosticians. In these field trials, clinicians also rated positive symptoms as a single item on a 5-point scale, which, despite its brevity, improved reliability to .65[297]. Patients' self-ratings of psychosis on a dimensional measure were even more reliable, with coefficients ranging from .72 to .79[297]. This pattern suggests that dimensional scores retain more useful information than categorical ratings, consistent with extensive prior research[2].

Of note, a field study of ICD-11 reported higher inter-rater reliabilities than DSM-5 field trials, but it used a less stringent design, making high reliability easier to achieve[298].

Psychoticism and detachment demonstrated high reliability in patients (McDonald's omega = .87 and .75, respectively)[299] and even higher reliability in the general population[300]. They also showed high short-term stability, with 2-week test-retest correlations ranging from .81 to .89[301,302], and impressive long-term reliability, with 17-month test-retest correlations ranging from .62 to .74[39]. The overall meta-analytic reliability estimates were .81 for thought disorder and .85 for detachment[2].

In direct comparison, reliability of DSM diagnoses was inferior to HiTOP dimensions, with 2-week stability of .63 for paranoid, .62 for schizoid, .44 for schizotypal, and .63 for avoidant personality disorders, compared to .88 for psychoticism and .89 for detachment[301]. Overall, HiTOP offers >50% improvement in reliability over the DSM in characterizing psychosis-related psychopathology.

Table 2 Validators of the thought disorder and detachment spectra

	Both spectra		Thought disorder spectrum			Detachment spectrum				
	Schizophrenia	Schizotypal PD	Positive symptoms, psychotic experiences	Trait psychoticism	Bipolar I	Negative symptoms	Trait detachment	Schizoid PD	Avoidant PD	Summary of specificity
Genetics										
Family/twin psychoticism	+++			+	+++					T
Family/twin detachment	+++	+					+++	+++	+++	D
Polygenic risk to schizophrenia	+++		+		+++	++	+			B
Burden of copy number variants	+++		+							T
Environment										
Ethnic minority status	+++		+++	+		++				B
Living in urban environment	+++		+++	+						T
Childhood adversity	+++		+++	+++	++	+	+			T
Heavy cannabis use	++		++	+++			++			B
Cognition/Neurobiology										
Cognitive deficits	+++	++			+++	+++	++			B
Reward processing deficits	+++	++			–	+++				D
Small hippocampal volume	+++	+++	++		+++					T
Low white mater integrity in CC	+++		+		+++	+				T
Functional hypoconnectivity	+++		+++	+	+++	++				B
Hypoactive ventral striatum	++					++				B
Altered activation of executive system	+++		++	+		++				B
Cortical thinning	++					++				D
Inhibitory deficits	+++	+++			++					T
Blunted P300	+++	++	++		++					T
Blunted mismatch negativity	+++	++	++		++					T
Blunted error-related negativity	+++	++				+				D

Table 2 Validators of the thought disorder and detachment spectra *(continued)*

	Both spectra		Thought disorder spectrum			Detachment spectrum				
	Schizophrenia	Schizotypal PD	Positive symptoms, psychotic experiences	Trait psychoticism	Bipolar I	Negative symptoms	Trait detachment	Schizoid PD	Avoidant PD	Summary of specificity
Biomarkers										
Pro-inflammatory markers	+++				++					T
Reduced BDNF blood levels	++				++					T
Transcriptomic schizophrenia profile	++				++					T
Antecedents/Course										
Psychoticism in childhood/adolescence	+	++	+++	++						T
Detachment in childhood/adolescence	+	++	++			++		++		B
High chronicity/stability	+++	+		+	−−−		+		+	B
Poor functional outcome	+++	+	+	+	−−	++	+		+	B
Treatment										
Response to antipsychotics	+++	+	+++	+	+++	++				B
Response to CBT			+++			+++				B
Response to ACT			++							T
Response to meta-cognitive therapy			+++							T
Response to social skills training						++	+			D
Response to cognitive remediation						+++				D

+: some evidence for effect, ++: some replications; +++: repeatedly replicated finding, −: some evidence for reverse effect, −−: some replications; −−−: repeatedly replicated reverse effect, T – linked to thought disorder, D – linked to detachment, B – linked to both, CC – corpus callosum, BDNF – brain-derived neurotrophic factor, CBT – cognitive behavioral therapy, ACT – acceptance and commitment therapy

Explanatory and prognostic power is a particularly valuable feature of diagnosis. A meta-analysis found greater validity for dimensional than categorical operationalization of thought disorder and detachment[2]. For thought disorder, the mean validity coefficient (correlation with a validator) was .31 for a category and .42 for a dimension, which indicates a substantial advantage for the latter. For detachment, the advantage was even larger, with mean validity of .32 for a category and .48 for a dimension. However, these estimates were based largely on cross-sectional associations.

A large longitudinal study found the same pattern when comparing ability of personality disorder diagnoses and maladaptive traits included in HiTOP to predict functional and clinical outcomes ten years later[303]. The mean predictive power (R^2) was 0.25 for dimensions vs 0.12 for diagnoses, indicating substantial superiority of the HiTOP approach. However, this study considered all maladaptive traits together and all personality disorders together, and did not report results for psychoticism and detachment separately.

Several studies compared specific dimensions included in the psychosis superspectrum to diagnoses of psychotic disorders by analyzing their cross-sectional associations with validators. Dimensions explained more variance in risk factors[304], psychosis biotypes derived from neurophysiological markers[8], cognitive deficits[305,306], real-world functioning[304,305], and utilization of inpatient services[304]. In contrast, diagnoses outperformed dimensions only in accounting for illness course and utilization of outpatient services[304].

Another study used diagnoses (e.g., schizophrenia and schizotypal personality disorder) to model the psychosis superspectrum, and found that it fully accounted for family risk and illness course over the next ten years, with individual diagnoses contributing no additional variance[57].

Overall, existing research indicates that the HiTOP characterization of psychotic disorders can explain and predict twice as much variance in validators as the DSM, thus increasing value of diagnosis for research and for clinical prognostication.

Although diagnostic reliability and prognostic power are important for clinical applications, a distinct set of considerations may be classified as clinical utility, i.e., the ability of a diagnostic system or diagnostic feature to facilitate implementation, conceptualization, communication, treatment selection/planning, and outcome improvement[307-310]. Existing research relied on practitioner ratings to evaluate utility of a diagnostic system in these domains.

Comparisons of HiTOP and DSM approaches has been largely focused on personality disorders, and global ratings for the system rather than each individual feature. Initial studies asked practitioners to consider vignettes of fictitious cases developed based on the DSM, which confounded results[311,312]. Recent studies requested that practitioners consider actual patients in their caseload, and dimensional approaches generally received higher ratings than DSM categories across most indices of clinical utility[313-317]. Moreover, dimensional measures included in the DSM-5 were rated by 80% of clinicians as moderately to extremely helpful[318].

Overall, existing data strongly support clinical utility of the dimensional approach[319,320]. Nevertheless, it is important to expand studies of clinical utility to include frank psychosis and also compare diagnostic systems on objective criteria, such as fostering better treatment outcomes.

Clinical acceptability of HiTOP is consistent with the aim of the system to formalize and improve existing clinical decision-making practices, as practitioners often rely on presenting signs and symptoms more than on traditional diagnoses[321]. Limitations on the utility of traditional diagnoses are further evident in clinicians forgoing criteria sets and employing abbreviated approaches in making diagnoses[322-324], as well as in extensive off-label prescribing[325]. HiTOP builds on an established practice of dimensional, symptom-oriented and personality-informed case conceptualization to provide clinicians with both a rigorous framework for this approach and validated brief tools to assess these dimensions.

Application of dimensional measures in clinical practice faces practical challenges, including limited reimbursement for assessment, patient burden, and need for categorical decisions (e.g., to treat or wait)[20]. In other fields of medicine, these challenges have not precluded a widespread use of dimensional markers, such as testing levels of metabolites in blood or pathogens in cerebrospinal fluid. Indeed, effective strategies have been developed to justify cost, reduce patient burden, and translate these dimensional metrics into clinical decisions[326,327].

Perhaps, the most direct evidence of clinical utility is the widespread use of dimensional measures in mental health practice. Indeed, rating scales for psychosis and related symptoms have been part of clinical practice and research for decades, including the Brief Psychiatric Rating Scale (BPRS)[328], the Scale for the Assessment of Negative Symptoms (SANS)[329], the Scale for Assessment of Positive Symptoms (SAPS)[330], and the Positive and Negative Syndrome Scale (PANSS)[331]. They have proven clinical acceptability and are required in clinical trials for psychotic disorders[332].

Moreover, programs that treat patients with clinically high risk for psychosis or attenuated psychosis syndrome routinely utilize dimensional symptom measures, especially the Scale of Prodromal Symptoms (SOPS)[91], which is extensively validated and used worldwide[333].

Structural studies identified subscales in each of these measures that align with the HiTOP model[7,91,114,334-337]. Indeed, components of the model were informed by this research.

It is notable that diagnostic manuals now recognize the need for a dimensional characterization of psychosis and related symptoms. The DSM-5 introduced eight dimensional ratings that capture reality distortion (hallucinations and delusions), disorganization (disorganized speech and abnormal psychomotor behavior), negative symptoms (restricted expression and avolition), and mania (manic mood), as well as depression and impaired cognition[74]. The ICD-11 included six dimensional symptom-based qualifiers for psychotic disorders: positive, negative and mania, as well as depressive, psychomotor/catatonic and cogni-

tive impairment[338]. Although these additions are very encouraging, evidence for their clinical utility is currently limited[318].

MEASUREMENT

Several measures are available to apply HiTOP in research and care for psychosis-related psychopathology. We highlight instruments that have both sound psychometric properties and established clinical cutoffs (e.g., categorize severity of psychopathology or define clinically significant change).

Both the PANSS and SANS/SAPS offer psychometrically sound interviewer-rated scales for thought disorder (specifically, positive symptoms) and detachment (negative symptoms)[339,340]. Additional subscales were developed in these measures for reality distortion, disorganization, inexpressivity and avolition, among other dimensions[7,335,337].

Two new interviews were developed for negative symptoms: the Clinical Assessment Interview for Negative Symptoms (CAINS)[111] and the Brief Negative Symptom Scale (BNSS)[341]. Both have psychometrically sound subscales for inexpressivity and avolition[342].

The SOPS is the measure of choice in populations with subthreshold symptoms. It includes four subscales that measure reality distortion, disorganization, negative symptoms, and distress. They largely align with the corresponding scales of the PANSS, SANS and SAPS[343], although factor analytic support for the SOPS subscales has been mixed[344].

The Achenbach System of Empirically Based Assessment (ASEBA)[345,346] includes scales for psychoticism (named thought problems) and detachment (withdrawn). They can be rated by self-report or informant report in both children and adults. These scales have been extensively validated.

Clinical cutoffs are available for the SOPS[333], ASEBA[345,346], and spectra-level scales of the PANSS and SANS/SAPS[339,347]. These measures are ready for both clinical and research use. The component-level scales of the PANSS and SANS/SAPS, as well as the CAINS and BNSS, lack established cutoffs and can be considered research instruments.

Psychoticism and detachment traits can be assessed with high resolution using omnibus measures of personality pathology, such as the Personality Inventory for DSM-5 (PID-5)[348] and the Computerized Adaptive Test of Personality Disorder (CAT-PD)[78]. The Community Assessment of Psychic Experiences (CAPE)[349,350] is a self-report symptom measure, and provides high-resolution assessment of thought disorder and detachment, as well as their subdimensions. These measures are psychometrically sound and have been normed in the general population, and thus can be used clinically to compare a patient's scores to the normal range of functioning. They also assess subdimensions within psychoticism and detachment domains, including all traits in Figure 1[68].

Other measures of these maladaptive traits are available, but are less comprehensive or lack norms and hence are not discussed here. Finally, the DSM-5 and ICD-11 dimensional symptom ratings have not been sufficiently studied to be recommended fully, but they show considerable promise as screening tools and can help to introduce dimensional assessments to settings where thorough evaluations are infeasible.

IMPLICATIONS

The HiTOP offers a reconceptualization of psychosis and related psychopathology to closer align nosology with data. It aims to advance understanding of these conditions in three respects.

First, it underscores that psychotic disorders reflect influences of two major dimensions of psychopathology which are rather distinct with regard to their phenomenology, etiology, prognostic implications, and treatment response. These thought disorder and detachment spectra also show similarities, consistent with the notion of the overarching psychosis superspectrum.

The two-spectra conceptualization agrees with an established observation that some patients primarily suffer from positive symptoms and some are largely burdened by negative symptoms[30,351,352]. Furthermore, this model does not consider psychosis a necessary feature and can characterize people with prominent negative symptoms who have never been psychotic. Of note, internalizing (e.g., depression) and externalizing (e.g., substance abuse) problems are classified on other HiTOP spectra, but are common in psychotic disorders. To characterize a patient fully, all six HiTOP spectra have to be considered, as detailed in previous publications[1,20].

Second, the HiTOP reinforces the emerging consensus that psychosis is on a continuum with normal functioning, maladaptive traits, and subthreshold symptoms[46-49]. The model identifies specific trait manifestations of the spectra: psychoticism and detachment. Elevations on these traits often precede onset of psychosis and are valuable as risk factors. Moreover, levels of psychoticism and detachment vary across the general population, making them more informative targets for etiologic research than psychosis, which is a rare and extreme phenomenon. Overall, the dimensional approach helps to understand how psychosis-related problems are distributed in the population, what processes underpin them, and how preventive interventions can be most effective.

Third, the HiTOP further addresses heterogeneity within psychotic disorders by explicating specific trait and symptom dimensions that constitute the thought disorder and detachment spectra (Figure 1). Included dimensions were established to be internally consistent and distinct, but future research may reveal that more need to be added. In particular, catatonia symptoms and cognitive impairments have not been incorporated into the model.

In the psychosis superspectrum, patients can be represented as profiles of elevations on the corresponding 14 specific dimensions, along with the mean score on the two spectra and on the superspectrum. These dimensions capture both current problems (symptoms) and long-standing problems (maladaptive traits). Validated tools are available to assess these scores by in-

terview, self-report and informant report.

The placement of mania and dissociation on the thought disorder spectrum remains provisional. Dissociation has shown many phenotypic similarities to reality distortion and psychoticism, but the evidence was too limited to include it in our review of validity. Further research is needed to resolve its placement. Mania has been studied extensively and exhibited a profile similar, although generally less extreme, to other thought disorder conditions on numerous validators. The exceptions are course and certain neural substrates. It is possible that mania is a distinct manifestation of a common liability to thought disorder and largely shares etiology and treatment response with non-affective psychosis, although it usually is less disabling. This account remains a hypothesis, as existing data are insufficient to test it definitively.

The HiTOP is a static model at present. Its focus is on characterizing dimensions of psychopathology and accurately assessing a person's current standing on each. However, the hierarchical and dimensional conceptualization is very compatible with developmental models, such as the staging model of psychosis that describes how subthreshold problems evolve into chronic psychosis[51-53]. Once dimensions are identified, the next task is to characterize how patients progress along these dimensions toward greater pathology or improvement.

The understanding of how thought disorder and detachment spectra develop is quite limited at present, although it appears that the core traits are already present in childhood and constitute risk for onset of psychotic disorders. This is consistent with findings for other HiTOP spectra, which received more attention in developmental research[353-355]. Specifically, vulnerabilities can often be observed in childhood, and future disorders tend to emerge out of related vulnerabilities, whereas it is fairly uncommon for psychopathology to shift from one spectrum to another. It is less clear what processes and exposures drive progression along a spectrum to full-blown disorder, which remains a crucial topic for future research[356].

Research implications

The HiTOP model has specific implications for research design, from the sampling, measurement, analytic and conceptual viewpoints.

With regard to sampling, the HiTOP highlights major limitations of case-control studies, which sample people from extreme ends of a dimension. This can maximize statistical power, but has two downsides. First, these analyses exclude people in the middle of the distribution, which makes identified effects not representative of the population. Indeed, this design ignores a sizable proportion of the general population. Second, cases differ from controls in many respects not relevant to the construct of interest, as they are usually recruited from clinical settings, and treatment-seeking is associated with particularly high rates of distress, impairment, comorbidities (including physical ones), and exposure to medication, all of which may confound results.

These limitations of the case-control design are well-known [357,358]. The HiTOP provides an impetus for an alternative design with population-based sampling (perhaps oversampling for high scores). This design is reasonable, even desirable, given the continuous nature of psychopathology and the availability of measures that capture the full range of its manifestations, from normative to subclinical to severe[19]. The population-based strategy can be cost-effective, in that recruitment of cases with first episode psychosis or clinical high risk tends to be slow and costly, whereas high scorers on psychoticism and detachment can be identified rapidly using self-report tools. This design can be further strengthened with follow-up interview-based assessments to evaluate the spectra and their subdimensions with maximum rigor. Another implication is that research on psychotic disorders should not solely focus on reality distortion, but also include participants who are elevated on detachment alone. In general, inclusion criteria for HiTOP-conformant research can be very broad, with the main concern being whether valid assessment can be obtained. Comorbidities and other confounds can be managed statistically provided adequate sample size.

For measurement, HiTOP-conformant measures described earlier promise more reliable and informative assessments than diagnoses. We recommend assessing both maladaptive traits and symptoms, to obtain a comprehensive picture with a modest increase in patient burden, especially if brief and self-administered instruments are used. The spectra can be usually estimated from categorical diagnoses, but it is preferable to measure them directly within HiTOP-conformant instruments, as this maximizes reliability and information obtained[359].

Analytically, HiTOP dimensions can be measured directly and analyzed in the whole sample using conventional statistics. If a diagnostic assessment was completed, it may be useful to test the transdiagnostic nature of relationships of interest, such as whether diagnosis moderates the association between a psychoticism scale and a validator[219]. Latent variable modeling is not required for a HiTOP study, but can be informative. For example, it can facilitate secondary analyses of existing data, where HiTOP-conformant measures were not included, by estimating latent dimensions from standard diagnostic and symptom assessments[7,8,57,59,306].

A conceptual implication is that conditions included in a given spectrum tend to have many commonalities with regard to etiology, clinical features, and treatment. This aspect of the model can be leveraged in two ways. First, the spectra can be studied directly, as they provide more parsimonious and robust phenotypes than individual conditions. Second, effects found for one condition are expected to generalize across the spectrum. This will not be true in every case and should always be confirmed empirically, but can be considered a strong hypothesis.

On the balance, some effects will be specific to narrow dimensions rather than the general spectrum. The HiTOP provides the framework for identifying specific and general features of psychopathology. This hierarchical arrangement can help to understand the role of risk factors, outcomes and treatments across mental disorders. Specificity of effects is challenging to investigate under traditional systems that include numerous disorders

and lack a robust hierarchical organization. Our review of validity evidence spotlighted many gaps in knowledge of specificity, and the HiTOP offers a framework to addressing them.

Clinical implications

The HiTOP approach has several implications for clinical care. First, HiTOP diagnosis is a profile of relevant psychopathology dimensions, and the patient is conceptualized in terms of deviations from the healthy range. Traditional diagnosis is de-emphasized, but can be assigned in parallel with HiTOP, such as to meet administrative requirements. Indeed, the consortium developed a cross-walk from HiTOP to ICD-10 codes (https://hitop.unt.edu/clinical-tools/billing-hitop).

At some point, scores have to be dichotomized to inform categorical clinical decisions. Of note, traditional diagnoses are dichotomous, but the cutoffs are not optimized for any particular clinical action, and reasons for their selection have not been explicit[18]. Optimal use requires development of multiple purpose-built cutoffs (e.g., one for initiating treatment with antipsychotics, another for hospitalization), as has been done in medicine for such dimensional variables as blood pressure, cholesterol, or weight[360]. This research has not been completed in psychiatry yet, but categories based on degree of statistical deviance (e.g., normal, mild, moderate and high severity) are already available for many measures.

Another consideration is that psychopathology dimensions may interact with each other and with other clinical parameters (e.g., age, medical comorbidities) in ways that change treatment indications and even meaning of scores, such as psychosis that emerges in late life in the context of dementia versus in young adulthood. Many of these interactions are well known, but systematic research is limited. The HiTOP model offers a framework for investigating this question.

Second, the HiTOP offers a hierarchical case conceptualization describing both general and specific features of psychopathology. For example, general dimensions (e.g., p factor) can identify high utilizers of care, thus helping to guide public health policy or policies of a given clinic[361]. In addition, a patient's standing on the thought disorder spectrum may suggest that antipsychotics are indicated. Moreover, on the specific level, an elevation on avolition symptoms may suggest social skills training. Importantly, a move to HiTOP case conceptualization does not negate prior research on traditional diagnoses. Information on treatment efficacy for disorders linked to the spectrum is retained and applied to people elevated on this dimension, although it will be important to verify treatment effects in HiTOP-based treatment studies.

Third, dimensional conceptualization of psychopathology emphasizes continuity with healthy functioning, which can facilitate communication with patients and family members, and help to reduce the stigma of psychopathology. Communication among providers may sometimes benefit from a simpler formulation than an exact score that a patient received on a dimension, and categorization can be applied based on the aforementioned cutoffs. For example, "moderately elevated detachment" could be used instead of listing the specific score.

A salient pragmatic concern is assessment burden on clinics. Many HiTOP assessments have been digitized, so that the questionnaire can be sent to patients for completion at home or in a waiting room, with results scored automatically and provided to clinicians in real time. Importantly, these measures do not aim to replace an intake interview, but to guide clinicians' interviewing, thus improving speed and comprehensiveness of an intake and subsequent monitoring, much like lab tests do in medicine.

FUTURE DIRECTIONS

The proposed HiTOP model of the psychosis superspectrum is based on extensive evidence. Nevertheless, further research is needed to verify assignment of mania and dissociation, as well as to incorporate other dimensions in the model (e.g., cognitive impairment and catatonia). The HiTOP is meant to include all empirical psychopathological entities, whether dimensional or categorical in nature. Only dimensions have been established empirically to date[18]. However, latent classes likely exist[362], so they need to be identified and added to the psychosis superspectrum alongside dimensions.

Research is also needed on optimal cutoffs for specific clinical decisions. Interactions among dimensions and with other clinical features need to be investigated systematically. It will be particularly important to verify and expand knowledge of treatment efficacy with dimensions as treatment targets. Finally, thought disorder and detachment spectra have been extensively validated, but gaps remain for a number of validators, such as childhood antecedents and biomarkers. Developmental processes, in particular, need more attention. This research can build on the strong base of knowledge and scientific framework provided by HiTOP.

CONCLUSIONS

The HiTOP offers a dimensional and hierarchical conceptualization of psychotic disorders that was derived strictly from data, free of political considerations. It has been extensively validated and already demonstrated considerable utility. Validated measures are available for spectra and their subdimensions for both symptoms and traits.

Further research is needed, but the model is ready for use by scientists and clinicians interested in psychotic disorders. Its application offers to address problems of heterogeneity, comorbidity and low reliability, providing more valid and predictive descriptions of patients.

APPENDIX

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The application of implementation science to community mental health

Behavioral health disorders account for the largest proportion of the global burden of diseases, measured by years lived with disability[1]. This burden could be greatly diminished if individuals and populations had access to programs and services with established effectiveness – so-called evidence-based practices (EBPs). Implementation science has been defined as the study of "methods and strategies to promote the uptake of interventions that have proven effective into routine practice, with the aim of improving population health"[2].

Implementation science does *not* focus on developing new behavioral health interventions and proving their effectiveness. Rather, a successful implementation science trial teaches how to increase the use of EBPs in a care system. The successful application of implementation science to community mental health is thus central to the challenge of addressing the devastating impact of behavioral health disorders in the global community. Here we outline the role of implementation science in the future of community mental health.

What do community mental health leaders need to understand about implementation science? It is important to note that, in contrast to quality improvement programs, which address a specific problem within a specific health care system, implementation science aims to produce *generalizable* knowledge that would be applicable across different systems. Also, implementation science reaches beyond dissemination, which is more focused on the spread of information.

Implementation science almost always involves multiple stakeholders, including patients, providers, supervisors, agency leads and payors. Inattention to multiple levels of stakeholders may cause an effort to fail, because durable change is often complicated and multiple factors contribute to the *status quo*.

Implementation science relies on the use of theories, models and frameworks[3] to guide: a) the step-by-step planning and execution of EBP implementation, from pre-implementation to sustainability; b) the identification of barriers and facilitators to implementing EBPs; and c) the evaluation of implementation, to know if efforts have produced change at the organization, provider or patient levels[4].

Finally, implementation science provides direction on how to select from an array of implementation strategies[5] (e.g., audit and feedback, educational outreach, e-learning, inter-professional education, managerial supervision), based on their effectiveness[6], and adapt them to the local setting.

Specialized organizations, called intermediary and purveyor organizations (IPOs), support the spread of EBPs in community mental health. A purveyor organization focuses on one specific practice, whereas an intermediary organization supports the development and implementation of multiple best practices, along with infrastructure to sustain them[7]. IPOs cultivate partnerships and link academic researchers, treatment developers, implementation specialists, service system authorities, behavioral health agency administrators, service providers, service recipients and other community stakeholders.

One example of a government-funded IPO in the US is the Center for Practice Innovations (CPI) at Columbia Psychiatry and the New York State Psychiatric Institute. CPI is supported by the New York State Office of Mental Health to promote the widespread use of recovery-oriented EBPs for adults with serious mental illness, through scalable training and implementation support to over 41,000 behavioral health clinicians statewide.

Core initiatives of CPI include assertive community treatment (ACT), supported employment/education via individual placement and support (IPS), treatment of co-occurring mental health and substance use disorders, coordinated specialty care for first-episode psychosis (called OnTrackNY), and suicide prevention. The work of these CPI initiatives is guided by an implementation science-informed practice change model that considers inner (i.e., program-practice fit, leadership investment, organizational culture, time and resources available for practice implementation) and outer setting of the organization, program or clinic (i.e., policy, regulatory and financial environment of practice change)[8,9].

CPI recognizes that training is not enough to change practitioners' daily actions and achieve high quality implementation of the desired EBP. It thus offers empirically driven support to supervisors, managers and practitioners focused upon their implementation efforts. As clinicians at an organization engage in online training, we conduct formative evaluation to plan for post-training implementation support. Barriers identified during this process are mapped to corresponding strategies and vetted by key stakeholders.

Selected strategies will inform the implementation plan and determine mode of implementation support delivery. This may include interactive webinars, an online resource library with practical tools (e.g., manuals and fidelity checklists), consultations, and learning collaboratives during which program staff share successes and receive consultation from peers and experts on their implementation challenges. These learning collaboratives frequently use performance indicators and fidelity self-assessments to help guide programs through continuous quality improvement projects. This data allows programs to identify challenges in implementation, and work with CPI staff to address these challenges.

Summative evaluation in our initiatives helps us to understand the impact of implementation strategies and clinician- and patient-level outcomes. For example, in our IPS initiative, between 45% and 55% of individuals receiving IPS services in New York State are employed competitively each month. This compares very favorably with national benchmarks established by the developers of IPS. In OnTrackNY, among young adults with a schizophrenia-spectrum diagnosis, engagement in work and

school increases from 41% in the 3 months prior to enrollment to 70% by the second quarter of enrollment, a rate which is largely sustained over the course of treatment.

This systematic, implementation science-informed approach is now also being applied to a new initiative to increase clinician competency in guideline-concordant care for adults and children with obsessive-compulsive disorder, an undertreated illness identified as an important cause of global health-related disability.

Community mental health plays a crucial role in the global pursuit of reducing the burden of behavioral health disorders, by increasing access to programs and services that have established effectiveness. As a field, implementation science produces tools and knowledge of great relevance to this effort. Community mental health leaders need to understand if and how these tools may be locally applied. IPOs can play a role in the future of community mental health as translators of the science and natural laboratories for understanding and evaluating if applying implementation science products and tools can help reduce the gaps in behavioral health care.

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School mental health: a necessary component of youth mental health policy and plans

Approximately 70% of cases of mental disorder have their onset prior to 25 years of age. Thus, effective mental health interventions should be applied in youth for life-long benefits. Globally, most young people spend much of their day in schools, and they can be more easily reached there than through any other single public health or clinic-based intervention. Resultingly, effectively addressing mental health and early onset of mental disorders in schools must be an essential component of youth-focused mental health policy.

The realization that school mental health is an important aspect of promotion, early intervention and treatment is not new. The World Health Organization report in 1994[1] was an early foray into this territory, and recent years have seen many school mental health activities across the globe[2]. A substantial corpus of work has now been published, allowing us to critically consider what components of school mental health interventions are both essential and can be systematically and frugally applied with success. These are: mental health literacy for both students and educators; training for both in-service and pre-service teachers; and school site provision of integrated mental health care to youth who require it.

Mental health literacy has been defined as knowledge and competencies that encompass four separate but intertwined domains: understanding how to obtain and maintain good mental health; understanding mental disorders and their treatments; decreasing stigma; enhancing help seeking efficacy (knowing when and where to seek help, and learning skills to apply in the help seeking interaction)[3].

Mental health literacy has been considered to be the foundation for mental health promotion, prevention, early identification, and intervention and ongoing care[3]. In the school setting, it is essential that mental health literacy interventions are evidence-based, developmentally appropriate, integrated into curriculum, applied by appropriately trained teachers, frugal and easily accessible.

While a few different approaches have been promoted globally, school and other educational institutions in many countries have been applying two evidence-based and freely accessible mental health literacy resources: the Mental Health & High School Curriculum Guide[4] for students aged 12-18, and the Transitions[5] resource for first-year college students.

The Guide features classroom-based modules that are easily embedded in the school curriculum, and has been adapted and extensively studied using robust research designs in various countries, demonstrating similar outcomes in significantly, substantively and sustainably improving all aspects of mental health literacy for youth[4-6].

Transitions blends mental health into a life skill resource to help first-year college students' transition into post-secondary settings. Freely accessible, it addresses mental health in a destigmatizing manner, with evidence supporting its international application[5].

Currently, there is a substantial gap in addressing mental health literacy at the elementary school level, highlighting the pressing need for relevant resources among this age cohort.

It is essential that, in addition to applying best available evidence-based mental health literacy curriculum resources, teachers be well trained in understanding pertinent aspects of student mental health. Teachers do not usually receive substantial education in this domain in teacher's college, nor do they receive

substantive professional development when in practice, despite their concerns about needing to improve student mental health[7].

Fundamentally, teacher training should not only explore in depth all the aspects of mental health literacy, but also provide practical classroom strategies, and further focus on early identification of mental disorders and how to link students in need with appropriate services within and outside the school community. Moreover, teacher training should consider guiding teachers to learn how to care for their own mental health.

Recognizing the lack of progress in this area to date, Canadian educators have begun to address this issue. For example, informed by inputs from more than 30 faculties of education in Canada, a freely available online learning platform has been created that can be applied in both undergraduate or postgraduate teacher education as well as for self-study professional development (www.teachmentalhealth.org). This is now being used in many faculties of education across Canada and globally by interested stakeholders. Robust research evaluating the effectiveness of this intervention is underway, but has yet to be published.

Lastly, school-based health centers, which comprise full health/human services embedded into schools, may be the most parsimonious approach to addressing student's mental health care needs, while concurrently supporting their other health care needs and social service requirements.

Some of their advantages are that: a) they provide the greatest ease of access for the largest number of young people; b) they are designed to be youth friendly; c) they can provide a full range of health/mental health interventions (from promotion to prevention to care); d) they can be seamlessly linked to primary health care providers; e) they are relatively inexpensive to establish (i.e., require limited new infrastructure costs); f) they provide an easily accessible site for additional human health services; g) they can be enhanced by adding human resources such as mental health clinicians, h) they have a reasonable evidence base of positive results, that include better and more equitable academic, health and social outcomes[8].

When properly implemented, such centers can provide both site-based integration of services and horizontal integration into primary health care and social services. However, governance can be a challenge (who "owns" and who funds). They are not likely to be "branded" and so may not be good at raising funds from non-government sources. While well established in some developed countries, they are not well known in other countries; and full services sites may not be economically feasible in very small schools.

Taken together, the above three components constitute the essential core elements of school mental health, and have a reasonable body of research that demonstrates their positive impact. They can be integrated into existing education and health infrastructure and are ready for scale-out in both low- and high-income settings[9].

Globally, governments should consider applying these school mental health interventions into their youth mental health policies, plans and programs.

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Intergenerational psychiatry: a new look at a powerful perspective

Intergenerational psychiatry focuses on disorder-related phenotypes in one generation following the manifestation of a psychiatric disorder, or the exposure to adversity, in the prior one.

Intense interest in families has a long history in psychiatry. We argue that new concepts, tools and research findings coalescing around the area of intergenerational psychiatry have the potential to make the focus on familial risk even more relevant to understanding the roots of mental disorders and, most importantly, how, when and with whom to intervene.

Intergenerational psychiatry integrates three lines of investigation. The first, *familial high-risk studies*, examines risk of mental disorder as it travels within families[1,2]. Studying individuals at risk by virtue of their familial background, this approach helps isolate pathways by which mental disorder is transmitted in families, as well as endophenotypes predating disorder onset such as, for instance, cortical thinning and altered neural connectivity[3].

The second, *intergenerational effects of trauma*, considers the effects of parental exposure to trauma on psychiatric outcomes in the next generation. These studies have, for example, started to identify variation in stress regulation in children of Holocaust survivors as well as war veterans, independent of the children's direct exposure to significant life stressors[4].

Finally, *fetal programming studies* have shown that "the womb may be as important as the home" in putting a child at risk for compromised neurobehavioral outcomes following prenatal exposures to stress or anxiety/depression. This work establishes an individual's first environment as the *in utero* milieu.

Whereas the first approach emphasizes parental psychopathology as the primary component of intergenerational processes, the second highlights parental trauma, and principally, trauma

occurring during parents' adulthood prior to conceiving children. Finally, the third emphasizes gestation as the time period during which familial non-genetic influences on child outcomes can occur. We argue for integrating these paradigms to encompass the life course nature of risk and exposure emanating from the parent (and grandparents) to impact the child.

Our current understanding of the mechanisms of intergenerational transmission is still in its early stages. Familial high-risk studies have excelled in identifying parent-to-offspring transmission and correlates of psychiatric risk. They have shed light on certain mechanistic processes by which disorders are transferred from one generation to the next, suggesting, for example, neural endophenotypes of risk and resilience.

Studies focused on intergenerational effects of trauma have produced additional mechanistic insights. These include germline epigenetic effects of pre-conception trauma, both maternal and paternal. Yet, most of these preclinical insights remain unproven in humans[5].

Finally, fetal programming studies have mostly focused on gestational experiences versus those from a mother's lifetime (or her mother's) that might influence her oocyte and/or her health during childbearing years.

Building on these foundational paradigms, intergenerational psychiatry can apply a wider investigative lens in terms of the sources (maternal and paternal), types, and timing of exposures. It considers, as relevant exposures for the next generation, parental psychopathology and trauma as well as experiences of psychosocial adversity (e.g., famine/starvation, social isolation, discrimination, poverty) and expands the time frame of these exposures, by considering parents' adulthood experiences, as well as those of their childhood, or even before.

Central hypotheses of intergenerational psychiatry are ripe for testing. First, advances in fetal and perinatal neurobehavioral assessments have converged with our capacity to detect disruptions in brain circuitry in the first days following birth, or even before, *in utero* (e.g., fetal brain imaging). Second, the steady progress in molecular psychiatry, with advances in genetic[6], epigenetic and other molecular techniques, is providing unparalleled opportunities to identify variations in gene regulatory pathways and quantify heritable effects on psychiatric phenotypes (e.g., polygenic risk scores). Third, data science offers the methods to harness the large number of variables needed to test complex interactions (e.g., environment x gene x epigenome x development) inherent in intergenerational processes. Leveraging these research tools, intergenerational psychiatry will generate predictive models of behaviors across generations with greater and earlier explanatory capability than the ones we currently have.

As fruitful as this line of inquiry is, intergenerational human cohorts in psychiatry are uncommon. The examples that do exist still lack the depth of phenotypical and biological information needed. One solution is to pursue intergenerational assessments of existing large initiatives – e.g., the Avon Longitudinal Study of Parents and Children (ALSPAC) G2 Cohort[7] – which could be joined by others – e.g., US National Institutes of Health's Environmental Influence on Child Health Outcomes (ECHO) and All of Us Research Program; UK Biobank; and Scandinavian Registries.

The investment will pay off. Knowledge about familial determinants of mental disorders beyond shared genes of risk or shared current environment would expand personalized medicine to include the family's life course and the individual's cumulative attempts to adapt to it.

Intergenerational psychiatry will identify new prevention targets. We know, for example, that if we successfully treat depressed mothers, their symptomatic children improve, even if we have never directly cared for their offspring[2]. Would we increase our impact, potentially preventing the onset of child symptoms, if mothers were treated during pregnancy (e.g., ClinicalTrials.gov NCT03011801, NCT03283254), or long before conception? How much do we gain by treating fathers or targeting those exposed to adversities? Within this life course approach, interventions can be staged at the optimal developmental time.

The observation of the familial nature of mental disorders has intrigued psychiatry since its earliest days, from Freud to the Genain quadruplets[8]. We argue that established lines of research (familial high-risk studies, intergenerational trauma, fetal programming model), furthered by the application of new technologies (fetal/perinatal assessments and imaging, molecular psychiatry, and advances in data science) can provide novel information with a dramatic impact on prevention.

This new look means expanding our lens away from a focus on the individual and immediate context to look across family members over their life courses. Ultimately, it may even potentially re-define mental illness — a descriptor of an individual in static time versus the manifestation of cumulative adaptations related to developmental influences over at least a generation.

Intergenerational psychiatry is poised to bring unprecedented information about how psychiatric dysfunction may get handed off from one generation to the next, amplifying our opportunities and choices about how to intervene.

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Experimental approaches to social disconnection in the general community: can we learn from schizophrenia research?

We live in a socially disconnected age. In a survey of 26 European countries (European Union Survey on Income and Living Conditions), 7% of respondents stated that they *never* meet friends or relatives, not even once a year. The same percentage (7%) stated that they are unable to ask any relative, friend or neighbor for help (ec.europa.eu/eurostat).

These statements reflect extreme forms of social disconnection, which can be defined as an objective lack of social and family relationships, and minimal participation in community activities. The disconnection trend extends globally, such as to Japan, where large numbers of young adults, typically males, isolate themselves for years in their homes, a socio-cultural phenomenon known as hikikomori. The trend also includes the US. The former Surgeon General, V. Murthy, declared that the greatest pathology in that country was not cancer or heart disease; he said it was social isolation.

Does it matter if people are socially isolated? Perhaps anyone who wants to be alone should have that right. However, problems start once we consider the public health implications. It is abundantly clear that social disconnection is not good for your health – it leads to early mortality. Across studies, the hazard ratio for early mortality from social disconnection is around 1.5, roughly the same rate as smoking and poverty, and higher than the rate for obesity[1,2]. Phrased in stark terms, if you are in your mid 60s, your odds of being alive in 7 years are 50% greater if you have social connections than if you do not.

It is important to note the differences between objective social isolation (i.e., social disconnection) and subjective feelings of isolation (i.e., loneliness). We know that both social disconnection and loneliness lead to about the same rates of early mortality, but their effects are rarely examined together in the same study. Also, the correlations between the two are surprisingly low, around r=.25[3]. This means that being disconnected and feeling lonely are two rather different things, neither of which are good for your health.

Why should the readers of this journal care about social disconnection in the general population? Psychiatric diagnostic systems have rather little to say about this phenomenon. Social dysfunction generally, including social disconnection, clearly exists in psychiatric conditions – for example, it is a feature of schizophrenia and it is a central component of avoidant and schizoid personality disorders. There were also unsuccessful attempts to include hikikomori as a diagnosable culture-bound syndrome in revisions to DSM and ICD. However, social disconnection by itself is not a clinical disorder.

Perhaps a more relevant question for clinical researchers is whether an experimental approach can provide insights on why people become disconnected in the first place. Our knowledge of the determinants of social disconnection in schizophrenia provides a road map of what to consider in the general population. This work has been guided by developments in social and affective neuroscience and, in contrast to data from large surveys and health records, requires a deep phenotyping approach with in-person interviews and assessments.

The first challenge for an experimental approach to social disconnection in the community is to recruit a suitable sample. In an ongoing study, we found that placing ads on the Internet asking for people who have few friends and little contact with family yields a sample that is heavily skewed toward social disconnection[4]. In general, we get individuals who are in their 40s, with a higher percent of males, and most are working full or part time. Based on extensive interviews, very few of the respondents have a history of a psychotic illness or are in the autism spectrum.

The study of social disconnection in schizophrenia can guide us regarding which types of determinants to evaluate. Social processing deficits in schizophrenia can be roughly divided into *ability* versus *motivation*. Most frequently, the problems in schizophrenia refer to social processing ability (i.e., social cognition). These include one's ability to perceive social cues from faces or gestures, infer what others are thinking, accurately read momentary changes in the mood of others, and regulate emotions, among others. People with schizophrenia have impairment in most, but not all, of these ability areas[5]. In contrast to social ability is social motivation, or the degree to which someone wants to interact with others, which is associated with different neural structures and networks from those of social processing ability[6]. Social motivation has historically been evaluated in schizophrenia as part of social anhedonia or asociality (e.g., in negative symptom scales). We know from extensive work that both social processing ability and social motivation are linked to social functioning in schizophrenia[7].

Hence, the first major branching in the experimental study of social disconnection in the general community should be between social processing ability and social motivation. Further, each of these large branches can be meaningfully divided into smaller branches. Social processing ability can be divided into low-level processes (e.g., social cue perception), higher-level processes (e.g., mentalizing), and integrative processes (e.g., empathy). Similarly, social motivation can be divided into two processes: social approach motivation (desire to be with other people) and social avoidance motivation (desire to be away from other people). Once we know which of these processes account for social disconnection, we will have a much clearer sense regarding the relevant constructs, neural processes, and associated interventions for the responsible processes[8,9].

Based on preliminary analyses of ability and motivation in our community sample enriched for social disconnection (N=140), we find no association between level of disconnection and any of the ability measures. Individuals seem to be highly comparable in their ability to process social cues and make social infer-

ences, regardless of their level of disconnection. Similarly, social avoidance motivation is not related to disconnection. In contrast, social approach motivation is strongly related to the level of connection, even after controlling for degree of loneliness. In other words, social disconnection in the community seems to be related to a social indifference (i.e., low approach motivation), but not to social processing ability, or to social discomfort (i.e., high avoidance motivation).

In many ways, the experimental study of social disconnection in the general community falls through the cracks. Most of social and affective neuroscience has been devoted to a few broad categories: preclinical animal models, normal social processing in healthy individuals, or the study of particular clinical disorders, such as schizophrenia and autism. Social disconnection fits none of these. It is a common, maladaptive and unhealthy condition seen worldwide that is not tied to any specific diagnosable mental disorder. Research on schizophrenia provides a principled way to approach experimental studies of social disconnection in the broader community.

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Assessing the public health impacts of legalizing recreational cannabis use: the US experience

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The sale of cannabis for adult recreational use has been made legal in nine US states since 2012, and nationally in Uruguay in 2013 and Canada in 2018. We review US research on the effects of legalization on cannabis use among adults and adolescents and on cannabis-related harms; the impact of legalizing adult recreational use on cannabis price, availability, potency and use; and regulatory policies that may increase or limit adverse effects of legalization. The legalization of recreational cannabis use in the US has substantially reduced the price of cannabis, increased its potency, and made cannabis more available to adult users. It appears to have increased the frequency of cannabis use among adults, but not so far among youth. It has also increased emergency department attendances and hospitalizations for some cannabis-related harms. The relatively modest effects on cannabis use to date probably reflect restrictions on the number and locations of retail cannabis outlets and the constraints on commercialization under a continued federal prohibition of cannabis. Future evaluations of legalization should monitor: cannabis sales volumes, prices and content of tetrahydrocannabinol; prevalence and frequency of cannabis use among adolescents and adults in household and high school surveys; car crash fatalities and injuries involving drivers who are cannabis-impaired; emergency department presentations related to cannabis; the demand for treatment of cannabis use disorders; and the prevalence of regular cannabis use among vulnerable young people in mental health services, schools and the criminal justice system. Governments that propose to legalize and regulate cannabis use need to fund research to monitor the impacts of these policy changes on public health, and take advantage of this research to develop ways of regulating cannabis use that minimize adverse effects on public health.

Key words: Cannabis, legalization, recreational use, public health impacts, cannabis potency, cannabis-related harms, emergency department attendances, vulnerable young people

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Cannabis is globally the most widely used illicit drug under international control. In 2017 it was estimated to be used by 188 million adults (range 164-219 million) worldwide or 3.8% of the global adult population[1]. Cannabis use is more common in North America and high-income countries in Europe and Oceania[2]. Its use has increased in some low- and middle-income countries, but remains low in Asia[1].

The inclusion of cannabis in the same schedules of the international drug control treaties as heroin, cocaine and amphetamines has been controversial, and public campaigns to legalize its use have been ongoing since the late 1960s[3]. The route to legalization of adult use in the US began with citizen-initiated referenda that legalized the medical use of cannabis, initially for serious illnesses like cancer, but progressively under liberal regulations that allowed the supply of cannabis by retail commercial cannabis "dispensaries". These changes helped to reduce public opposition to the legalization of adult cannabis use, which was first achieved by the passage of referenda in two states with some of the most liberal medical cannabis laws, Colorado and Washington State, in 2012[4].

Combinations of arguments attracted public support for recreational cannabis legalization in the US, as indicated by citizen-initiated referenda[5]. The first is that cannabis use is common among young adults and causes less harm than alcohol, tobacco and opioids[6,7]. The second is that making cannabis use a criminal offence causes more harm than cannabis use itself, because some users are arrested and receive criminal records. The third is that these criminal laws disproportionately affect cannabis users in minority populations, such as African Americans and Latinos. The fourth is that legalization of adult use is a better social policy than criminalization because: a) it eliminates the illicit market; b) it enables cannabis use to be regulated to minimize adolescent access and protect adult cannabis consumers – e.g., by controlling the tetrahydrocannabinol (THC) content of cannabis products and reducing levels of contaminants – such as fungi, heavy metals and pesticides – found in illicitly produced cannabis; c) it reduces the costs of policing the prohibition of cannabis use (freeing police resources to address more serious crimes); and d) it enables governments to raise revenue by taxing the sale of cannabis products[5].

In principle, adult cannabis use could be legalized in a range of different ways[8]. Individuals could be allowed to grow cannabis for their own use and gift it to others. They could be allowed to form cannabis growers' clubs that produce cannabis solely for their members' use. The government could create a monopoly in cannabis production and sales in order to minimize the promotion of cannabis use, as some US states and Canadian provinces have done with alcohol. The government could license non-profit cooperatives or charitable cooperatives that produce and sell cannabis without making a profit. Finally, governments could allow the commercialization of cannabis production and sale under a for-profit model like that used for alcohol[8].

Since 2012, eleven US states and the nation states Canada and Uruguay have passed legislation that has made it legal

for adults to produce, process and use cannabis. Nine US states, Uruguay and Canada now permit legal retail cannabis sales as well. In Washington DC and Vermont, it is legal for adults to grow cannabis for their personal use and to give it to friends, but it remains illegal to sell it[8-10].

The creation of a legal cannabis market is more radical than the policy changes during the 1970s, which removed criminal penalties or imprisonment for personal use and possession, but left the supply of cannabis to the illicit market. Legalization permits the establishment of a legal cannabis industry that has an interest in promoting cannabis use and, unlike policies that legalize medical cannabis use, it allows adults to use cannabis for any purpose.

Most US states that have legalized retail cannabis sales have followed Colorado and Washington State[1] in using the same regulatory approach as for alcohol, i.e. licensing companies to produce and sell cannabis for a profit[11,12]. States differ in whether they separately license growers, processers, suppliers and retail sellers or whether they allow licensees to perform all of these roles ("vertical integration")[13,14].

All states have set the same minimum legal purchase age for cannabis as for alcohol, i.e. 21 years. Many have limited the quantity of cannabis that an adult can legally carry to 28.5 g[15,16]. In most states, cannabis products are taxed on their sale price[17], but tax rates vary between states[1]. Drug-impaired driving is an offence in all states that have legalized cannabis (and in many US states that have not), but states differ in how they have enforced this law[13].

In 2013, Uruguay became the first nation to legalize adult cannabis use. It did so by allowing adults to use cannabis if they registered with the state and used one of three ways to obtain cannabis[18]: they could grow their own cannabis, join a cannabis growers' club that would produce enough cannabis for its members, or purchase cannabis (produced under government licence) from pharmacies[19,20]. The policy was introduced in phases. In the first, registered cannabis users were allowed to grow their own cannabis. In the second, cannabis growers' clubs were licensed. In the third, a small number of pharmacies were licensed to supply cannabis to registered users[1].

The Uruguayan model is still in the early stage of implementation. So, it is difficult to assess whether it has achieved its goals. Some have argued that the model is too restrictive to undermine the illicit cannabis market[20,21]. So far only 6,965 persons have registered to grow their own cannabis and there are 115 cannabis clubs with 3,406 registered members. Only 16 pharmacies (from a total of 1,200) supply cannabis, and 34,696 persons[1] have registered to purchase cannabis from pharmacies[22]. The total of 45,067 registered cannabis users comprise just under half the estimated number of cannabis users in Uruguay. We do not yet know what proportion of registered and unregistered cannabis users still purchase cannabis from the illicit market.

In October 2018, Canada became the second nation to legalize the sale of cannabis to adults[23,24]. The goals of legalization were to eliminate the illicit cannabis market and regulate the production and sale of cannabis to protect public health and minimize youth uptake[25]. The federal government licenses and regulates cannabis producers; advertising of cannabis is not permitted; and cannabis products must be sold in plain packaging with health warnings. The minimum legal purchase age is 18 (unless a provincial government sets a higher one), and it is an offence to drive while impaired by cannabis.

Provincial governments in Canada regulate wholesale and retail cannabis sales in the same way as they regulate alcohol[26]. Provinces with an alcohol retail monopoly can use the same regulatory approach for cannabis, and retail cannabis sales are allowed in provinces that licence for-profit retailers of alcohol. The Canadian federal government collects taxes on cannabis and shares these revenues with provincial governments. The sale of edible cannabis products and cannabis extracts began in October 2019, with taxes based on their THC content.

As is the case with Uruguay, Canadian policy is still at an early stage of implementation. So, it is too early to evaluate its impact. The remainder of this paper accordingly focuses on the impacts to date of the legalization of recreational cannabis use in the US.

HOW HAS RECREATIONAL LEGALIZATION AFFECTED CANNABIS MARKETS IN THE US?

The legalization of recreational cannabis use in the US has had a number of effects. First, it has been followed by a substantial decrease of the retail price of cannabis[17]. Second, it has allowed adults to obtain a regular supply of cannabis without risk of criminal penalty. Third, it has produced a major diversification of the cannabis products for sale[27]. In addition to cannabis flower, cannabis retail outlets also sell high-potency cannabis extracts (wax, shatter), edible cannabis (e.g., gummy bears, candy and chocolates), and cannabis infused beverages[17]. These products presumably meet the needs of a broader range of adult consumers than the illicit market primarily catered to, namely, daily or near daily cannabis smokers[17]. The increased availability and marketing of cannabis, and more publicly visible cannabis use by adults, may make cannabis use more socially acceptable and enable more adults to use cannabis for a longer period of their lives than has been the case under prohibition.

Cannabis prices have fallen steeply in the US states that have legalized its recreational use[17,28,29]. Prices no longer need to include a premium to compensate illicit producers and sellers for the risks of being arrested or imprisoned or subjected to violence by other illicit market participants. Legal cannabis production is no longer small scale and clandestine, allowing growers to increase the scale of production, reduce their costs, and pass these on to consumers in the form of lower prices. If states allow licensees to grow, process and sell cannabis wholesale and retail, as in Colorado, then cannabis production can become even more efficient[29].

Most US legalization states have imposed taxes on the retail price of cannabis products[29]. This method of taxing cannabis has had two consequences: state cannabis tax revenue has declined as retail prices have fallen; and cannabis producers and retailers have had an incentive to increase the THC content per gram of product to reduce prices and increase profits[29]. Taxes may have contributed to

the increased sale of cannabis extracts with a THC content of 70% or more (21% of all sales in some states). The increase in cannabis potency presumably satisfies the preferences of daily cannabis users (who account for most sales). A cap on THC content or a minimum unit price or tax based on THC content would reduce this incentive[8], but so far no US state has adopted any of these policies.

Cannabis prices may decline further. Local regulations have restricted up to now the number and location of retail outlets in some states to the larger cities[30]. Cannabis prices are likely to fall much further if legalization of adult use becomes US national policy, because this would allow cannabis production on a larger scale, potentially permit the establishment of inter-state commerce, facilitate the increase in multi-state operations, allow the development of US-based multinational companies via mergers and acquisitions, and attract large scale investment from the alcohol, tobacco and finance industries.

Historical experiences with the regulation of alcohol and tobacco[31,32] suggest that, in the short term, increasing access to more potent cannabis products at a lower price is likely to increase the frequency of cannabis use among current users. In the longer term, a profit-seeking legal cannabis industry is likely to attempt to increase the number of cannabis users, and the regularity of their use, in order to maximize its profits. This will involve a combination of promotional activities (e.g., media advertising, price discounts, and discounts for regular purchasers) that aim to increase the number of daily cannabis users and the proportion of adults who use cannabis. There is considerable uncertainty about how much and how soon such promotional activities will succeed. Experience with alcohol suggests, however, that the larger the proportion of the population that uses cannabis, and the more often they do so, the larger will be any adverse public health impacts of cannabis legalization[31].

In the remainder of this paper, we review evidence on the public health effects to date of the legalization of recreational cannabis use in the US. As an early adopter, the US is likely to influence the policies adopted in other countries that decide to legalize cannabis use. Moreover, the US collects survey data on patterns of cannabis use in the population and health data on cannabis- and alcohol-related harms. As Canada and Uruguay proceed to implement cannabis legalization, similar high quality survey[33,34] and other data will be collected to assess the public health impacts of legalization in these countries.

WHAT ADVERSE HEALTH EFFECTS MAY INCREASE AFTER CANNABIS LEGALIZATION?

We summarize here the adverse effects that may increase if harmful patterns of cannabis use, especially daily use, increase as a result of legalization. The content is based on reviews of the evidence on the adverse health effects of cannabis[35-37] and analyses of health outcomes that should be monitored after cannabis legalization [38-40].

Acute effects

Car accidents may increase if more cannabis users drive, or drive more often, while impaired, or if cannabis users who drive use more potent cannabis products[36,37]. More cannabis users may present to emergency departments with acute psychological distress and psychotic symptoms if they use more potent cannabis products such as extracts[36]. Adverse effects of cannabis on fetal development[36,37] may increase if more women use cannabis during pregnancy, as appears to be the case in the US[41].

Relationships between cannabis use and the use of alcohol, tobacco and opioids will substantially affect the public health impacts of cannabis legalization[38,40,42]. The public health burdens of these drugs could be reduced if cannabis becomes a substitute, while their impact could be amplified if there is more concurrent use of cannabis and these drugs[38,40].

Chronic effects

More frequent use of potent cannabis may increase the prevalence of cannabis dependence, i.e. more cannabis users will experience impaired control over their cannabis use despite such use harming them[43]. The 9% risk of dependence among lifetime users in the US in the early 1990s may increase in those who use more potent cannabis products[44].

Daily cannabis users have impaired cognitive performance that appears to be reversed by abstinence[45]. Adolescents and young adults who are regularly intoxicated during their schooling have poorer educational attainment[46]. Cannabis-related cognitive impairment may also occur in older adults who regularly use cannabis for recreational purposes[47].

Daily cannabis use is associated with an increased risk of psychotic symptoms or a diagnosis of a schizophreniform psychosis in prospective epidemiological studies[48,49]. These risks are higher in those who begin cannabis use in adolescence, those who use it more often and for longer[48], and those who use strains with high THC and/or low cannabidiol[50]. Psychotic symptoms occur two years earlier on average in regular cannabis users[51], and persons with a psychosis who continue to use cannabis have more frequent episodes and longer periods of hospitalization for their illnesses[52]. In major European cities, an association has been reported between average cannabis potency and the incidence of psychosis[53].

Heavy cannabis users can develop a hyperemesis syndrome[54], with severe abdominal pain and cyclical vomiting. The syndrome is most often reported by daily cannabis users in the absence of any other medical cause[55]. It is relieved by hot bathing[56], resolves when users abstain from using cannabis, and may recur if they restart cannabis[54]. A small number of deaths have been attributed to complications of this syndrome[57].

Case series and a case-control study[58] suggest that heavy cannabis smoking may increase cardiovascular disease risk in young heavy cannabis smokers[59-61]. Middle-aged men who have had a myocardial infarction may experience angina if they smoke cannabis[62], and are at increased risk of a recurrence if they are cannabis users[63-65].

Cannabis-only smokers report more

cough, sputum and wheezing than persons who do not smoke cannabis[66-71], and these symptoms remit if they quit[72]. However, cannabis smokers do not appear to be at higher risk of chronic obstructive pulmonary disease[72,73].

Systematic reviews have not found an association between cannabis use and head or neck cancer[74], or lung cancer[75]. By contrast, a meta-analysis of three studies[76] found a small increase in risk of testicular cancer among high-frequency cannabis users and in those who had used cannabis for ten or more years.

HEALTH EFFECTS OF LEGALIZING RECREATIONAL CANNABIS USE IN THE US

State level legalization of recreational cannabis use for adults was only implemented about five years ago in Washington State and Colorado, the US jurisdictions with the longest experience of a legal regime to date. This is probably too short a period to judge the full effects of legalization. It has taken time to produce dependable supplies of cannabis within states that have legalized, and there are a limited number of retail outlets available in a relatively small number of locations in these states[1]. For these reasons, evaluations of the first five or so years after legalization may provide a poor indication of the impacts of cannabis use on public health when the industry develops over a decade or more[42,77].

Effects on cannabis use

If experience with alcohol and tobacco is a reasonable guide, we would expect declines in cannabis prices to be followed by increases in the frequency of use among existing users[31,32,78]. There is some evidence of increased frequency of use in response to the relatively small declines in cannabis prices that occurred under prohibition[79]. It is more difficult to estimate how much cannabis use may increase when cannabis prices fall by 30-50%[80].

Household survey data suggest that lower cannabis prices have increased the frequency of use among adult cannabis users in US states that have legalized recreational cannabis[78,81,82]. Surveys in Colorado and Washington State have found mixed evidence on the impacts of cannabis legalization on adolescent cannabis use. There was an increase in cannabis use among students after legalization in Washington State, but a decrease among adolescents in Colorado[83,84]. No changes in cannabis use were reported among youth in two surveys in Washington State conducted the year before and the year after legalization of recreational use was implemented[84]. Darnell and Bitney[85] did not find changes in youth cannabis use in Washington State between 2002 and 2016. Anderson et al[86] failed to find an increase in youth cannabis use in the Youth Risk Behavior Surveys in the four years before and the three years after the legalization of recreational use. Dilley et al[87] reported very similar results in analyses of Youth Risk Behaviour Surveys in Washington State.

Cerdá et al[81] recently compared trends in regular past 30 day cannabis use and cannabis use disorders among adolescents and young adults in US states that have and have not legalized recreational cannabis use, using data from the US drug household survey, the National Survey on Drug Use and Health. They found suggestive evidence of a small increase in these outcomes among 12-17 year olds, but did not find any similar effects among those aged 18-25 years. They were cautious in interpreting the former, because they estimated that the small increases could be due to unmeasured confounders. This was a less plausible explanation for similar increases observed in regular cannabis use and cannabis use disorders among adults 26 years and older[81].

Effects on cannabis-related hospitalizations

Cannabis-related hospitalizations have increased in Colorado after recreational cannabis use was legalized. These increases have been in addition to earlier increases that occurred after the legalization of medical cannabis use[88]. After cannabis legalization in Colorado there have also been increases in hospitalizations for cannabis abuse and dependence[89], motor vehicle accidents and injuries related to cannabis abuse[90], and head injuries attributed to an increase in falls[91].

An increase in emergency department presentations for hyperemesis in Aurora, Colorado was reported after medical cannabis use was legalized in 2000, and a further increase after recreational use legalization[92]. A 46% increase in the incidence of cyclic vomiting was reported between 2010 and 2014 in the Colorado State Inpatient Database[93].

An increase in cannabis-related emergency department presentations has been reported after legalization in Boulder, Colorado for childhood poisonings, psychological distress in adults, severe vomiting, and severe burns in users who had attempted to extract THC from cannabis oils using butane[94].

Calcaterra et al[95] analyzed trends in cannabis- and alcohol-related presentations to a hospital network in Colorado that provided emergency medical care to low-income patients in two periods: January 2009 to December 2013 and January 2014 to December 2015. The rate of cannabis-related presentations increased steeply in the latter period, while presentations involving alcohol were unchanged. Cannabis-related presentations were more likely to involve younger adults and more likely to lead to hospitalization, especially for psychiatric care.

In Colorado, emergency department presentations for mental illness with a cannabis-related code increased five times faster than mental illness presentations without such a code between 2012 and 2014[88]. The largest increases were for persons who received diagnoses of schizophrenia and other psychotic disorders, suicide and intentional self-harm, and mood disorders[96].

A review of pediatric cases from 1975 to 2015 found more unintentional cannabis ingestion by children in US states that had legalized medical and recreational cannabis use[97]. This increase prompted limits on package and serving sizes of edible cannabis products in 2017[98]. Despite these changes, pediatric hospital visits and calls to poison centres for cannabis

ingestion increased after 2017. Similar increases in accidental poisoning among children and adolescents were reported in Massachusetts before and after the legalization of medical cannabis use, despite the use of child-proof packaging and warning labels[99].

Effects on road crashes

Studies of the effects of cannabis legalization on traffic accidents have produced mixed findings.

Chung et al[100] reported an increase in the rate of patients admitted to Colorado hospitals for traumatic injury who were cannabis-positive between 2012 and 2015, in the absence of any corresponding increase in neighbouring states that had not legalized cannabis.

However, Aydelotte et al[101] did not find greater changes in traffic fatality rates in Washington State and Colorado using Fatality Analysis Reporting System (FARS) data than in neighbouring states that had not legalized cannabis. Sevigny[102] analyzed FARS data (1993-2014) using data imputation to address the large amount of missing data, and did not find an impact of legalization on cannabis-positive driving among people involved in a fatal crash. Lane and Hall[103] found a short-term increase in traffic fatalities in both US states that had legalized the commercial sale of cannabis (i.e., Colorado, Washington State and Oregon) and their neighbouring jurisdictions.

Treatment seeking for cannabis use disorders

Darnell and Bitney[85] compared trends in treatment seeking for cannabis use disorders in the Treatment Episode Data Set in Washington State in the first two years after legalization with trends in a synthetic cohort comprising a weighted sample of other US states that had not legalized cannabis. Treatment demand declined in Washington State after legalization, but at the same rate as it declined in states that had not legalized cannabis.

MONITORING THE FUTURE PUBLIC HEALTH IMPACT OF CANNABIS LEGALIZATION

There are a number of reasons why the effects of cannabis legalization to date may underestimate its full impacts on public health in the longer term.

First, the commercialization of the cannabis industry is incomplete in the US. While cannabis remains prohibited under US federal law, there are also prohibitions on inter-state commerce in cannabis and investment by the alcohol, tobacco and finance industries. It is difficult for cannabis businesses to use banks or to advertise cannabis, because it remains an illegal commodity. National cannabis legalization would remove these constraints and allow the full commercialization of the cannabis industry under constitutional protections including the "commercial freedom of speech".

Second, it is too soon to evaluate the effects of cannabis legalization in Canada and Uruguay. Both countries are still implementing their models, so it will take time for legalization to become fully operational.

Third, even after legalization is fully implemented, one would expect a delay between any increases in cannabis use and the detection of increased problems related to regular cannabis use in the health care system. The following section discusses indicators that should be monitored to evaluate the longer-term public health impacts of cannabis legalization.

Potential indicators of future cannabis-related harm

Studies of the public health impacts of legalization should monitor trends in acute harms that are likely to increase if more adults use more potent cannabis products more often. These include: car crash fatalities and injuries involving cannabis-impaired drivers; emergency department attendances for myocardial infarctions, acute coronary syndromes and strokes in young adults[58,104-106], and cyclic vomiting in young adults.

Treatment seeking for cannabis dependence should also be monitored. It is uncertain how legalization may affect it. One would expect a decline in treatment seeking among adult cannabis users who will no longer be legally coerced into treatment as an alternative to imprisonment. Adolescents with cannabis use problems may still be arrested[107] and coerced into treatment, and their numbers may increase if courts use treatment as an alternative to their criminal prosecution if they are caught using cannabis.

Legalization may also reduce treatment seeking among persons with cannabis problems if increased access to legal and cheap cannabis products reduces the economic costs of cannabis use and social pressure from families and friends to stop using cannabis. On the other hand, legalization of adult use may reduce the stigma attached to problem cannabis use and thereby encourage earlier treatment seeking, e.g. if education campaigns increase public recognition of cannabis use disorders and encourage users to seek treatment.

The US national treatment data[108] will provide useful information on these trends. These data could be expanded to include information from new treatment entrants on: reasons for seeking treatment; the type and amounts of cannabis used; usual routes of administration; and where they obtained their cannabis (to assess how many problem users are still using the illicit market).

A major research priority should be to improve assessments of the role that cannabis-impaired driving plays in fatal motor vehicle accidents. This research should assess the degree to which cannabis is a substitute for alcohol among young men, and the extent to which it reduces other types of alcohol-related harm, such as suicides and assaults.

It will be important to monitor any effects that cannabis legalization has on tobacco smoking and alcohol use among adolescents and young adults. With the decline in youth tobacco use, suggestive evidence has emerged of a "reverse gateway effect", in which initiation of cannabis smoking has increased tobacco smoking among young adults[109].

The social distributional effects of can-

nabis legalization should also be examined. One major motivation for cannabis legalization has been to eliminate the unequal enforcement of criminal penalties against minority cannabis users. Legalization has reduced arrests, but it is too early to assess its impact on rates of incarceration and minority differentials in imprisonment. It will also be important to see if minorities are over-represented among problem cannabis users who seek treatment[110].

Research should also monitor any adverse health effects that cannabis legalization has on cannabis users over the age of 50. US surveys report an increase in use among this age group since legalization[111,112], probably for a combination of medical and quasi-medical reasons (e.g., to assist with sleep, control pain, stimulate appetite). Older users may be at higher risk of some adverse health effects, such as car crashes, cardiovascular disease and cognitive impairment.

We need more rigorous evaluations of the public health impacts of cannabis legalization[42]. Comparisons of differences between states in time series data on various causes of hospitalization and death are of limited value because they are not able to test alternative explanations of state level differences[77]. We also need large prospective studies of the effects of these policy changes on the use of cannabis and other drugs and their impact on health outcomes in individuals[42].

CONCLUSIONS

The legalization of recreational cannabis use in Canada, Uruguay and an increasing number of states in the US is a large scale policy experiment whose effects may not be known for a decade or more. So far legalization has not produced large increases in cannabis use among youth in the US. As expected, it has increased regular cannabis use among adult users. It has also increased acute cannabis-related presentations to emergency departments in adults and children for physical and mental health problems related to cannabis use (e.g., psychological distress, vomiting syndromes, and accidental poisonings in children). Studies of the effects of the legalization on motor vehicle crashes are inconsistent. There are limited data on the impacts on treatment seeking for cannabis use disorders.

It would be unwise to assume that the modest effects of cannabis legalization observed to date will predict its longer-term effects. The legalization of cannabis markets has already substantially reduced the price of cannabis and increased its potency, and prices are likely to fall further if legalization becomes national policy in the US. Legalization on the limited scale to date has increased regular cannabis use among adults and it may have increased cannabis use disorders among adult users, although the evidence on this issue is insufficient. In the longer term, experience with alcohol suggests that more liberal regulation that provides legal access to cheaper, more potent cannabis products will increase the number of regular users and probably the number of new cannabis users. There is considerable uncertainty about by how many and how soon this may occur.

Future evaluations of the public health impacts of cannabis legalization should assess its effects on: attitudes towards cannabis use in young people; the frequency of cannabis use in high-risk youth and young adults (e.g., those who seek help for mental health problems and those in the criminal justice system); cannabis-related car crashes and emergency department attendances for cannabis-related problems; treatment seeking for cannabis use disorders and its outcomes; and persons seeking treatment for mental disorders.

Research should also assess how legalization affects the use and harms of alcohol and tobacco and other drug use (e.g., opioids) among youth and young and older adults. In the longer term we need to assess the effects of legalization on the duration of cannabis use in adulthood, because it is likely that legalization will extend the duration of cannabis use beyond the late 20s, the age at which most users desisted under prohibition[113]. There is some suggestive evidence that the duration of cannabis use has already increased among recent birth cohorts[114].

These evaluations should inform the design of policies to reduce cannabis-related harm after legalization. These may include: tighter regulation of youth access to cannabis; using taxes to discourage heavy cannabis use (e.g., by setting minimum prices for cannabis products, imposing potency caps, and basing cannabis taxes on THC content[115]); consumer-tested health warnings about the risks of cannabis use, especially daily cannabis use, such as cognitive impairment and cannabis dependence; and research to develop more effective ways of discouraging adolescents from starting cannabis use[116].

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Considering the health and social welfare impacts of non-medical cannabis legalization

With the implementation of non-medical cannabis legalization in jurisdictions across North and South America over recent years, a major policy experiment in alternative control of this widely used, and previously illicit, substance has been unfolding.

Hall and Lynskey[1] review the state of knowledge to date regarding cannabis legalization's impact on public health outcomes. As they correctly observe, the current (mostly North America-based) evidence base regarding the impacts of legalization is limited, and mixed, including heterogeneous effects on cannabis use and related harms. For example, while cannabis use rates among young people seem to have remained stable in the wake of legal availability, use among others and some severe harm outcomes (e.g., hospitalizations) appear to have increased. Thus, it is yet impossible to conclude if legalization has been an overall success or failure for public health.

This likely relates to several reasons beyond those mentioned by the authors. First, effects observed to date may be driven by "strawfire" (or "novelty") dynamics. Second, the full public health impact of cannabis legalization will likely hinge on a combination of outcomes, including use prevalence and initiation among youth; high-risk use patterns (such as frequent and/or high-tetrahydrocannabinol use); cannabis-impaired driving and consequent motor vehicle crashes and related injuries; use disorders and related treatment needs; hospitalizations for cannabis-related problems; use substitution or interactions with alcohol, tobacco or other psychotropics[2].

The robust assessment of such primary outcomes as related to legalization faces a number of challenges. The first one is integrating individual outcome measurements into a combined (e.g., index-type) measure, such as burden of disease, to enable overall public health impact assessment and monitoring[2]. Of note, such measurements commonly omit, but should ideally include, impacts on marginalized or non-general (e.g., indigenous) populations. A second challenge is that pre-legalization trends must be taken into account, as several of the aforementioned outcomes had featured marked pre-legalization increases. Hence, even just a trend-change could constitute a relevant impact associated with the policy change.

The "big picture" evidence on cannabis legalization public health impacts may, even in the long run, remain mixed, inconclusive or even contradictory. In that scenario, particular importance may need to be assigned to possible developments in social – including social justice – benefits or harms. While currently no empirical "social burden" (akin to "disease burden") outcome measure exists, such assessment would need to capture legalization's impacts on reducing the criminalization and stigmatization of large numbers of – predominantly young and often socio-economically marginalized/racialized – cannabis users, and the severe, long-term consequences of these punitive processes on young lives[3,4]. Such a reduction in social harms, indeed, may need to be considered a (or the) quintessential collective benefit of legalization[5]. In some – such as Latin American – countries, social harms have translated into widespread violence, including numerous deaths, related to illegal cannabis markets, which legalization may at least somewhat temper.

Legalization has not eliminated all pitfalls of punitive control and consequences. For example, in select provinces in Canada, the possession of any amounts of cannabis by under-age persons (mostly <19 years) may result in a civil fine. Repeat occurrences or possession amounts of >5 g will draw a charge under the Youth Criminal Justice Act, with subsequent criminal justice system involvement. Given that adolescents' cannabis use rates (about 25% or more) are among the highest, these punitive provisions, combined with commonly arbitrary enforcement practices, could mean extenuation, rather than removal, of prohibition harms for young and vulnerable members of society under the veil of legalization.

In the long run, further developments of cannabis-associated health outcomes under legalization may hinge on the extent to which public health-oriented regulations (e.g., on legal product properties and quality, availability and access) and education on safer use will effectively outweigh dynamics pushing for riskier use behaviors and patterns among consumers[6].

The pivotal factor here – despite declared intentions for effective control in this realm – may rest in the dynamics of the commercialization of legal cannabis production and distribution. For example, in Canada, despite the prohibition of direct cannabis advertisements and promotion, a vastly expansive cannabis industry – striving for sale and profit maximization in highly competitive settings – is driving a commercialized environment in which the armory of public health may simply be too slow and weak for effective checks and protections[7].

Additional developments include cannabis industry-related corporate mergers and combinations with other psychoactive consumption products, such as alcohol, nicotine products and soft drinks, and the widely normalized discourse of cannabis as a universally "therapeutic" consumption good, tacitly drawing on far-reaching yet often un-evidenced medicinal use claims[8]. Decreasing cannabis prices and trends towards higher-potency product distribution, as mentioned by Hall and Lynskey, may further amplify a momentum pushing towards adverse outcomes.

The experiences with alcohol, tobacco and many prescription pharmaceuticals have shown that commercially-driven approaches to psychoactive product design, marketing and distribution can be difficult to control, as well as catastrophic for public health, even with well-intended regulations[9]. Here, cannabis legalization regimes like that of Canada, comprising strong emphasis on user/demand side regulations, had alternatives to full-scale commercialization of cannabis production and distribution, yet opted against them. It would be

disastrous if, in due time, the cannabis legalization experiment simply repeated the histories of other commodified substances and their collateral public health impacts.

In that same vein, cannabis legalization ought not to support a *de facto* re-colonization of vulnerable (e.g., indigenous) populations or communities by psychoactive commodities, yet rather protect free, culturally appropriate choice-making and governance. In these overall respects, Uruguay's model of legalization[10], with its more restrained parameters of commercial cannabis production and availability (yet arguably minus "user registration" requirements and related "surveillance" concerns), may be a worthy sketch for a public health-oriented model.

The idea of cannabis legalization should continue to be considered a potentially beneficial concept for public health and welfare. A number of "second generation" jurisdictions (e.g., New Zealand, Luxembourg) are contemplating legalization options. But the transfer of experiences and evidence on outcomes between complex policy ecologies is not straightforward. Nevertheless, legalization candidates should heed emerging lessons from ongoing legalization experiments. Concretely, they should consider implementing cautious and restrained approaches to legalized cannabis product supply, distribution and availability.

While easily overlooked in societies with predominant "free market" doctrines, alternatives to fully commercialized models – including full or partial government monopolies, cooperatives (e.g., regulated social clubs), community trusts – exist for consideration[3,10]. These can be adapted towards principally furthering the goal of public health through the policy framework of cannabis legalization.

As currently ongoing cannabis legalization experiments in different countries demonstrate, there is much that can be proactively designed and anticipated in the *a priori* planning of major policy reform. It is equally important to carefully monitor both – and especially unexpected or adverse – policy outcomes and their drivers following implementation, and consequently adjust or correct these with best empirical knowledge and tools available. If that occurs successfully, future commentaries in this space may indeed offer overall positive conclusions on the public health impacts of cannabis legalization.

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To legalize or not to legalize cannabis, that is the question!

The wave of changes in cannabis laws coming from the US and more recently Canada has pushed many countries, including the land of Shakespeare, into the dilemma of legalizing or not legalizing cannabis use.

In the UK, a first step took place in November 2019, when medicinal cannabis became legal. Now British specialist physicians can prescribe cannabis for a handful of medical conditions. However, has the American experiment yet convinced its more cautious British allies to go all the way and legalize cannabis for recreational use?

As a clinician and an academic living in UK and working on the link between cannabis use and psychotic disorder, I have been watching the American experiment very closely.

Hall and Lynskey[1] highlight that two of the key arguments of the legalization lobby are: a) that it will reduce adolescent access, and b) that the available cannabis will be safer and less potent because of state-controlled levels of its active ingredient, tetrahydrocannabinol (THC). These are cleverly chosen predictions to reassure both concerned parents and mental health professionals against the well-established association between cannabis use – especially when started in adolescence[2] and of high potency types[3] – and the risk to develop a psychotic disorder. But, have these two predictions held up against the evidence of time?

Hall and Lynskey give a comprehensive snapshot of the outcomes that have followed the changes in cannabis law since 2012 in the US. So, what about adolescents use?

The authors report that, while rates of cannabis use have increased among adults in states that have legalized cannabis, they have not changed among adolescents. Not surprisingly, as Canada, Uruguay and the US have legalized cannabis for adult use, whereas use remains illegal for adolescents, the latter continue to buy it from criminal gangs and they risk criminal prosecution for using it. Moreover, experience with both tobacco and alcohol has shown that adolescents' choices are not influenced as much as adults' by the legal status of a recreational drug. Furthermore, it is still early days to see whether the increase in rates of cannabis use among adults leaks down to influence younger groups.

Indeed, data from a large and nationally representative US survey[4] quoted by the authors, based on state-level estimates spanning 2008-2016, tentatively suggest trends of increase in cannabis use among young adolescents (12-17 years old) in

those states where recreational cannabis use is legal.

Similarly, in December 2019, the US Substance Abuse and Mental Health Administration (SAMHSA) released the data from their 2017-18 National Survey on Drug Use and Health. This showed that, in states where recreational cannabis is legal, past-month youth use is 40% higher, past-year youth use is almost 30% higher, and first-time youth use 30% higher compared to states where cannabis use is still illegal[5]. These data are quoted by Smart Approaches to Marijuana (SAM), the influential American anti-cannabis legalization campaign group[6]. SAM further remarks, with great concern, that past-month youth (aged 12-17) use continues on an upward trend in states with commercial sales. For instance, in Washington, where cannabis use is legal, over the past year there has been the largest surge in past-month youth use, with an 11% increase compared to a 4% increase in Colorado.

What about cannabis potency where recreational use is legal? There is no doubt that, despite the declared intention, the potency of the types of cannabis legally available has gone up. Potent edible types are often available, and their price has gone down. For example, in Washington, where past-month youth use is going up, cannabis potency is spiralling up, reaching THC content equal to 70% or more[7].

Hall and Lynskey rightly point out that the reported widespread increase in types of cannabis with high levels of THC available at low prices exposes cannabis users to an increased risk to develop both cannabis use disorders[8] and psychotic disorders.

While only a minority of cannabis users develop a psychotic disorder, my colleagues and I have shown that users who consume daily types of cannabis with THC ≥10% are over 5 times more likely to suffer from a psychotic disorder than never users. Furthermore, we measured across 11 European cities how high availability of potent types of cannabis (THC ≥10%) impacts, at a population level, on rates of psychotic disorder. We found that in Amsterdam, where types of cannabis with an average THC of 29%, like Nederhasj, are commonly sold in coffee shops, up to 50% of new cases of psychotic disorder can be attributed to the use of high-potency cannabis. These data suggest that 50% of the new cases of psychosis in Amsterdam could have been prevented if these individuals had not added to their cluster of risk factors the use of high-potency cannabis, the most preventable among them. Indeed, in our study, the three cities with the highest incidence rates of psychotic disorder – London, Amsterdam and Paris – also had the highest rates of use of high-potency cannabis in the control samples representing their general populations[9].

So, while it is early days to measure the impact on rates of psychotic disorder of the increase in THC in the cannabis sold where recreational use is legal, it is an evidence-based prediction that the reported greater availability of high-potency cannabis will result in more people presenting with psychotic disorders associated with their cannabis use.

Therefore, while we cannot stop the commercial force driving the cannabis business interests, we can learn how to act from our colleagues that have cautioned against the harmful effects of alcohol and tobacco. None of the countries that have legalized recreational cannabis, nor those which are considering to follow, have invested sufficient resources in education campaigns to engage the general public and especially young people in learning about the effects of cannabis on their developing brain, on their educational achievements, and on their risk to become dependent. There has been no attempt to use modern technology to test their knowledge on the topic and provide them with data.

As the famous American jazz trumpeter and cannabis user Miles Davis said, "knowledge is freedom and ignorance is slavery". Therefore, the freedom that comes from legal access to cannabis might be only an illusion if it is not accompanied by knowledge of its harmful effects.

Rather than dwelling on "to legalize or not to legalize", we should move on to ask for more education. We need public education to enable individuals to make an informed choice about whether and how to use cannabis, and to counter the influence of commercial pressures at a time where, for instance, in Colorado there are now more cannabis shops than Starbucks and McDonald's[10].

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Mapping and mitigating the health risks of legalizing recreational cannabis use: a call for synergy between research and policy

In the past decade, a growing body of studies has been documenting the health risks of recreational cannabis use[1]. Short-term risks include (but are not limited to) impaired memory and psychomotor performance, and risky behaviors such as driving and working while intoxicated, which can result in car crashes and accidents at work. Long-term risks include adverse

physical health outcomes (e.g., respiratory problems, testicular cancer, and abnormal fetus development), impaired cognitive performance and educational attainment, changes in brain integrity[2], mental disorders (e.g., psychoses, depression, anxiety disorders, and bipolar disorder), and cannabis use disorders. Emerging evidence shows that the use of high-potency cannabis products, daily or almost daily use, and younger age at cannabis use onset exacerbate adverse health outcomes in recreational cannabis users[3].

Hall and Lynskey[4] describe several public health developments which have occurred in US after the legalization of recreational cannabis use. Cannabis products are more potent, cheaper and more available to adults. Adults are increasingly using the drug, and more of them are using it daily now. In emergency departments, more cannabis-related attendances and hospitalizations of adults, but also of adolescents and children, have emerged. The detailed review of recent studies shows that the legalization of recreational cannabis use poses (largely unmet) public health challenges. But do these surveys provide sufficient data to reveal "the full picture" so far?

There are three reasons why this may not be the case. First, it is difficult to map the health effects of existing cannabis regulatory frameworks, as they have heterogeneous content and implementation and change at a different pace in distinct regions. This variability of conditions makes it difficult to interpret trends of changes in cannabis products, use levels and cannabis-related health problems within one state and hampers comparisons across jurisdictions[5].

Second, legalization is leading to a dynamic and broad cannabis market in the US. Many new products have become available (e.g., edibles, oils, infusions, vapes, liquids, dabbing, home-grown cannabis). There is no consistent guidance, oversight or monitoring of their distribution and sale[5]. Therefore, the products' content, quality, labelling and packaging control is uneven. There is no consistent agreed-upon measure to systematically evaluate and compare their properties (e.g., serving size, potency and mode of administration). Consequently, the health risks of novel cannabis products are largely unknown.

Third, "gold standard" measures of cannabis exposure are lacking. Decades of research on cannabis use and related harms (and benefits) have been relying on heterogeneous and often somewhat superficial measures of exposure, e.g. binary definition of user vs. non-user that do not segregate dependent daily users from occasional non-problem users. Research lacks details on which cannabis products are used (e.g., dabs, edibles, liquids), how they are administered (e.g., joints, bongs) and levels of exposure (e.g., frequency, quantity).

Further, household surveys have been evaluating the prevalence of cannabis use, misuse and related harms in normative samples. They have failed to represent hard-to-reach populations that might be more vulnerable to the adverse health risks of cannabis use (e.g., socially disadvantaged or marginalized groups).

To sum up, the evidence on the health risk of legalizing recreational cannabis use is still inadequate. There is an urgent need for an improved evaluation of the novel public health challenges (and resources). But how can the situation be improved? We need a vision of an improved surveillance of cannabis-related risks in jurisdictions which legalized cannabis for recreational use – and beyond. Hereby, several public health strategies are suggested.

First, we need to create an overarching framework. To systematically map regulatory frameworks, cannabis markets, trends in cannabis use and adverse health consequences, societies will need time and monetary resources. Governments may benefit from a multi-step approach on their way to establish systematic cannabis monitoring systems. In a first step, they can use information from existing resources, such as already available datasets[6]. In the medium term, large scale surveys within and across international jurisdictions with varying legal cannabis statuses could be run. In the long term, multi-country longitudinal surveys using consistent testing tools ("gold standards") may be conducted to monitor different regulatory frameworks.

Second, we need to involve key players, in order to bridge the gap between science and policy. International networks of scientists, stakeholders (e.g., medical professionals, government agencies, public health organs, advocacy groups) and policy makers should come together and co-design the much needed "gold standard" measures of cannabis exposure. To keep up with the new challenges and resources of rapidly changing cannabis markets, new tools need to be developed to assess the properties and unknown health effects of new cannabis products.

Third, we should use available key indicators. For instance: a) socio-demographic characteristics of consumers (e.g., age, gender, socio-economic status) and socio-economic index of the area where cannabis is sold; b) regulatory framework; c) prevalence and patterns of cannabis use, including risk perceptions; d) problem cannabis use; e) adverse outcomes (e.g., problems from acute exposure, car crashes, working accidents, poison calls, mental and physical or social problems); f) treatment demand (e.g., emergency department visits, outpatient treatment, hospital admissions).

Household and high school surveys can be used to get representative population data[7]. Information from colleges, universities and job centres, the criminal justice system, emergency departments, as well as mental health and addiction services, could also be used. To gain information on marginalized or hard-to-reach populations will be more difficult. New innovative search strategies need to be developed, requiring additional monetary resources.

Fourth, we need to develop new key indicators. It is important to monitor the broad cannabis markets and to gain insight in the properties of novel cannabis products. New assessment instruments are needed to evaluate cannabis product types, features and modes; potency (tetrahydrocannabinol content), price, addiction liability, and adverse health outcomes. As suggested by Hall and Lynskey, sales volumes should be monitored too.

Finally, cannabis research should become a top priority. Cannabis is the most widely used controlled drug worldwide, yet it remains largely understudied. To catch up with the new public health challenges posed by changing cannabis regulations, more research is needed. Significantly higher research budgets will be required to

get high-quality studies, independent from the expanding cannabis industry. To facilitate research, regulatory barriers for the conduct of experimental studies will need to be removed.

In conclusion, there is emerging evidence about cannabis-related risks, but knowledge about the effects of legalizing recreational cannabis use is still at an embryonic stage. Scientists, stakeholders and policy makers will need to join forces to address this gap.

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Recreational cannabis legalization presents an opportunity to reduce the harms of the US medical cannabis industry

Hall and Lynskey's masterful essay[1] provides a comprehensive assessment of the public health consequences of recreational cannabis legalization, which wise policymakers will consider as they design regulatory systems. We urge US policy-makers to recognize that recreational cannabis legalization changes the political environment in a way that creates an important public health opportunity: cleaning up the underregulated and frequently harmful US medical cannabis industry.

Medical cannabis legalization initially emerged as a political cause in California in the mid-1990s. The explicit goal of many of its advocates was to pave the way for recreational legalization by exploiting both the public's compassion for seriously ill individuals and the public's trust in medicine. Of course, some individuals with serious diseases did access legalized medical cannabis and some of them may well have benefited from it. But the bulk of the "medical" customer base were young adult males with a long history of consuming cannabis along with a range of other drugs[2]. From a regulatory viewpoint, the system was medical in name only, functioning instead as an aggressively commercialized, quasi-recreational cannabis industry.

California was not unique in this respect: in many states implementing or planning to implement recreational cannabis, "medical" providers operate both lines of business. Most of the states with legalized recreational cannabis thus have a pre-existent medical industry that could be likened to a vestigial organ, except that it does significant harm, including but not limited to the following.

First, unlike a truly medical industry, the "medical" cannabis industry develops, promotes and sells drug products without submitting them to the Food and Drug Administration (FDA) for approval. So, physicians are in the awkward position of discussing drug products with patients without any reassurance that they are safe or effective. Lack of FDA approval and standardization for all but a few cannabis-based products also means that physician recommendation letters cannot specify dose, frequency, route of administration, strength, or any other attribute. This means that vulnerable patients are being sent out to try drugs under the false belief that the normal protections they expect from the health care system are in place.

Second, the public may view cannabis dispensaries as analogous to pharmacies, but they are not subject to the regulation that make pharmacies beneficial. Any written advice from a physician in no way constrains what putatively medical cannabis products are dispensed to customers. Point-of-sale advice comes from "budtenders" who have no medical training. In this role, they sometimes give unsound advice, such as encouraging pregnant women to smoke cannabis[3]. Such potentially harmful advice is probably more likely to be followed than it would be in a strictly retail setting, because it comes wrapped in medical trappings.

Third, unlike in real medicine, individuals harmed by the "medical" cannabis industry have no right to redress. If following the medical advice of a physician caused a birth defect in a woman's newborn, she would have grounds to sue or petition for removal of the physician's license. But budtenders have no medical license to remove and are not responsible as physicians are for the advice they give. Similarly, in an industry that sells non-FDA approved drug products, there is no way for a regulator to pull from all shelves a product that is discovered to cause detrimental side effects.

Fourth, medical cannabis product labelling, unlike FDA-approved drug labelling, is loosely regulated and minimally enforced. Audit studies show that the dose and contents reported on medical cannabis industry product labels are frequently incorrect[4], which can lead to undesired effects, including acute poisoning.

Fifth, medical cannabis products with no evidence of effectiveness compete with life-saving treatments, potentially causing needless deaths. Multiple companies promote using cannabis to replace buprenorphine for opioid addiction treatment, despite zero evidence of the benefits of the former and multiple clinical trials for the benefits of the latter[5]. Other for-profit companies publically claim that medical cannabis legalization will reverse the opioid overdose epidemic as a promotional strategy, despite the evidence that no such pop-

ulation-level benefit exists[6]. Just as tragic are reports from oncologists that some cancer patients drop out of care because they have heard that medical cannabis can cure their disease[7].

Finally, because heavy cannabis use now has the cultural imprimatur of medicine, physicians (particularly psychiatrists) often struggle to persuade patients whose illness is exacerbated by cannabis use to reduce or cease use.

Prior to recreational cannabis legalization, policy-makers who attempted to address problems such as the above through tightened regulation faced the opposition of deep-pocketed for-profit "medical" cannabis providers, as well as risked being painted as cutting off legions of desperately sick individuals from their medicine. However, with recreational legalization in place, neither of those concerns are politically relevant, allowing steps such as the following to be taken by regulators.

First, medical cannabis programs should be folded into the recreational industry (as the State of Washington recently did). To facilitate this, states can automatically convert licensed medical dispensaries to licensed recreational dispensaries. This prevents recreational customers from using the medical cannabis system to evade taxes (medical cannabis is often taxed at a lower rate). Combining systems preserves access to medical cannabis for genuinely sick individuals without subjecting them to a potentially dangerous false promise of medical-level regulation and consumer protection[8]. It also protects public trust in genuine medicine by not labelling an under-regulated and frequently unsafe industry as medical.

Second, state health commissions which – to their discredit – have endorsed indications for medical cannabis with no evidence (e.g., for opioid use disorder treatment[5]) should withdraw all such recommendations immediately. No further such recommendations should be made without the FDA-level evidence required for health commissions to make recommendations for any other drug.

Third, the FDA should become substantially more engaged with removing misleading advertisements, withdrawing licenses from fraudulent sellers, and recalling dangerous and mislabeled products just as they do for genuinely medical industries. Though the FDA has the authority to regulate claims by medical cannabis operators, to date that action has been limited to a few companies among hundreds making unfounded and harmful medical claims. In 2019, the FDA sent warning letters to 22 companies over unsupported medical claims about their products (e.g., treating breast cancer, depression, Alzheimer's disease, anxiety) and illegally selling cannabidiol products[9]. These letters, which provide instructions to voluntarily correct a violation, are a good start, but they must be built upon rapidly with industry-wide standards and consequences.

Finally, coverage of cannabis in medical school curricula should be updated to reflect how legalization may impact a patient's health – from reducing some social consequences of use, to making decisions and having conversations analogous to those about alcohol and tobacco during pregnancy.

None of these regulatory steps would threaten genuinely sick individuals' access to cannabis. Indeed, they would better protect such individuals by subjecting cannabis-based treatments to the same safety and effectiveness standards as all other medications. Some elements in the US medical cannabis industry will adopt the rules and standards of the rest of medicine. Such ethical actors should be welcomed, licensed, and allowed to provide services. But the rest of the industry should no longer be granted the status and trust of medicine without the ethical, scientific and professional standards from which that status and trust are derived.

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Cannabis and public health: a global experiment without control

Every few weeks, new findings on the effects of legalizing recreational cannabis use are published. Thus, the review of Hall and Lynskey[1] – or any review for that matter – can only provide a preliminary summary of the collected evidence to date.

Looking into public health effects of legalization, two seemingly easy indicators may be prevalence and patterns of cannabis use, as both are potentially linked to health and social problems in the presence or absence of legalization[2]. However, the main source for both indicators are surveys, with their severe limitations, as today's surveys are neither based on representative sampling frames nor on high response rates. In addition, in the case of cannabis, we are dealing with a (formerly) illicit and stigmatized substance, making comparisons over time even more challenging. More reliable measures such as wastewater analyses are needed here, but these measures cannot assess patterns of use or individual behaviors.

There are good indications that cannabis-related hospital (emergency rooms, psychiatric wards) admissions have increased in legalizing US states, possibly driven by an increase in frequent use. In addition to further monitoring these trends

in harms, Hall and Lynskey[1] suggest tracking treatment demand to allow for a short-term evaluation of legalization's effects. However, as the authors acknowledge, there are many confounding determinants involved in such evaluations, including access to and availability of treatment, coercion, potency of used products, use of synthetic cannabinoids, help-seeking behavior, stigmatization and public perception of cannabis use and associated problems. For instance, despite the liberalization of cannabis in Canada, with increases in use over the past years, there have been decreases in treatment rates, partly because liberalization seems to have led to higher thresholds for treatment seeking, as use *per se* is no longer considered problematic[3]. As long as these confounding determinants cannot be disentangled, treatment demand data should probably not be used as an indicator to evaluate the public health effects of legalization.

We also disagree with the statement that it is too early to evaluate the consequences of legalization on the legal system. We do not see why other domains can be evaluated now but not this one, one which has been put forth as the main argument by opponents of prohibition, and could quite easily be measured.

However, there are some general limitations in any evaluation at this point, especially since circumstances associated with legalization seem to be changing rapidly. In other words, legalization is not a clearly defined phenomenon, because it takes myriad forms on a spectrum ranging from tight control to open markets, even within a country (such as in the US or Canada, where states or provinces decide on implementation).

Looking at the evidence gathered in the US so far, it becomes apparent that most evaluations will fail to identify causal determinants. For instance, if a potential rise in traffic fatalities in legalizing states is found, it may be attributed to "legalization" *per se*, when the underlying reason may in fact be a greater impairment of the drivers due to an increased use of high-potency products – a phenomenon only accelerated by legalization.

Thus, identifying causal agents and processes poses methodological challenges which may not be overcome easily in analyzing natural, large-scale experiments. To improve understanding of the effects of legalization, we strongly advocate for small-scale, controlled experiments, such as those proposed in the city of Berlin, Germany[4]. There, the effects of legal access to cannabis are to be studied in a restricted sample of registered users, while users without legal access serve as controls. Such experiments – limited both spatially and temporally – will allow researchers to examine how increased availability impacts on consumption patterns and related risks in greater detail, and thereby provide an evidence base for formulating large-scale regulation models.

In any experiment, pre-defined outcomes (e.g., changes in cannabis-related arrests) may be in the limelight, but unintended consequences should not be ignored. One prime example is the dramatic increase of tetrahydrocannabinol (THC) exposure in North America, driven by new products and modes of administration, which facilitate the intake of higher doses of THC compared to, for instance, smoking cannabis in a joint.

Specifically, oil cartridges can contain several hundreds of doses of THC, and regular users may use more of those cartridges a day. As such products are more widely available in jurisdictions with legal access to cannabis, and as THC has been linked to cognitive impairment, use disorder severity, and psychotic symptoms, the catalyzing effects of legal cannabis markets with regard to THC exposure should be thoroughly evaluated and compared to illegal markets. The main barrier here, however, would be to obtain reliable and comparable estimates for the control group (with no access to legal cannabis). Again, these methodological limitations reiterate the need for small-scale, more tentatively conducted experiments.

Active experimentation is in line with Campbell's vision of an experimenting society to solve complex problems[5]. Part of this vision is a more active role for policy formulation, but also some clear empirical principles for evaluation. If experiments such as cannabis legalization fall short according to pre-determined criteria, societies should be able to adapt and change directions.

Largely irrespective of the evidence collected so far, current politics seem to be final and one-directional: once a widening of the cannabis market via more liberal medical marijuana policies or via legalization is sanctioned, market forces seem to be the sole drivers of the future course, and mainly fueled by the desire to increase revenues and shareholder values.

This development also extends to low- and middle-income countries[6]. Thailand provides a prime example. In this society with less than 1% prevalence of cannabis use, medical marijuana has been introduced, and the government announced future legalization of recreational cannabis use based on unrealistic claims of massive income benefits for households growing and selling cannabis to industry[6].

As a result of these market utopias, rational exploration of alternative governance models – which are more public health oriented – stand little chance. Canada provides a good example here: what started as "legalization with strict control" has evolved into quick increases in availability and looser controls, led entirely by market forces. With a legalized market now in place, the illegal market is still thriving, and there is no sign that it will cease to[7].

For example, in Canada's major magazine *Maclean's*, an article published one year after legalization contrasted the purchase of legal cannabis (taxed, more expensive, of lower quality) in a licensed store at considerable distance with "placing a delivery order from my friendly, local unlicensed shop; they take credit card payment at the door, I can redeem loyalty points, it's less expensive, and the weed? Well, it's dank"[8]. The existence of such options was confirmed by federal police, who warned about continued illegal sales for just such reasons: home delivery, options for credit card payment, and nation-wide shipping, in addition to often significantly lower prices[7]. Yet there is no push by government to enforce business practices for the legal options.

In this situation, all that seems to be left for public health is to document the consequences of these developments. In this respect, contributions like the review of Hall and Lynskey[1] are important, but they also show the difficulties in arriving at any firm conclusions.

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Being thoughtful about cannabis legalization and social equity

Hall and Lynskey[1] highlight several outcomes featured in cannabis policy debates and correctly note that they will be shaped by the type of legalization that is implemented. Their excellent review of the emerging evidence about how the commercial approach influences health outcomes will hopefully inform future debates in the US and elsewhere.

A related outcome increasingly receiving attention in these debates is whether cannabis legalization can be used to promote social equity and help communities of color that have been and still are disproportionately affected by prohibition. Indeed, at a time when some in the US are discussing reparations and how to acknowledge and address the fact that the country's economy was heavily built on slavery, this is a particularly salient issue to consider.

Cannabis arrests have dropped dramatically in legalization states, although in some places they were already falling before the policy change[2,3]. Overall, fewer people of color are being arrested for cannabis in legalization states, but this does not mean that legalization will eliminate racial and ethnic disparities in cannabis arrests[3].

Having a criminal record has implications for health and economic well-being and, in the US, there are additional consequences associated with having a drug offense on one's criminal record[4]. For example, in some places a cannabis offense can make it harder to access public housing or work in the newly legal industry. While the early efforts to legalize cannabis in the US did not directly address expunging criminal records, jurisdictions soon began to make it easier for individuals to clear these cannabis offenses from their records[5]. Some places have gone further by automatically expunging these offenses.

Beyond issues surrounding criminalization, an increasing number of US jurisdictions are implementing social equity programs which give preferences for business licenses to people from communities disproportionately affected by cannabis prohibition[5]. Some of these programs also provide technical assistance for those who are new to the process of starting and growing a business. There are also some efforts to directly target cannabis tax revenues to support these communities. For example, one Chicago suburb (Evanston) recently announced that it plans to set aside some of its cannabis tax revenues to help fund its new local reparations program for African Americans.

While it is too early to evaluate the effectiveness of these efforts, their utility must be considered in the context of the economic realities of cannabis legalization, especially as they are unfolding in the US. In theory, there are multiple reasons why legalization will push down cannabis production and distribution costs, which can in turn influence prices[5,6]. First, legalization reduces the risk of arrest for sellers, which decreases the risk premium they must be paid. Second, the "structural consequences of illegality" create inefficiencies that will no longer exist in a legal market[7]. Third, firms can take advantage of increasing economies of scale if large producers are allowed. Fourth, with legalization it will be easier for producers and processors to benefit from improvements in technology. With declining costs in a competitive market, we would expect prices to decline.

Large declines in cannabis prices can affect revenues for governments and businesses, which can in turn affect efforts to promote social equity. If cannabis taxes are set as a function of its price (e.g., Washington applies a 37% excise tax on retail purchases) and the price declines, so will the tax revenue available for social equity programs (although this could be offset by an increase in total cannabis sales). Price declines can also make it harder for small businesses to stay competitive with larger firms. Thus, giving a license preference to a small business that does not have much of a chance in a lightly-regulated commercial market could be counterproductive. It might make some people worse off than if they invested their money elsewhere.

This is not a theoretical concern. Hall and Lynskey note that cannabis prices are already falling in places that have legalized. Further, in early legalization states such as Washington, there are reports of small cannabis businesses closing down or being bought out at a steep discount by larger firms[8].

While an increasing number of US states are creating commercial cannabis regimes, this activity remains illegal under federal law. Among other consequences, federal prohibition is preventing some of the largest corporations, including alcohol and tobacco companies, from getting involved in the industry. US federal legalization could cause cannabis prices to bottom out, especially if imports are allowed and Amazon can deliver. This will make it even harder for small businesses to compete.

But there are many approaches to legalization[5,6]. Hall and Lynskey mention a few, including a government monopoly on cannabis production and sales. Govern-

ment stores could play an important role in promoting social equity if the revenues are thoughtfully allocated. Since the government would set the price instead of the market, this could prevent the large price declines. Further, this approach would allow the government to keep the revenue instead of having it go to profit-maximizing firms. If a certain percentage of these revenues were allocated to evidence-based programs to build wealth for historically affected individuals, this might help improve economic conditions.

There could be other social equity and public health advantages to the government monopoly approach. In addition to stabilizing prices and revenues, it would be easier to limit the types of products and control marketing in the US with this approach versus the commercial model[6]. Further, liquor stores tend to concentrate in minority communities and there is some evidence suggesting that this is happening with cannabis outlets[9]. Thoughtful siting of state-operated retail stores could avoid this type of predatory concentration.

Of course, it is possible to both give license preferences and set aside tax revenues for programs supporting social equity; they are not mutually exclusive. But given declining prices and the dominance of the for-profit commercial model in US policy discussions, it is unclear whether license preferences will ultimately have the desired effect.

We applaud the public servants who have worked hard to implement social equity programs in places that have legalized cannabis. Our hope is that jurisdictions considering alternatives to cannabis supply prohibition and seeking to improve social equity outcomes – and public health – not limit their discussions to the "for-profit with license preference" model. We encourage these jurisdictions to consider the pros and cons of various legalization options as well as use the growing evidence about the economics of legalization to implement an approach that is most likely to succeed in its social and economic goals.

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The effects of recreational cannabis legalization might depend upon the policy model

Since 2012, when Colorado and Washington State started the path to legalize cannabis for recreational purposes, the trend has been growing. Uruguay became in 2013 the first country to legalize the whole process: from production to distribution, commercialization and consumption. Canada followed suit in 2018. By January 2020, eleven states in the US, Uruguay and Canada have legal access to recreational cannabis for adults, and other countries have started the legalization process or the discussion about it, as is the case of Luxembourg and New Zealand.

Each of these experiences of legalizing cannabis is different from the others[1]. Legalization in the US and Canada has followed a deeply commercial model, while legalization in Uruguay is heavily regulated and controlled by the government[2]. Even in Canada, there are significant differences in the set of rules that each province has opted to follow while legalizing. For example, in some Canadian territories the minimum age for use is 18 years, while in others it is 21.

The features of each legalization policy model might have a different impact on the expected outcomes. Some regulatory policies might increase certain legalization adverse effects, while decreasing other negative impacts. For example, the Uruguayan cannabis legislation forbids the selling of cannabis edibles, which might reduce intoxications among minors but increases the percentage of users that smoke cannabis.

So, it is important to compare the effects of the different models of cannabis legalization and not assume that all the experiences will produce the same results. In other words, it is important to take advantage of the existing variance of policy design. The way in which you regulate might lead to different effects on public health and the other objectives that the policy is designed for[3].

Hall and Lynskey's paper[4] mentions several ways to assess the public health impact of legalizing recreational cannabis use, on the basis of the US experience. The authors provide a very significant contribution to the emerging debate on the importance of reaching an agreement on a group of indicators to be monitored, possibly aggregating them in an index to measure their overall impact on public health[5].

They also recommend that the evaluation looks at outcomes in the short run but also in the long term. For example, they point out that legalization might "enable more adults to use cannabis for a longer period of their lives". It will be necessary to keep track of the impact of this prolonged use on car crash fatalities and injuries, as well as on emergency department attendances related to cannabis consumption. The authors also call the attention to the possibility that cannabis legalization becomes a federal national policy in the US, which will reduce cannabis prices, because cannabis industry will try to enhance profits by increasing the size of the market.

In order to evaluate the impact of the current legalization experiences, it is crucial to measure their effects both on public health and on users' criminalization and contacts with illegal activities. The Uruguayan cannabis regulation model is a middle-ground option between prohibition and commercialization, in which the government imposes strict regulations for users: mandatory registry, maximum amount of cannabis per user (40 g per month and 480 g per year), no advertisement, no selling to tourists, no edibles allowed. These restrictions were planned to control consumption and accomplish the public health goal of the regulation.

The Uruguayan government-oriented model with strict regulations has had a positive impact on controlling substance quality as well as on reducing users' contact with illegal activities. Available data on frequent cannabis users suggest that Uruguayans abandoned *prensado*, a poor quality cannabis sold illegally, and moved to use flowers. Also, they reduced their contacts with illegal dealers and selling points. In that sense, in Uruguay, the regulation made cannabis use safer than before[5]. However, the same restrictions might have kept the black market alive, because many users refuse the registry.

Among the goals that cannabis legalizations pursue, minimizing youth consumption is frequently mentioned (see, for example, the Canadian Cannabis Act[6]). In Uruguay, at this moment, there is no evidence about the impact of legalization on youth consumption produced by research using a control group, but cannabis use among young people had been increasing before 2013, and the trend has apparently remained almost the same after legalization was implemented[7]. Regardless of the evidence, why should we expect a reduction in consumption among adolescents with legalization? It could be argued that, although minors do not have legal access, the increase in cannabis accessibility is likely to lead to more youth consumption.

Hall and Lynskey emphasize the importance of assessing the public health effects of cannabis legalization. I would add that it is essential to evaluate the effects of the different legalization policies on all the outcomes they are designed to accomplish, keeping in mind that each legalization model could improve some outcomes while worsening others.

In order to do that, funding to collect good quality data and conduct research that includes control groups is essential. Coming up with agreements about which indicators should be monitored would be extremely useful, in order to allow collection of comparable data in the different territories where legalization is taking place. By doing that, we will be able to evaluate the impact of different policy designs and contribute to a more evidence-based discussion about the pros and cons of each model.

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Legalizing recreational cannabis use: a promising journey into the unknown

There are many arguments in favor of legalization of recreational use of cannabis. Legalization removes incentives for criminal organizations to be involved, allows for quality control, raises tax revenues, and facilitates researchers to collect and analyze high-quality data.

Hall and Lynskey[1] provide an interesting overview of the public health consequences of legalizing recreational cannabis use. With this legalization, some US states have become frontrunners in international cannabis policy. Research-wise and policy-wise, there are two main issues, i.e. how legalization affects cannabis use and how cannabis use affects health. My reading of Hall and Lynskey's paper is that there are quite a few uncertainties regarding both issues.

From the research viewpoint, any study that aims to investigate determinants and consequences of cannabis use is hampered by the lack of a suitable experimental setup. It is difficult to imagine research on legalization of cannabis use or cannabis use itself implemented through a randomized controlled trial. As far as I am aware, there is only one such study available[2]. This was conducted over a period of 98 days in Toronto, Canada, and aimed to explore the relationship between cannabis use and workplace behavior.

Participants were recruited from volunteers who had been using cannabis for about two years. During the experiment, participants could earn income by weaving sash belts on portable hand-looms. Workplace behavior was measured as daily production, daily working time and output per hour. Participants were randomly assigned to an experiment group or a control group. Those in the experiment group were required to smoke every day two cigarettes each containing 8 mg of tetrahydrocannabinol (THC). For them, cannabis use was legalized, as they were allowed to purchase a further unlimited number of cannabis cigarettes at a low price. Those in the control group were not required to smoke cannabis cigarettes. These cigarettes were available for them to buy, but had a substantially lower THC content. Two main conclusions could be drawn from the experiment. First, legalization did not result in substantially

higher levels of cannabis use. Second, large scheduled doses of cannabis had no adverse effects on any production measure.

This study was limited due to the peculiar design and the brief duration of the experiment, and because the effects were measured in terms of workplace behavior rather than mental health. When it comes to mental health effects, a further complicating matter is the measurement issue, regarding both the outcomes to be measured and the assessment instruments to be used[3].

When considering the effects of legalizing recreational cannabis use, it is important to keep in mind that the initial decision to make cannabis illegal was not well motivated. Apparently, it was Egypt that put cannabis on the League of Nations' international agenda. However, medical knowledge on the relationship between cannabis use and mental health problems at the time was based on presumptions rather than proof[4]. The main "evidence" seems to have been based on interviews with patients at a hospital for the insane. Anyway, in that study, prohibition of cannabis was deemed unwise because "its place would be taken by another euphoric agent, probably alcohol", and alcohol was thought to be a "fertile cause" of insanity[5]. Unfortunately, this policy advice was ignored, and the 1925 International Opium Convention in Geneva decided that cannabis was as addictive and dangerous as opium.

Liberalization of cannabis use may sometimes be unintended. In 2017, low-THC cannabis was legalized in Italy as a by-product of a law that regulated the production and commercialization of hemp. Thus, the use of light cannabis (C-light) was unintentionally liberalized[6]. This apparently affected both the supply of illegal cannabis and the use of regular prescription drugs. With the legalization there was a reduction in confiscations of illegal cannabis, suggesting that criminal organizations suffered from the unintentional legalization[6]. The legalization of C-light also reduced the use of prescription medicines such as anxiolytics (–11.4%), antipsychotics (–4.8%), opioids (–1.2%) and antidepressants (–1.2%)[7]. So, self-medication through C-light apparently replaced in part the use of prescription medicines treating symptoms for which cannabidiol is considered to be effective. Interestingly, this substitution increased the costs for users, as regular prescription medicine is either fully reimbursed or subject to a small co-payment, whereas C-light is not cheap.

Thus, cannabis has been declared illegal almost by coincidence, without an appropriate balancing of the pros and cons of doing so. Its illegal nature has made it difficult to explore its potential as a medicine. Indeed, "cannabis sits in an unusual medical no-man's-land: neither licensed for most of the uses for which people want it, nor tested to the standards that patients usually expect from medicines"[8]. The good face of cannabis is that it in some cases it may be a substitute for prescription medicines; the bad face is that in other cases it may have negative mental health effects. The balancing between these effects has become impossible to make.

Clearly, legalizing cannabis is going to have complex consequences for cannabis use and thus for public health. However, legalization also provides opportunities to better understand how cannabis may be beneficial for mental health. Indeed, as Hall and Lynskey argue, the legalization of recreational cannabis use in Canada, Uruguay and various US states "is a large scale policy experiment whose effects may not be known for a decade or more"[1]. The experiment is there because *ex ante* its net effects were expected to be positive. I am inclined to think that also *ex post* the experiment will turn out to be successful.

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Assessing the public health effects of cannabis use: can legalization improve the evidence base?

Hall and Lynskey[1] elegantly review evidence on the effects of legalization of recreational cannabis. The trouble is – as they conclude – that it is too early to tell. So, what matters going forwards is whether there will be sufficient investment in generating evidence and conducting research into both the association of cannabis use with health and social harms and the impact of alternative methods of legislating cannabis consumption on the prevention of those harms.

As Hall predicted in earlier reviews of cannabis policy and health[2], permitting "medical use" of cannabis, especially in an under-regulated commercially driven health system, was the thin edge of the wedge to promoting "de-criminalization" and full legalization. This was illustrated in some US states – prior to legalization – by the growth in young people requiring and obtaining cannabis prescription to manage idiopathic neuropathic complications.

Permitting medical use of cannabis importantly also challenges the stance of many politicians and policy-makers in other countries – such as the UK – for not removing criminal sanction on cannabis possession due to a "precautionary principle". That is, that there remain sufficient reasons and uncertainties over the risks of use to people's health – especially in relation to psychosis – that cannabis should continue to be controlled as a harmful illegal substance.

Indeed, cannabis exposure is associated with poor school performance (under-emphasized in Hall and Lynskey's review)[3], drug dependence, mental health and physical morbidity. However, there is little trial

or observational evidence that criminal sanction prevents cannabis use in the population, and for a significant minority of people – often the most vulnerable in society – being penalized through drug law offences decreases future employment opportunities and may increase social and health inequalities. We now have an opportunity to assess properly what strategies are more likely to reduce cannabis related harm. Here we focus on two areas – potency and natural experiments.

There is evidence that use of higher potency cannabis is associated with higher risks for mental health outcomes and dependence[4]. The observed increase in tetrahydrocannabinol content in legalized states is of concern, but legalization does provide consumers with access to accurate information about the potency of the product they are using. The resultant increase in accuracy in assessments of cannabis potency in legal markets will be vital for improving our understanding of the relationship between cannabis potency and mental health.

One effect of the legalization of cannabis in the US is the proliferation of different products, such as edible cannabis (e.g., gummy bears, candy and chocolates) and high-potency cannabis extracts (wax, shatter). Such products allow cannabis consumption without the need for combustion. In the absence of these products, cannabis is commonly consumed in combination with tobacco, which may confound the relationship between cannabis and mental health[5]. However, given that factors such as the route of administration will affect the bioavailability of the drug, there is a need to develop a standard unit of cannabis exposure – similar to alcohol – so that we can better understand and measure the acute and long-term effects of the exposure[6].

Hall and Lynskey suggest that legalization provides opportunities to minimize adolescent access to cannabis. However, as noted above, there has been a rise in cannabis products (chocolates and candy) that may be attractive to children, and little evidence for a fall in adolescent cannabis use in states where cannabis is legalized. Additionally, adolescents will also be exposed to increased marketing and perceived societal acceptability of cannabis use. Given restrictions on purchase age (21 years and over), adolescents are excluded from legal purchase, but will still have access to an illicit market which may now include diverted products.

We know that risks for dependence, mental health problems and negative socioeconomic outcomes are associated with initiation of drug use during adolescence, and that progression to cannabis dependence occurs as part of a profile of other drug dependences and mental health issues[7]. However, cannabis regulation provides new opportunities to instigate public health interventions and information campaigns related to cannabis, and monitor the effect of these on preventing harms amongst adolescents who are most vulnerable to developing problem use.

Furthermore, there are research opportunities afforded by changes in legislation and policy that can enable us to generate better evidence as to the causal nature of some of the associations between cannabis and negative outcomes, such as poor mental health and memory impairment. For example, within the US, where neighbouring states can have vastly different policies in place, the conditions making it possible to conduct a natural experiment have arisen. This could be conceptualized as a cross-contextual study, whereby the demographics (or other potential confounding factors) of individuals choosing to use cannabis in the different regions may differ due to these policy differences.

If associations seen between cannabis and health outcomes remain the same under these different conditions, this is stronger evidence that the associations seen are causal. If, instead, associations are mostly seen in conditions where prohibition is in place, this could provide evidence that some of these associations are likely to be confounded by factors either related to prohibition itself, or to the demographics of who is likely to use cannabis under these different circumstances.

We have argued before that there needs to be better use of alternative methods to establish causal association between cannabis and health and other harms. One example may be the use of Mendelian randomization studies (i.e., studies based on genetic polymorphisms associated with measures of exposure, or "genetic instruments", that are not confounded by other exposures or subject to selection bias or reverse causation)[8]. We do not yet have genetic instruments of cannabis dependence and/or hazardous use, moving beyond measures of early first use[9], but with legalization there is an opportunity to generate larger studies of richer phenotypes of levels of cannabis exposure.

Given the research and public debate around the strength of evidence for public health risks from cannabis use, the research community can now capitalize on the unique opportunity that these changes in legislation present to us, and use the findings to inform evidence-based policy changes throughout the rest of the world.

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Association of preceding psychosis risk states and non-psychotic mental disorders with incidence of clinical psychosis in the general population: a prospective study in the NEMESIS-2 cohort

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The validity and clinical utility of the concept of "clinical high risk" (CHR) for psychosis have so far been investigated only in risk-enriched samples in clinical settings. In this population-based prospective study, we aimed – for the first time – to assess the incidence rate of clinical psychosis and estimate the population attributable fraction (PAF) of that incidence for preceding psychosis risk states and DSM-IV diagnoses of non-psychotic mental disorders (mood disorders, anxiety disorders, alcohol use disorders, and drug use disorders). All analyses were adjusted for age, gender and education. The incidence rate of clinical psychosis was 63.0 per 100,000 person-years. The mutually-adjusted Cox proportional hazards model indicated that preceding diagnoses of mood disorders (hazard ratio, HR=10.67, 95% CI: 3.12-36.49), psychosis high-risk state (HR=7.86, 95% CI: 2.76-22.42) and drug use disorders (HR=5.33, 95% CI: 1.61-17.64) were associated with an increased risk for clinical psychosis incidence. Of the clinical psychosis incidence in the population, 85.5% (95% CI: 64.6-94.1) was attributable to prior psychopathology, with mood disorders (PAF=66.2, 95% CI: 33.4-82.9), psychosis high-risk state (PAF=36.9, 95% CI: 11.3-55.1), and drug use disorders (PAF=18.7, 95% CI: –0.9 to 34.6) as the most important factors. Although the psychosis high-risk state displayed a high relative risk for clinical psychosis outcome even after adjusting for other psychopathology, the PAF was comparatively low, given the low prevalence of psychosis high-risk states in the population. These findings provide empirical evidence for the "prevention paradox" of targeted CHR early intervention. A comprehensive prevention strategy with a focus on broader psychopathology may be more effective than the current psychosis-focused approach for achieving population-based improvements in prevention of psychotic disorders.

Key words: Psychosis, ultra-high risk, clinical high risk, mood disorders, drug use disorders, early intervention, prevention, at risk mental states

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Early intervention in psychosis has been an active area of investigation in the mental health field over the past quarter century. Compelling evidence indicates that specialized early intervention services for first-episode psychosis yield better short-term clinical outcomes in all measurable domains compared to usual treatment[1]. In addition, it has been suggested that shortening the duration of untreated psychosis leads to a better prognosis over the course of the illness[2]. The field has thus moved forward with the idea of intervening even earlier by detecting psychosis at the preclinical phase of "ultra-high risk" (UHR), also known as "clinical high risk" (CHR).

Over the last decade, the validity and clinical utility of the CHR paradigm have been widely investigated in help-seeking participants sampled in clinical settings (risk-enriched samples)[3]. The CHR paradigm relies on the frequency and severity of positive psychotic symptoms to identify the at-risk state and determine the risk of transition to psychosis[3].

Early studies reported up to 40% transition rates in CHR samples, but these rates consistently decreased as data accumulated over time, with recent meta-analytical estimates showing less than half of the initially reported rates: 15% over a mean period of 38 months[4], or 4.7% per year. This sizeable reduction in the transition rates may be due to a dilution effect, which is the by-product of the increased awareness of subtle psychotic states and broader outreach of early intervention services, leading to an increase in self-referrals, and thereby inflating false positives in more recent CHR samples.

Following our critical perspective papers on the CHR concept[3,5], an intense debate has started, splitting the field into proponents[6-8], opponents[9-12], and those with ambivalent attitudes toward that concept[13-16].

In parallel with the growing interest in understanding early stages of psychopathology for early detection and intervention in clinical settings, the psychosis phenotype has been widely studied in general population datasets.

These population-based epidemiological studies have revealed two important findings. First, subtle positive psychotic experiences (PEs) are not as rare as once assumed, with prevalence rates varying between 5 and 8%[17]. Second, PEs are temporally associated with help-seeking[18], suicidal behavior[19,20], poor functioning[21,22], decline in cognitive capacity[23], affective dysregulation, and a multitude of mental disorders, including but not limited to psychosis spectrum disorder[24-26]. In that sense, PEs in the general population appear to be clinically valuable as a severity marker, but they do not imply diagnostic specificity.

With the exception of the cross-sectional Bern Epidemiological At-Risk (BEAR) study, these two lines of research – clinical and population-based – have yet to be crossed. Particularly relevant is the issue of help-seeking behavior of individuals, which is included in the CHR concept but not in the population studies of PEs. The BEAR study demonstrated that the CHR is not a frequent but a clinically relevant state, which is associated with

increased odds for present mental disorder diagnosis and impaired functioning[27]. Further, the CHR entity shares the same etiological factors with PEs in community studies and psychotic disorders in the clinical samples, providing support for the notion of etiological continuity across the psychosis spectrum.

Although the findings from the cross-sectional BEAR study may provide some insight into the characteristics of the CHR state in an epidemiologically representative sample, the core issue of progression of psychosis in the framework of the CHR-transition paradigm has not been longitudinally tested to date in an unbiased general population cohort.

In this study, we aimed to explore the notions of "risk" and "transition" in the general population, for the first time, by estimating the population attributable fraction (PAF) of clinical psychosis incidence (the proportion of clinical psychosis outcome that would have been avoided, had the risk factors been eliminated) for the preceding psychosis risk states and DSM-IV diagnoses of non-psychotic mental disorders.

METHODS

Study cohort

The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) was designed to investigate the prevalence, incidence, course and consequences of mental disorders in the Dutch general population. The study was approved by the Medical Ethics Review Committee for Institutions on Mental Health Care, and written informed consent was collected from participants at each wave[28,29].

A multistage random sampling procedure was applied to ensure sample representativeness in regard to age (between 18 and 65 years), region, as well as population density. Participants were excluded if they were not proficient in Dutch.

The NEMESIS-2 cohort includes four waves. The baseline data (T0) were assessed from 2007 to 2009, and were followed up at year 3 (T1), year 6 (T2) and year 9 (T3). The first wave (T0) enrolled 6,646 participants (response rate 65.1%; average interview duration: 95 min). Response rates at T1, T2 and T3 were 80.4% (N=5,303; average interview duration: 84 min), 87.8% (N=4,618; average interview duration: 83 min), and 86.8% (N=4,007; average interview duration: 102 min), respectively[30].

Non-clinician, trained interviewers applied the Composite International Diagnostic Interview (CIDI) version 3.0[31,32] and additional questionnaires during home visits. Rates at baseline reflect lifetime occurrence; rates at T1, T2 and T3 reflect 3-year interval occurrence. Attrition between T0 and T3 was not significantly associated with any of the individual 12-month mental disorders at T0 after controlling for socio-demographic characteristics[33].

Psychosis risk strata

In accordance with the clinical high-risk framework[3] and previous analyses conducted in the NEMESIS-2 cohort[34,35], psychosis risk strata were defined based on the degree of positive psychotic symptomatology, help-seeking attempt, antipsychotic treatment, and service use and admission for psychotic symptomatology.

At each time point, positive psychotic symptoms were assessed using a 20-item binary-response questionnaire that is based on CIDI 1.1 and specifically developed for evaluating psychotic symptoms[36,37], since previous studies have demonstrated that earlier CIDI versions were not adequately capturing positive psychotic symptomatology. Positive reports (positive response to at least one item) were reassessed and validated over a clinical telephone interview conducted by trained graduate psychologists and discussed with a clinically experienced psychiatrist[38], and participants were asked whether they had sought help for these symptoms. At each time point, antipsychotic prescription, service use and admission were explored using an adaptation of the self-constructed NEMESIS-1 questionnaire[39].

Psychosis risk strata consisted of the following non-overlapping categories: reference group (no psychosis expression), low-risk (endorsement of a single positive psychotic item that did not require help-seeking or treatment), moderate-risk (endorsement of multiple positive psychotic items that did not require help-seeking or treatment), high-risk (endorsement of at least one positive psychotic item that required help-seeking but not antipsychotic treatment or admission), and clinical psychosis (endorsement of at least one positive psychotic item that required help-seeking and antipsychotic treatment or admission to a health care service). The primary outcome of the study was the category of clinical psychosis. The low-risk, moderate-risk, and high-risk strata served as risk states.

Preceding diagnosis of DSM-IV mental disorders

The CIDI 3.0[31] was used to assess the following four domains of DSM-IV mental disorders at each follow-up visit (diagnosis over the last 3-year period, such that T1 assessment covers the period between T0 and T1; T2 assessment covers the period from T1 to T2, and so on): mood disorders (major depressive disorder, bipolar disorder, dysthymia); anxiety disorders (social phobia, specific phobia, panic disorder, generalized anxiety disorder, agoraphobia without panic disorder); alcohol use disorders (alcohol abuse and dependence); and drug use disorders (drug abuse and dependence).

Statistical analyses

Analyses were conducted using Stata version 16.0. Participants diagnosed with psychotic disorders (N=43, 0.7%) or bipolar disorder I (N=73, 1.1%) at baseline were excluded from the analysis.

A priori defined psychosis risk strata were validated by using cumulative measures of environmental and genetic liability to schizophrenia.

Adopting our previously validated estimates for constructing

cumulative environmental load in a Dutch cohort (GROUP)[40], we generated the exposome score for schizophrenia (ES-SCZ) by summing log-odds weighted environmental exposures, including cannabis use, hearing impairment, winter birth, and five childhood adversity domains (sexual, physical and psychological abuse, emotional neglect and bullying). Analyses were carried out using the dichotomous environmental risk state: the highest quartile, ES-SCZ >75%, was considered the binary environmental vulnerability for schizophrenia, guided by the definition in our previous study (hereafter: ES-SCZ_{75})[41].

The validation of the psychosis risk strata using polygenic risk score for schizophrenia (PRS-SCZ) was performed in the genotyped sample (N=3,104). Analyses were carried out using the molecular genetic risk state, guided by the definition in our previous study[41]: the highest quartile of PRS-SCZ >75% was considered the binary genetic liability for schizophrenia (hereafter: PRS-SCZ_{75}).

Multinomial logistic regression models using the MLOGIT command were performed to analyze the association of psychosis risk strata ("no-risk" group as the reference) with ES-SCZ_{75} and PRS-SCZ_{75}, respectively. Consistent with our previous work in NEMESIS-2, the validation analysis of the strata included observations from all assessment points, that were analyzed multi-cross-sectionally in the "long format" (each participant contributing four observations: T0, T1, T2 and T3). To correct for the clustering of multiple observations within participants, the CLUSTER option was used to estimate cluster-robust standard errors (SEs).

The relative risk ratios (RRRs) at each psychosis risk stratum for ES-SCZ_{75} and PRS-SCZ_{75} were compared using the Wald test. All analyses were adjusted for gender, age (continuous), and four-level education (1- primary school, 2- lower secondary education, 3- higher secondary education, 4- higher professional education). Analyses of PRS-SCZ_{75} were additionally corrected for population stratification adjusted using the first three principal components.

The crude incidence rates with 95% CIs of each psychosis risk stratum per 100,000 person-years were estimated in participants with at least one follow-up interview. Two-sided exact significance tests were applied to compare incidence rates over and below 35 years of age at the study entry.

The Cox proportional hazards models, with the time-on-study as the time scale over the whole study period from T0 to T3, were used to estimate the adjusted (age, gender and education) and multivariable adjusted hazard ratios (HRs) and 95% CIs for the associations of clinical psychosis outcome with the time-varying factors of preceding psychosis risk states and diagnoses of anxiety, mood, alcohol use, and drug use disorders, respectively.

Efron's method was used for handling ties[42]. To take into account clustering of multiple observations within participants, a robust Hubert/White sandwich estimator was applied[43]. The proportional-hazards assumptions were confirmed using the Schoenfeld residuals and –ln(–ln[survival]) plots, also adjusted for covariates[44]. Potential bias due to unmeasured confounders was assessed using the E-value, which is the minimum strength of association that an unmeasured confounder must have with both the exposure and the outcome to negate the observed association[45].

By using the PUNAFCC command[46] with the UNCONDITIONAL option that accounts for the sampling variability of the covariates, the attributable fraction and the PAF with 95% CIs for each risk factor were estimated. Under the assumption that the different risk groups are causally associated with the clinical psychosis outcome, the PAF shows the proportion of clinical psychosis disease burden that might be prevented if the risk were eliminated[47]. The nominal significance threshold was set two-sided at p=0.05.

RESULTS

Table 1 shows the demographic features and the frequency of preceding psychosis risk states and DSM-IV diagnoses of non-psychotic mental disorders (as assessed at T0) in participants with at least one follow-up interview (N=5,303).

Table 2 reports the validation of the psychosis risk strata by using the ES-SCZ_{75} and PRS-SCZ_{75}. In comparison to the reference group, ES-SCZ_{75} and PRS-SCZ_{75} showed a progressively greater magnitude of association with increasing psychosis risk strata, with RRRs ranging between 1.44 and 3.49 for the ES-SCZ_{75}, and between 0.85 and 3.63 for the PRS-SCZ_{75}.

The ES-SCZ_{75} was significantly associated with the low-risk, moderate-risk, high-risk, and clinical psychosis strata. The PRS-SCZ_{75} was significantly associated with the high-risk and clinical psychosis strata, which were therefore validated. Additional *post-hoc* group comparisons of the ES-SCZ_{75} across strata showed significant differences in low-risk vs. moderate-risk, low-risk vs. high-risk, and low-risk vs. clinical psychosis; while analysis of the

Table 1 Sample characteristics (N=5,303 participants with at least one follow-up interview)

Age at T1 (years, mean±SD)	47.7±12.4
Gender (% female)	55.1
Education at T1 (%)	
Primary school	4.3
Lower secondary	25.9
Higher secondary	32.6
Higher professional	37.2
Preceding psychopathology (%, as assessed at T0)	
Psychosis low-risk state	7.1
Psychosis moderate-risk state	4.2
Psychosis high-risk state	3.7
Mood disorders	7.2
Anxiety disorders	7.2
Drug use disorders	0.9
Alcohol use disorders	3.5

Table 2 Validation of the psychosis risk strata

	Reference group ("no-risk")			Psychosis low-risk state		Psychosis moderate-risk state		Psychosis high-risk state	
	RRR	95% CI	p	Wald χ^2	p	Wald χ^2	p	Wald χ^2	p
ES-SCZ$_{75}$[a]									
Psychosis low-risk state	1.44	1.22-1.69	<0.001	-	-	-	-	-	-
Psychosis moderate-risk state	2.06	1.63-2.61	<0.001	7.40	0.007	-	-	-	-
Psychosis high-risk state	2.72	2.17-3.41	<0.001	23.15	<0.001	3.26	0.071	-	-
Clinical psychosis	3.49	1.80-6.79	<0.001	6.52	0.011	2.17	0.141	0.53	0.469
PRS-SCZ$_{75}$[a,b]									
Psychosis low-risk state	0.85	0.66-1.10	0.217	-	-	-	-	-	-
Psychosis moderate-risk state	1.25	0.88-1.79	0.215	3.77	0.052	-	-	-	-
Psychosis high-risk state	1.55	1.11-2.16	0.010	9.07	0.003	0.87	0.350	-	-
Clinical psychosis	3.63	1.23-10.71	0.020	6.62	0.010	3.43	0.064	2.33	0.127

RRR – relative risk ratio, ES-SCZ$_{75}$ – exposome score for schizophrenia (75% cut-point), PRS-SCZ$_{75}$ – polygenic risk score for schizophrenia (75% cut-point)
[a]adjusted for age, gender and education; [b]adjusted for three principal components

PRS-SCZ$_{75}$ across strata showed significant differences in low-risk vs. high-risk, and low-risk vs. clinical psychosis.

The incidence rate of clinical psychosis was 63.0 per 100,000 person-years (95% CI: 42.9-92.6), with comparable rates for individuals under 35 years (50.1 per 100,000 person-years, 95% CI: 20.9-120.5) and 35 years of age and above (67.1 per 100,000 person-years, 95% CI: 43.8-103.0; incidence rate ratio=1.34, 95% CI: 0.49-4.55, p=0.58).

Figures 1 and 2 show the HRs for psychosis risk categories and diagnoses of non-psychotic mental disorders. Preceding diagnoses of mood, drug use, and anxiety disorders, along with psychosis high-risk state, showed an increased risk for clinical psychosis incidence in the age, gender and education-adjusted model. In the multivariable adjusted model, the preceding diagnoses of mood disorders (HR=10.67, 95% CI: 3.12-36.49), psychosis high-risk state (HR=7.86, 95% CI: 2.76-22.42) and drug use disorders (HR=5.33, 95% CI: 1.61-17.64) were associated with an increased risk for clinical psychosis incidence.

The E-values for the association of incident clinical psychosis with preceding diagnoses and risk states were 20.8 for mood disorders, 15.2 for psychosis high-risk state, 10.1 for drug use disorders, 5.1 for psychosis low-risk state, 4.3 for anxiety disorders, 3.4 for alcohol use disorders, and 2.4 for psychosis moderate-risk state.

Figures 3 and 4 show the PAFs for psychosis risk categories and diagnoses of non-psychotic mental disorders. The estimation of the PAFs in the multivariable adjusted model indicated that 85.5% (95% CI: 64.6-94.1) of the clinical psychosis incidence could have been avoided if all psychosis risk states and non-psychotic mental disorders had been prevented. The most important factors were mood disorders (PAF=66.2, 95% CI: 33.4-82.9), psychosis high-risk state (PAF=36.9, 95% CI: 11.3-55.1), and drug use disorders (PAF=18.7, 95% CI: –0.9 to 34.6).

Further, we estimated the PAF for the subpopulation of the psychosis high-risk state. This restricted analysis revealed that 87.3% (95% CI: 63.7-95.5) of the clinical psychosis incidence

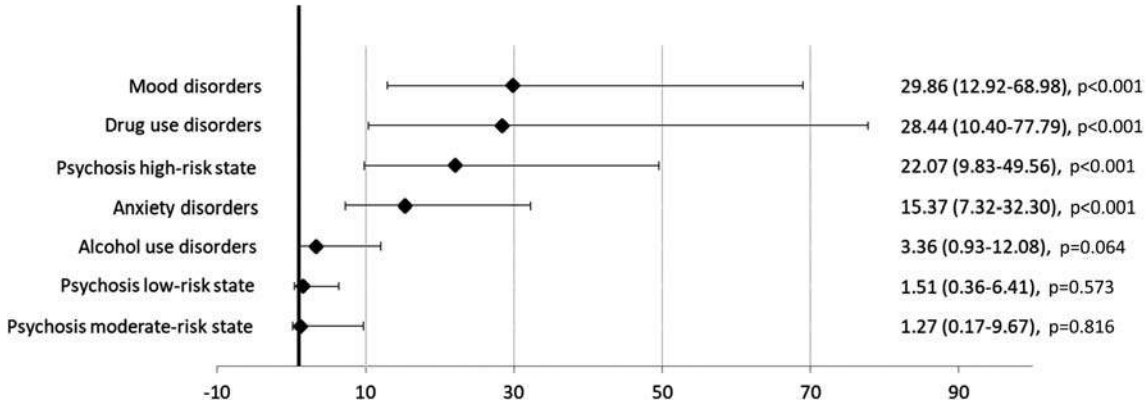

Figure 1 Hazard ratios (95% CI) for clinical psychosis incidence in the age, gender and education-adjusted model

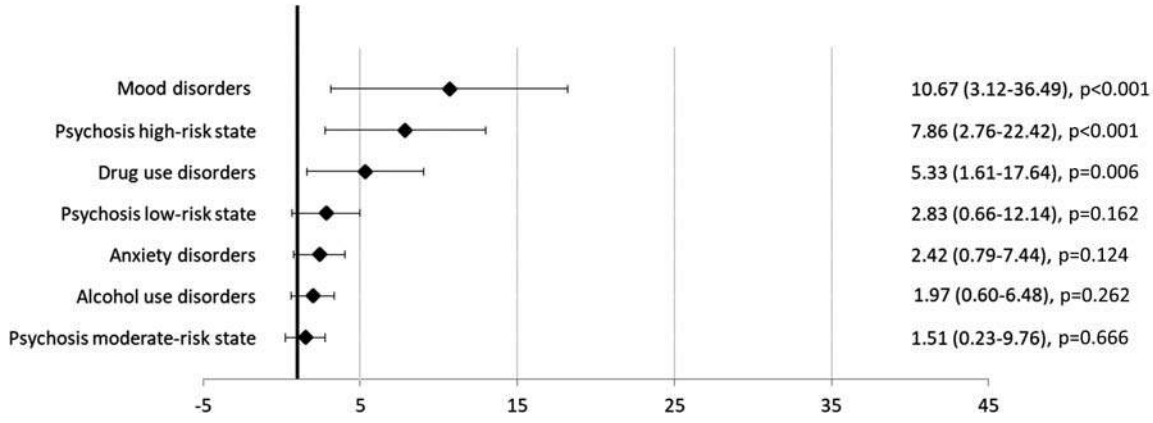

Figure 2 Hazard ratios (95% CI) for clinical psychosis incidence in the multivariable adjusted model

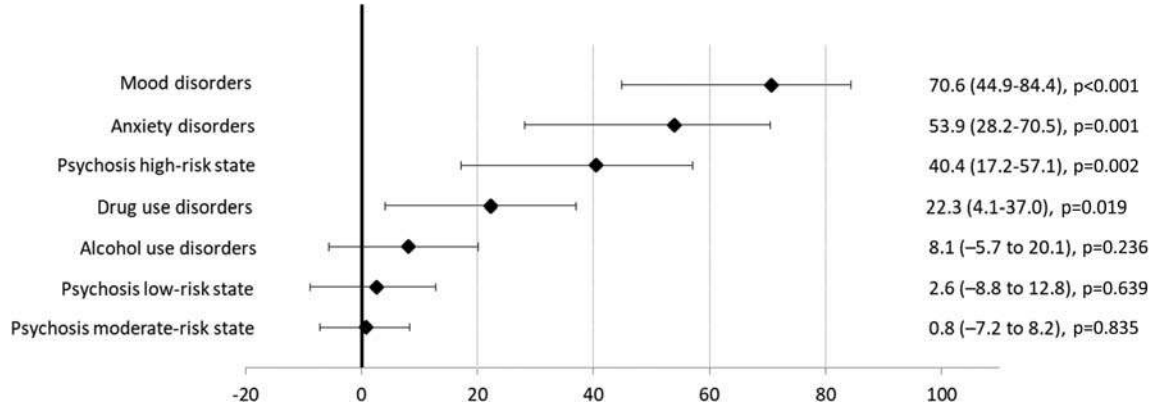

Figure 3 Population attributable fractions (95% CI) for clinical psychosis incidence in the age, gender and education-adjusted model

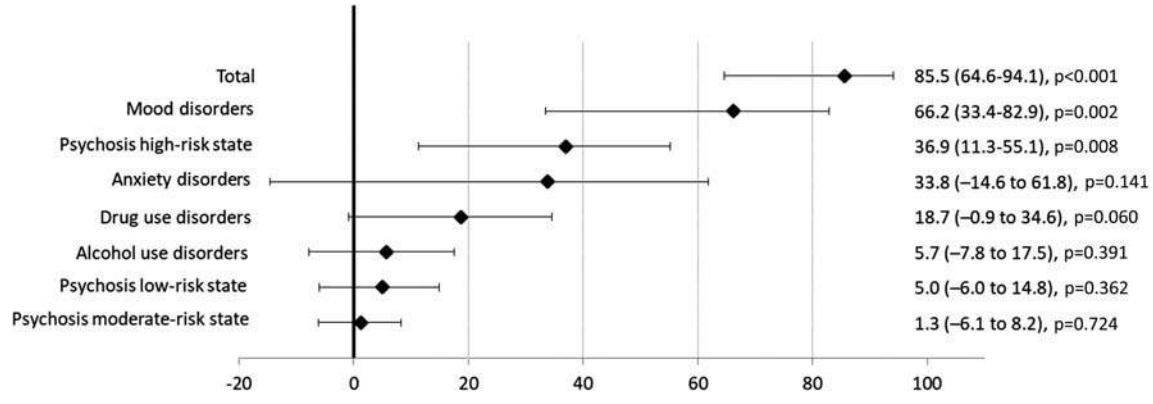

Figure 4 Population attributable fractions (95% CI) for clinical psychosis incidence in the multivariable adjusted model

could have been avoided if the psychosis high-risk state had been prevented when other psychopathology remained the same; while the combined PAF for non-psychotic DSM diagnoses was 71.8% (95% CI: 33.6-88.0) when all other factors remained as observed.

DISCUSSION

The main findings of this first population-based study of longitudinal risk for clinical psychosis as a function of the preceding psychosis risk states and DSM-IV diagnoses of non-psychotic

mental disorders were as follows: a) prior psychopathology accounted for a total of 85.5% of the incidence of clinical psychosis outcome in the multivariable analysis, with mood disorders, psychosis high-risk state, and drug use disorders independently contributing to clinical psychosis risk; b) the significant reduction of mutually-adjusted HRs in the multivariable model put the importance of comorbidity in perspective. These findings have important public health implications for early intervention strategies.

The PAFs for each psychopathology measure estimated in the final model were considerably lower than those estimated in the individual models, which were adjusted only for age, gender and education. The substantial differences in estimates between models demonstrate the importance of accounting for comorbidity beyond isolated measures of psychosis risk to yield more accurate PAF estimates for mental disorders.

We observed relatively large PAFs, except those for psychosis low-risk state, psychosis moderate-risk state, and alcohol use disorders, which were negligible. Preceding diagnosis of mood disorders was strongly associated with clinical psychosis outcome, and by far had the largest PAF, followed by psychosis high-risk state, anxiety disorders, and drug use disorders. In addition to the marked reduction of PAF estimates in the final model, PAF for anxiety disorders, although still noteworthy, was not statistically significant anymore.

From a public health perspective, a 10-fold increase in risk for clinical psychosis incidence attributable to mood disorders highlights the importance of addressing the prevention of these disorders to reduce the burden of psychosis in the general population.

Given the fact that non-psychotic disorders are highly prevalent among individuals with CHR and likely to influence the longitudinal outcomes[48-50], we estimated the risk attributable to these disorders in the subpopulation of participants with psychosis high-risk state. The joint PAF for all non-psychotic mental disorders was noteworthy but still lower than the individual PAF for psychosis high-risk state when everything else remained the same in this subpopulation.

Even though the psychosis high-risk state group displayed a high relative risk for clinical psychosis outcome even after adjusting for other psychopathology, the PAF was comparatively low. In contrast, anxiety disorders had a high PAF with respect to HR. This discrepancy between PAF and HR can be understood by examining the estimation method of PAF, which accounts for the prevalence of the risk factor in the population in addition to the strength of the association between outcome and risk factor.

In this regard, addressing the psychosis high-risk state in a sample enriched for clinical psychosis risk may appear to be an effective strategy at first glance. However, an early intervention strategy targeting high-risk state only will have minimal impact on reducing the population burden of psychotic disorders, because of the low prevalence of that state in the general population[27]. Further, efforts to case-finding will require major resources, given the rarity of psychosis high-risk state in the population. These findings provide empirical evidence for the "prevention paradox" and echo our concerns over the effectiveness and the economic feasibility of targeted CHR early intervention programs at the population level[3,5].

In this first study investigating the PAFs of psychopathology categories for clinical psychosis in the general population, we used multivariable modeling to yield more accurate estimates[51]. The large and representative population cohort collected at four time-points over 9 years was a major strength. The clinical psychosis outcome incidence and the point prevalence of psychosis high-risk state were comparable to the population estimates in the literature[27,52], thereby providing further support for the validity of our psychosis risk stratification approach in this population, that was guided by our previous work and verified using cumulative measures of environmental and genetic liability to schizophrenia. Nevertheless, future studies could benefit from a detailed clinical assessment and multi-source data including electronic health records to minimize measurement bias. Finally, the high E-values (20.8 for mood disorders, 15.2 for psychosis high-risk state, 10.1 for drug use disorders) show that unmeasured confounding is unlikely to influence the current significant findings. Notwithstanding, strong causal inferences should be avoided, considering the observational nature of the study.

Our results provide initial empirical evidence that a comprehensive prevention strategy with a focus on broader measures of psychopathology may be more effective than the current psychosis-focused approach in achieving population-based improvements for prevention of psychotic disorders. Guided by a public health approach, a fully-integrated universal mental health care system that ensures low-threshold entry and rapid access may serve as a more efficient strategy for improving population-based estimates of mental health, including psychosis prevention, and may counter the trend of balkanizing mental health care to smaller and competing units[53].

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The general factor of psychopathology: a comparison with the general factor of intelligence with respect to magnitude and predictive validity

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In recent years, there has been a surge of interest in the general factor of psychopathology ("p"), which is intended to summarize broad psychiatric comorbidity into a single index. In this study, rather than attempting to validate this model using statistical techniques, we compared the magnitude (as indicated by the variance explained in the respective indicators) and the predictive validity of the "p" factor with those of the general factor of intelligence ("g"). To compare the magnitude, for "g", we analyzed fifteen Wechsler Adult Intelligence Scale subtests (N=1,200). For "p", we analyzed fourteen psychiatric diagnoses in Swedish adults (N=909,699), eight self- and parent-rated psychopathology scales in Swedish adolescents (N=2,069), and sixteen parent-rated psychopathology scales in Swedish children (N=14,589). To compare the predictive validity, we analyzed Swedish male military conscripts (N=414,595, mean age: 18.3 years) with measures on both "g" and "p" (derived from eight psychiatric diagnoses). We then examined their unique associations with three intelligence-related outcomes (annual income, highest education, and university entrance exam scores), and sixteen adverse outcomes (e.g., suicidal behavior, psychotropic medication prescription, and criminality) retrieved from registers (mean age at follow-up = 29.2 years). Results indicated that the magnitudes of "g" and "p" were very similar. Controlling for "p", "g" significantly predicted later education (standardized beta, β=0.38, SE=0.01) and university entrance exam scores (β=0.48, SE=0.01). Controlling for "g", "p" significantly predicted all adverse outcomes (mean β=0.32; range: 0.15 to 0.47). These findings support the notion that psychopathology indicators can be combined into a single score, similar to how intelligence subtests are combined into a general intelligence score. This "p" score might supplement specific diagnoses when formulating a management plan and predicting prognosis.

Key words: General factor of psychopathology, p factor, general factor of intelligence, g factor, magnitude, predictive validity, psychiatric comorbidity, mental disorders, clinical utility

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Individuals who perform well on one intelligence subtest tend to perform well on all other intelligence subtests[1,2]. This empirical observation is the reason why intelligence subtests are combined into a single score, commonly labeled "g" (general intelligence factor). Introduced over a century ago, this factor has offered utility for researchers and clinicians[3-5]. For example, it predicts future education about as well as height predicts weight[6].

Similar to the intelligence domain, individuals who suffer from one mental health problem are at increased risk of suffering from virtually all other mental health problems[7-10]. For example, in a Danish population study of three million individuals, all psychiatric diagnoses were positively associated[11]. Recently, Lahey et al[12,13] proposed that a general factor of psychopathology could serve as a useful summary of this comorbidity. Caspi et al[14] replicated this general factor of psychopathology and labeled it "p", to highlight its similarity to "g".

Just as "g" predicts future education, studies indicate that "p" predicts future adverse outcomes, highlighting its clinical utility. For example, the cumulative burden of parent-rated psychiatric problems in childhood predicts adverse outcomes in adolescence and young adulthood over and above specific psychiatric problems[15-18]. To date, however, no studies have examined whether general psychopathology severe enough to warrant psychiatric diagnoses in late adolescence predicts register-based adverse outcomes in young adulthood. Furthermore, no studies have examined whether "p" predicts adverse outcomes over and above "g", which is important because they are moderately negatively associated[14,19].

The first goal of the present study was to compare the magnitude of the general factors of psychopathology and intelligence. The magnitude of a general factor is determined by the strength of the overlap among its indicators. For example, because the correlations among intelligence subtests are relatively large, the magnitude of "g" is also relatively large[20]. If "p" were to have a similar magnitude as "g", then it might be useful to combine indicators of psychopathology into a single "p" score, just as intelligence subtests are summed into a single "g" score.

The second goal of this study was to compare the predictive validity of "p" and "g", after adjusting for their overlap. If "p" were to uniquely predict unfavorable outcomes as well as "g" uniquely predicts favorable outcomes, then "p" might offer the psychiatric domain clinical and research utility. For example, it might supplement primary diagnoses when formulating the management plan and predicting prognosis.

METHODS

Samples

To measure the magnitude of the general intelligence factor, we relied on summary data from six US standardization subsamples published in the fourth edition of the Wechsler Adult Intelli-

gence Scale (WAIS-IV)[1]. We combined the six subsamples (20-25 years old; 25-30 years old; 30-35 years old; 35-45 years old; 45-55 years old; and 55-65 years old; each N=200) into a single sample (20-65 years old; N=1,200).

To measure the magnitude of the general psychopathology factor, we relied on three different samples.

First, we examined that magnitude in adulthood by analyzing all individuals born in Sweden between 1969 and 1979 from the Multi-Generation Register (N=1,056,041), such that the participants were between 35 and 45 years old at the end of the follow-up period at December 31, 2013. After excluding subjects who had died or migrated before the end of the study period, the final sample included 909,699 individuals.

Second, we examined that magnitude in adolescence by analyzing 16-year old individuals from the Swedish Twin Study of Child and Adolescent Development (TCHAD)[21]. At age 16, 1,067 (74%) of the parents and 2,369 (82%) of the twins responded. There was both self- and parent-report information on 2,069 individuals.

Third, we examined that magnitude in childhood by analyzing 9-year old individuals from the Child and Adolescent Twin Study in Sweden (CATSS) (N=14,589)[22]. The response rate was 75%.

To compare the predictive validity of the general factors of intelligence and psychopathology, we examined Swedish male military conscripts born between 1980 and 1992 (N=414,595; mean age: 18.3 years). Over 95% of all Swedish males attended the mandatory conscription evaluation[23]. We excluded all participants who had died (except from suicide) or migrated.

The study was approved by the Regional Ethical Review Board in Stockholm. Informed consent was acquired from the twin samples. By law, register data do not require informed consent because they are pseudonymized.

Measures

To measure the magnitude of the general factor of intelligence, we analyzed the Pearson correlations among the fifteen WAIS-IV subtests.

To measure the magnitude of the general factor of psychopathology among the 35-45 year old population sample, we linked the participants to the National Patient Register, which captures inpatient (1969-2013) and outpatient (2001-2013) psychiatric diagnoses according to the ICD-8 (1969-1986), ICD-9 (1987-1996) or ICD-10 (1997-present). This register covers 99% of psychiatric inpatient and 70 to 95% of psychiatric outpatient admissions[24]. We examined whether the individuals had ever been diagnosed with depression, anxiety, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), eating disorders, alcohol misuse, drug abuse, attention-deficit hyperactivity-disorder (ADHD), oppositional defiant/conduct disorder (ODD), autism, tics, bipolar disorder, schizophrenia, and schizoaffective disorder.

To measure the magnitude of the general factor of psychopathology among the 16-year olds, we relied on parent- and self-ratings from the Child Behavior Checklist (CBCL)[25]. This consists of eight continuous scales measuring anxiety/depression, withdrawn behavior, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. The CBCL is reliable and well-validated (e.g., the mean test-retest reliability of parent ratings was 0.90 across eight days, and 0.70 across 24 months)[26].

To measure the magnitude of the general factor of psychopathology among the 9-year olds, we relied on parent ratings on the Autism-Tics, AD/HD and other Comorbidities inventory (A-TAC)[27], which consists of continuous scales measuring problems with coordination, sensory issues, inattention, impulsivity, learning, organization, memory, language, sociability, flexibility, tics, compulsions, OCD, oppositional defiance, and conduct problems. Furthermore, we included the parent-rated Screen for Child Anxiety Related Emotional Disorders (SCARED), which measures anxiety, and the parent-rated Short Mood and Feelings Questionnaire (SMFQ), which measures depression. These scales have good psychometric properties (e.g., the mean test-retest reliability of the A-TAC scales based on clinician interviews across two months was 0.85)[27-30].

To measure the general factor of intelligence at conscription, we included general intelligence scores from the Computer Aided Testing - Swedish Enlistment Battery (CAT-SEB), administered during the conscription evaluation[23]. The CAT-SEB included 12 subtests (mean internal consistency = 0.83; range = 0.70 to 0.93) and took on average 62 min to complete. The general factor score reliability estimate was 0.90[31].

To measure the general factor of psychopathology at conscription, we linked the military conscripts to the National Patient Register to examine if they had been diagnosed with anxiety, depression, PTSD, bipolar disorder, drug abuse, alcohol misuse, ODD and ADHD *prior to* conscription (we excluded diagnoses of schizophrenia, schizoaffective disorder, autism, tics, and eating disorders because these did not co-occur frequently enough to estimate tetrachoric correlations).

We then examined whether the participants had experienced a wide variety of outcomes *after* conscription. We included three intelligence-related outcomes. From the Longitudinal Integration Database for Health Insurance and Labor Market Studies Register (LISA; coverage: 1990-2013), we included the highest annual log of income and the highest obtained education level. We also included the highest score on the Swedish Scholastic Aptitude Test (SweSAT), a voluntary test administered twice a year (end of coverage: 2015) that grants admission to Swedish universities[32].

We further examined sixteen adverse outcomes. From the National Patient Register, we included diagnoses of acute drug and alcohol intoxication (i.e., overdoses), and diagnoses of certain and uncertain suicide attempts. We combined certain suicide diagnoses with death from suicide (identified in the Death Register). From the Prescribed Drug Register (coverage: 2005-2013), we included prescriptions of anxiolytic, sedative, antidepressant, stimulant, anti-alcohol, anti-opioid, lithium, antiepileptic, and antipsychotic medications (classified according to the Ana-

tomical Therapeutic Chemical, ATC system). From the National Crime Register (coverage: 1973-2013), we included court convictions of property or violent crimes. From LISA, we included use of social welfare benefits. All adverse outcomes were treated as binary variables.

The mean follow-up time from date of conscription was 10.9± 3.3 years. We included year of birth as a covariate to adjust for unequal follow-up times and diagnostic secular trends. Table 1 displays prevalence rates and average time-to-event by outcome.

Statistical analyses

We estimated the magnitude of the general factors in three ways. We relied on a visual examination of the correlation distributions and their means; on the variance accounted for by the first principal component (PC_1); and on the explained common variance (ECV)[20]. The ECV is the ratio of the variance explained by the general factor divided by the variance explained by the full factor model[33,34]. It ranges from 0 (none of the modeled variance is attributable to the general factor) to 1 (all of the modeled variance is attributable to the general factor).

Table 1 Adverse outcome statistics

Outcome	Descriptive	Time-to-event (years, mean±SD)
Acute drug intoxication (%)	0.68	6.93±3.65
Acute alcohol intoxication (%)	1.80	5.12±3.67
Suicide attempt, certain (%)	1.10	6.05±3.64
Suicide attempt, uncertain (%)	1.57	5.54±3.50
Prescription of anxiolytics (%)	10.61	9.15±3.80
Prescription of sedatives (%)	9.08	9.46±3.79
Prescription of SSRIs (%)	12.25	9.89±3.82
Prescription of stimulants (%)	1.69	10.53±3.67
Prescription of anti-alcohol medication (%)	0.97	9.28±3.68
Prescription of anti-opioid medication (%)	0.13	11.84±3.17
Prescription of lithium (%)	0.26	10.67±3.56
Prescription of antiepileptics (%)	2.43	10.30±3.70
Prescription of antipsychotics (%)	2.19	9.96±3.78
Property crimes (%)	2.96	4.62±3.67
Violent crimes (%)	4.21	5.31±3.48
Use of social welfare benefits (%)	16.07	2.92±2.55
Highest median annual income in SEK (median absolute deviation)	254,400 (87,770)	8.59±3.52
Education level, range 1-7 (SD)	4.43 (1.12)	9.89±3.28
Highest SweSAT score, range 0.05-2 (SD)	1.01 (0.44)	3.98±3.04

SSRIs – selective serotonin reuptake inhibitors, SEK – Swedish krona, SweSAT – Swedish Scholastic Aptitude Test
Education level: 1= less than 9 years, 2= 9 years, 3= 1-2 years of high school, 4= 3 years of high school, 5= 1-2 years of undergraduate college, 6= 3 or more years of undergraduate college, 7= graduate studies

To derive the ECV, we conducted exploratory factor analyses (EFAs) of the intelligence and the mental health measures. We relied on exploratory rather than confirmatory factor analysis because we did not have strong hypotheses regarding the loading patterns, and because we expected the data to have a complex structure (i.e., that the cross-loadings would not equal zero).

We determined how many factors to extract based on the scree plot, which contrasts the eigenvalues against the eigenvectors (for the WAIS-IV subsamples, we computed the eigenvalues separately in each subsample, and then derived their means)[35]. Eigenvectors that account for less than one unit of variance might be attributable to sample variation[36]. We then rotated the extracted factors to a general and several specific factors using the Direct Schmid-Leiman rotation[37]. This rotation funnels the variance shared among all indicators into a general factor, and the variance unique to subsets of the indicators into uncorrelated specific factors. Simulations indicate that this rotation performs well[38].

For the adolescent sample, we only analyzed the overlap between the self- and parent-ratings to minimize potential rater bias. For the six WAIS-IV standardization subsamples, we combined all correlation matrices into a single histogram; computed the PC_1 separately in each subsample and derived their mean (PC_1); and estimated the ECV from a single EFA with the loadings constrained to equality across the six different age groups.

For the assessment of predictive validity, we examined the dimensionality of the eight mental disorders using the scree plot[35], and rotated the EFA solution toward one general and several uncorrelated specific factors using the Direct Schmid-Leiman approach[37]. Subsequently, we used exploratory structural equation modeling to regress each of the outcomes onto the general intelligence scale, the exploratory general and specific factors, and birth year in a multiple regression framework to estimate their unique effects[39].

We used probit regression for the binary outcomes, and linear regression after outcome standardization (mean = 0; variance = 1) for the continuous outcomes. This allowed for comparing the regression betas on the same scale across the differently distributed outcomes. All analyses were conducted with the Mplus software, and the rotation matrices were derived using the R-package GPArotation[40,41].

For the general factor magnitude sensitivity analyses, we extracted up to two factors more than that indicated by the scree plot because the ECV index varies by dimensionality. We subscripted the ECV index to display how many extracted factors it was based on (e.g., ECV_3 indicates that it was based on three extracted factors). Furthermore, because there are several ways to identify a general factor[42], we re-estimated the ECVs using a bifactor rotation[43]. For the six differently aged WAIS-IV standardization samples, we examined whether the factor loadings could be constrained to equality without a loss in model fit when

computing the ECV index.

For the predictive validity sensitivity analyses, we first conducted the analyses without a general factor, using an oblique (correlated) Geomin rotation. Second, we attempted to extract an additional factor above and beyond that indicated by the scree plot, and to use a bifactor rotation. Third, we re-ran the analyses after excluding all participants who had died (except from suicide) five or more years after conscription.

RESULTS

The scree plots for the four samples are displayed in Figure 1. Figure 2 displays that the distributions of the correlations were similar for the WAIS-IV subtests and the psychopathology measures. Furthermore, the mean correlations, the PC_1 and the ECV indices were highly similar in the two domains. This indicates that the magnitudes of the general factors of intelligence and psychopathology were largely indistinguishable.

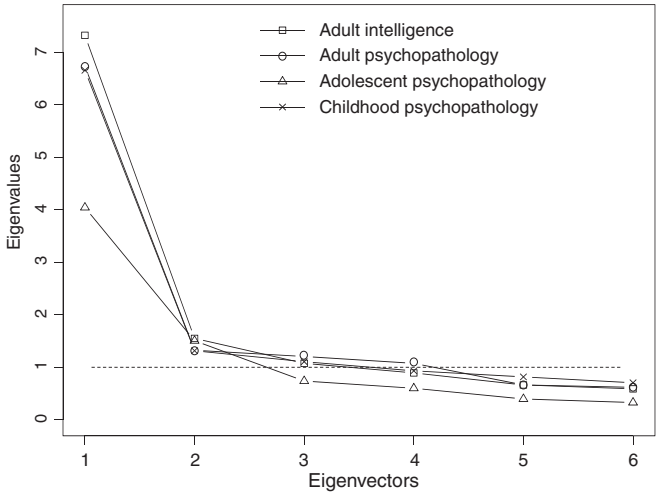

Figure 1 Scree plots for adult intelligence, and adult, adolescent and child psychopathology

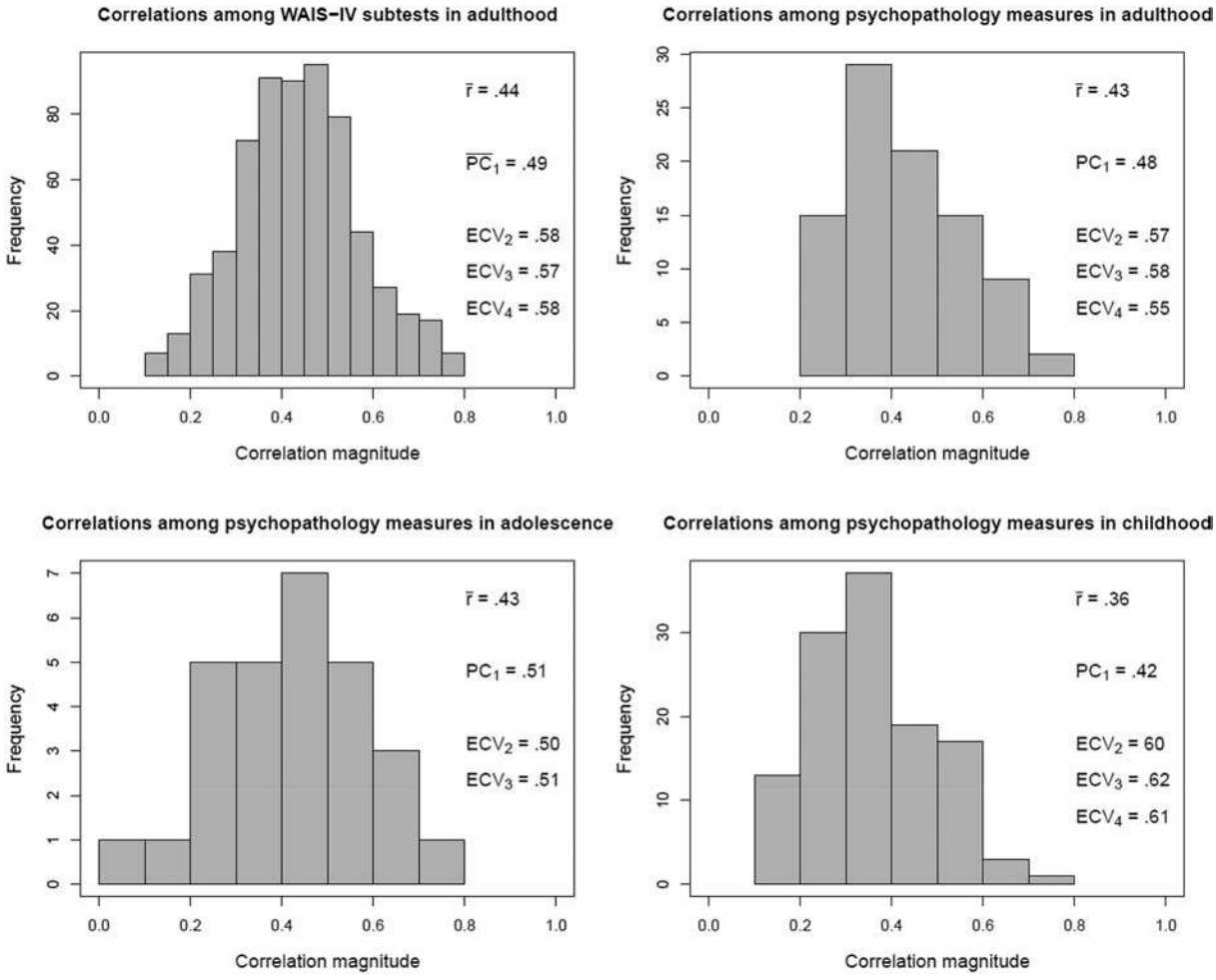

Figure 2 Histograms of correlations among Wechsler Adult Intelligence Scale (WAIS-IV) subtests in adulthood, and among psychopathology measures in adulthood, adolescence and childhood. PC_1= variance accounted for by first principal component, ECV= explained common variance index, where the sub-index indicates factor dimensionality

The scree plot of the eight mental disorders at conscription indicated the presence of two factors (Table 2). All disorders loaded substantially on the general factor (mean loading = .55; range: .44 to .66). The first specific factor captured internalizing problems (depression loading = .64; anxiety loading = .48), and the second specific factor captured externalizing problems (ODD loading = .52; drug abuse loading = .39).

We then regressed each outcome onto the general intelligence factor and the general and specific psychopathology factors in a multiple regression framework. Figure 3 displays that the general

Table 2 Exploratory factor analysis of psychiatric diagnoses assigned prior to conscription

	Rotation: Direct Schmid-Leiman		
Psychiatric diagnosis	**General psychopathology factor**	**Specific internalizing factor**	**Specific externalizing factor**
Depression	**0.66**	**0.64**	0.03
Anxiety	**0.53**	**0.48**	0.05
Post-traumatic stress disorder	**0.54**	**0.42**	0.12
Bipolar disorder	**0.55**	**0.33**	0.22
Alcohol misuse	**0.44**	0.07	**0.37**
Drug abuse	**0.54**	0.16	**0.39**
Oppositional-defiance/conduct disorder	**0.62**	0.10	**0.52**
Attention-deficit/hyperactivity disorder	**0.54**	0.09	**0.45**

Loadings equal to or greater than 0.30 are bolded
Root mean square error of approximation = 0.005, 90% CI: 0.004-0.005, confirmatory fit index = 0.983, Tucker-Lewis index = 0.963, χ^2=127.771, df=13, p<0.001

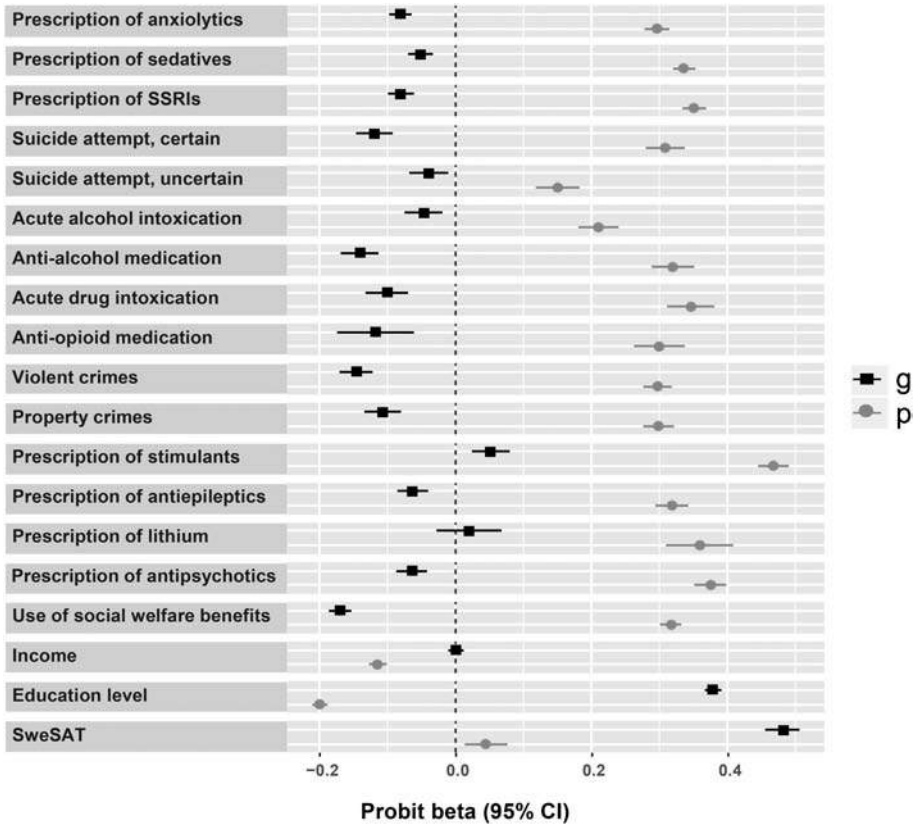

Figure 3 Unique associations between general psychopathology (p) and general intelligence (g) factors measured at conscription and later outcomes. The standardized betas for income, education level and SweSAT were based on linear regression. SSRIs – selective serotonin reuptake inhibitors, SweSAT – Swedish Scholastic Aptitude Test

intelligence factor uniquely and significantly predicted later education (β=0.38, SE=0.01) and SweSAT scores (β=0.48, SE=0.01), but not annual income (β=0.00, SE=0.01). The general factor of psychopathology uniquely and significantly predicted all sixteen adverse outcomes (mean β=0.32; range: 0.15 to 0.47). Individuals scoring one standard deviation above the mean on the general factor of psychopathology had, on average, after transforming the mean probit beta to an odds ratio, a 79% higher risk of suffering the adverse outcomes.

As displayed in Figure 4, the specific psychopathology factors primarily predicted related outcomes (e.g., the specific internalizing, but not the specific externalizing, factor predicted prescription of selective serotonin reuptake inhibitors, SSRIs), showing that covariation not accounted for by the general factor of psychopathology also had predictive validity.

For the magnitude comparison, the ECV indices remained similar between intelligence and psychopathology, regardless of dimensionality and general factor rotation. For the WAIS-IV subsamples, the factor loadings could be constrained to equality across the six subsamples without a loss in model fit (results available upon request).

For the predictive validity analyses, the betas based on the correlated factors model were similar to the specific factors in the original analyses, but obviously did not demonstrate the effect of the general factor. Although we attempted to extract a third exploratory factor from the eight mental disorders at conscription, this factor contained only small loadings (e.g., mean Varimax loading = –0.03; range: –0.07 to 0.10). This suggested over-extraction, and did not permit proceeding to a Direct Schmid-Leiman or bifactor rotation. The betas also remained similar when we re-ran the analyses after excluding all participants who had died (except from suicide) five years or later after conscription (results available upon request).

DISCUSSION

Our findings document that the general factors of intelligence and psychopathology have similar magnitudes, indicating that it might be useful to combine psychopathology indicators into a "p" score, just as WAIS-IV subtests are combined into a "g" score.

Furthermore, whereas previous research had demonstrated that parent-rated general psychopathology in childhood predicts adverse outcomes in adolescence and young adulthood[15-18], we additionally demonstrated that a general psychopathology factor based on psychiatric diagnoses predicts register-based adverse outcomes a decade later in young adulthood, even when holding general intelligence constant. To put the magnitude of these associations in context, the general factor of psychopathology predicted the adverse outcomes about as well as psychotherapy predicts subsequent well-being, or about as well as sleeping aid medication reduces short-term insomnia[6].

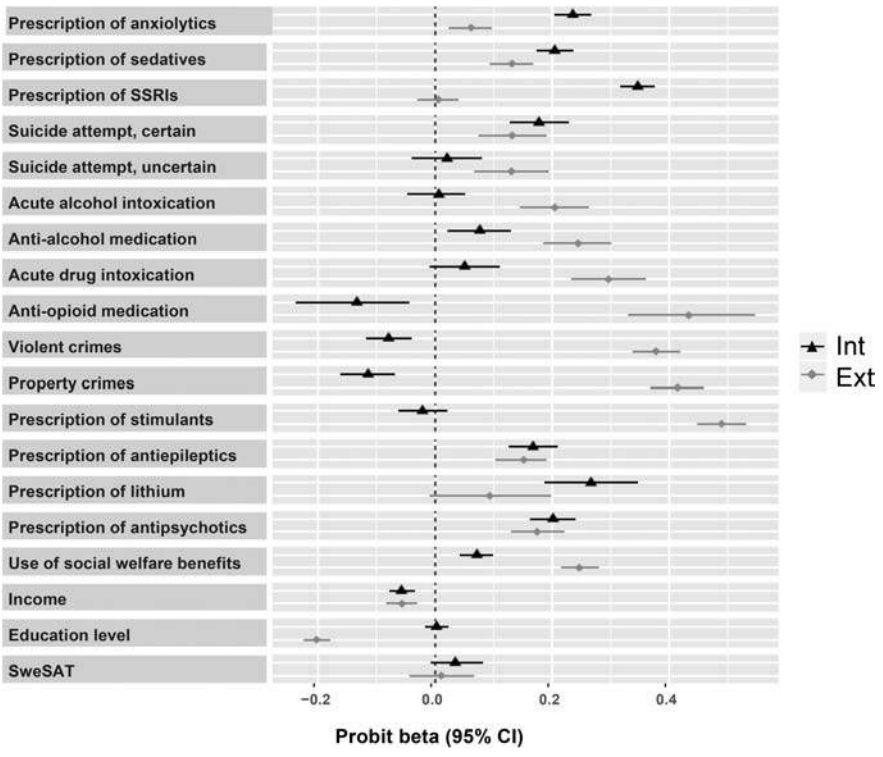

Figure 4 Unique associations between specific internalizing (Int) and externalizing (Ext) factors measured at conscription and later outcomes (all associations adjusted for general psychopathology and intelligence). The standardized betas for income, education level and SweSAT were based on linear regression. SSRIs – selective serotonin reuptake inhibitors, SweSAT – Swedish Scholastic Aptitude Test

It remains unclear what the general factor of psychopathology measures. Hypotheses include the personality trait neuroticism, impulsivity, or irrational thinking[44-46]. We speculate that the general factor of psychopathology might quantify overall distress and impairment, similar to how the general factor of intelligence quantifies gross abstract reasoning. However, given the lack of consensus about the meaning of the century-old general factor of intelligence[4], it might be unrealistic to expect a solution to this conundrum anytime soon.

Regardless of interpretation, the general factor of intelligence has offered clinical and research utility over the past century, suggesting that the general factor of psychopathology might do so too[47,48]. In terms of clinical utility, the general factor of psychopathology might supplement diagnoses. A continuous or binned (e.g., small, medium and large) general psychopathology score might assist with prognosis; might differentiate among patients with the same primary diagnosis to indicate who might need additional care; and might help individuals who present with a large number of symptoms, but fail to meet diagnostic criteria for a diagnosis, to gain access to care.

In terms of research utility, we echo past arguments that it might be beneficial to isolate the general factor of psychopathology when examining associations with risk factors[13,14]. As an analogy, a hypothetical association between processing speed and future level of education might not indicate specificity; however, if such an association were to remain after isolating general intelligence, it would lend stronger support to the unique role of rapid thinking in educational success.

This work should be interpreted in light of certain limitations. First, the predictive results were limited to men only. Although past research has demonstrated that a parent-rated general psychopathology factor predicted teacher-rated adverse outcomes years later in a sample of girls, it would be important to examine if these results replicate among females[17]. Furthermore, some of the diagnoses tend to co-occur with the outcomes (e.g., depression and prescription of SSRIs), which might have increased the associations. However, the adverse outcomes occurred on the average eight years after conscription, and the general psychopathology factor predicted more independent outcomes (e.g., criminality and use of social welfare benefits) equally well.

Second, it is possible that the associations among mental health indicators are influenced by collider bias[49]. Individuals with multiple disorders might be more prone to seek mental health assistance, leading to an overestimation of associations among disorders in national registers. In contrast, individuals with multiple syndromes might be less prone to participate in survey research, leading to an underestimation of associations among symptom scales. Despite these potential ascertainment biases, the general factor magnitude metrics were remarkably similar regardless of sampling method. On a related note, it is possible that the general factor of psychopathology might partly represent a rating bias; however, for the adolescent sample, we analyzed the magnitude only based on the overlap between self- and parent-report data. Furthermore, it seems unlikely that a rating bias would predict such a wide range of adverse outcomes years later.

Third, because it is challenging to predict time-to-event data in a structural equation modeling framework, we only predicted the probability of whether the outcomes occurred or not. Survival analyses would additionally have predicted the probability of the events as a function of time.

Fourth, it is important to keep in mind that observed data that appear to consist of a general factor could be generated by processes lacking a general factor[50-53]. Because it is difficult to infer the true data generating process, it is probably wise to harbor a healthy level of skepticism toward all nosological models to protect against reification[54]. Nevertheless, even if a process without a general factor had generated the observed data patterns in this study, the general factor of psychopathology might still be a convenient summary index of such underlying process.

Finally, although the general factors of intelligence and psychopathology had similar magnitude and predictive validity, there are also substantive differences between the two domains. In contrast to psychopathology, intelligence tests have a logically correct answer, whereas short-term fluctuations are generally more important in the mental health domain (e.g., a depressive episode might warrant temporary suicide prevention efforts).

In conclusion, whereas current diagnostic systems measure diagnoses relatively well, they place less emphasis on broad symptomatology. It might be useful to combine psychopathology indicators into a single score, similar to how intelligence subtests are combined into a general intelligence score. Such a single score might supplement specific diagnoses when developing treatment plans or predicting prognosis.

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Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects

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Mental disorders frequently begin in childhood or adolescence. Psychotropic medications have various indications for the treatment of mental disorders in this age group and are used not infrequently off-label. However, the adverse effects of these medications require special attention during developmentally sensitive periods of life. For this meta-review, we systematically searched network meta-analyses and meta-analyses of randomized controlled trials (RCTs), individual RCTs, and cohort studies reporting on 78 a priori selected adverse events across 19 categories of 80 psychotropic medications – including antidepressants, antipsychotics, anti-attention-deficit/hyperactivity disorder (ADHD) medications and mood stabilizers – in children and adolescents with mental disorders. We included data from nine network meta-analyses, 39 meta-analyses, 90 individual RCTs, and eight cohort studies, including 337,686 children and adolescents. Data on ≥20% of the 78 adverse events were available for six antidepressants (sertraline, escitalopram, paroxetine, fluoxetine, venlafaxine and vilazodone), eight antipsychotics (risperidone, quetiapine, aripiprazole, lurasidone, paliperidone, ziprasidone, olanzapine and asenapine), three anti-ADHD medications (methylphenidate, atomoxetine and guanfacine), and two mood stabilizers (valproate and lithium). Among these medications with data on ≥20% of the 78 adverse events, a safer profile emerged for escitalopram and fluoxetine among antidepressants, lurasidone for antipsychotics, methylphenidate among anti-ADHD medications, and lithium among mood stabilizers. The available literature raised most concerns about the safety of venlafaxine, olanzapine, atomoxetine, guanfacine and valproate. Nausea/vomiting and discontinuation due to adverse event were most frequently associated with antidepressants; sedation, extrapyramidal side effects, and weight gain with antipsychotics; anorexia and insomnia with anti-ADHD medications; sedation and weight gain with mood stabilizers. The results of this comprehensive and updated quantitative systematic meta-review of top-tier evidence regarding the safety of antidepressants, antipsychotics, anti-ADHD medications and mood stabilizers in children and adolescents can inform clinical practice, research and treatment guidelines.

Key words: Safety, tolerability, children, adolescents, psychopharmacology, antidepressants, antipsychotics, mood stabilizers, psychostimulants, meta-review

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Childhood and adolescence are a crucial time of biopsychosocial development[1]. Many, if not most, severe mental disorders have their onset prior to age 18[2]. Early intervention is a cornerstone of modern psychiatry which has demonstrated superior outcomes, for example, in psychotic disorders and bipolar disorder[3,4]. In addition to psychotherapeutic and psychosocial interventions, psychotropic medications are often necessary to treat severe mental disorders that result in subjective distress and/or significant dysfunction in youth.

Several antidepressants, antipsychotics, anti-attention-deficit/hyperactivity disorder (ADHD) medications and mood stabilizers indicated in adults have received regulatory approval for use in children and/or adolescents[5], and many are used off-label[6-10]. However, despite evidence for the efficacy of a number of psychotropic medications in youth, the duration of untreated illness in depressive disorder[11], bipolar disorder[12,13], schizophrenia[14], obsessive-compulsive disorder[15], anxiety disorders[16], and other mental disorders[17] is often long[18,19], which adversely affects long-term outcomes[14,20-24]. Such delay can be related to several factors. These certainly include reduced access to care due to stigma and self-stigma surrounding mental illness[25-27], but stigma-derived or data-based concerns about the safety of psychotropic medications in children and adolescents are also relevant[28-34].

The poor quality of data on safety of psychotropic medications can potentially induce a delay or refusal of treatment, despite evidence that medications used in psychiatry are generally not less effective than those prescribed in other fields of medicine[35]. For instance, poor reporting of adverse events in available randomized controlled trials (RCTs) may have led to inaccurate estimates of some serious events, such as suicidality with antidepressants[36]. In addition, regulatory agencies may issue boxed warnings for adverse events of medications, such as for antidepressants increasing suicidality in children, adolescents and young adults[37], which can impact prescribing habits in everyday clinical practice[38], but whose validity may then be ques-

tioned[39,40]. At the same time, evidence-based safety concerns and warnings are essential to inform treatment guidelines and clinical care and are crucial to protect patients according to the *primum non nocere* principle.

The evidence on safety of psychotropic agents in children and adolescents with mental disorders has been rapidly growing[41], but remains fragmented. The available network meta-analyses (NMAs) and meta-analyses (MAs) have generally considered efficacy as their primary outcome, while safety is usually not prioritized in the primary RCTs and related evidence syntheses. Moreover, NMAs and MAs only include RCTs, usually concerning one or, rarely, few related mental disorders.

While RCTs minimize the influence of several sources of bias on estimates of medication effects in a specific population, they also apply strict selection criteria, which reduces the generalizability and external validity of their findings. Moreover, RCTs are often relatively small and short in duration, which precludes the adequate identification of rare but serious or long-term adverse events[42]. Furthermore, NMAs and MAs generally focus on the use of medications in disorders for which they are indicated, excluding evidence about off-label use. Therefore, a comprehensive summary of the evidence concerning the safety of psychotropic medications for all the mental health conditions for which they are used in children and adolescents, based on RCTs as well as on large cohort studies including more generalizable samples and reflecting real-world use patterns, is important to inform clinical practice.

To the best of our knowledge, no systematic meta-review exists to date that has focused on the safety of psychotropic drugs in children and adolescents as its primary outcome, summarizing data from NMAs, MAs, largest individual RCTs, and well-designed matched cohort studies across all relevant mental disorders. The aim of the present meta-review was to provide the largest and most comprehensive evidence synthesis on the safety of four major psychotropic medication classes (antidepressants, antipsychotics, anti-ADHD drugs, mood stabilizers) in children and adolescents with mental disorders, in order to inform clinical decision making and guideline development, and to identify areas needing further research.

METHODS

Search, inclusion and exclusion criteria

This systematic meta-review followed an *a priori* protocol (available upon request). We conducted a systematic search in PubMed and PsycINFO, from database inception up to September 7, 2019, using an exhaustive combination of key words for both psychotropic medications and adverse health outcomes (full search string available upon request). Additional manual searches were performed on reference lists of included articles. Pairs of authors conducted title/abstract screening and full-text assessment, and extracted data into a pre-defined excel spreadsheet. A third author resolved any conflict.

Inclusion criteria were: a) NMAs, MAs, individual RCTs, and cohort studies controlling for confounding by indication (i.e., medication vs. placebo/no medication in subjects affected by the same disorder); b) data on the association between antidepressants, antipsychotics, anti-ADHD medications, or mood stabilizers and adverse health outcomes; c) population of children and/or adolescents with any mental disorder.

Exclusion criteria were: a) studies on conditions other than mental disorders for which psychotropic medications are indicated or used (e.g., epilepsy); b) confounding by indication (i.e., comparing patients on medications with healthy controls), even if they adjusted analyses for covariates; c) designs other than those indicated in inclusion criteria; d) no data on the association between the targeted medications and adverse health outcomes.

Included adverse events and psychotropic medications

The 78 *a priori* selected adverse events were subdivided into the following 19 categories: central nervous system (agitation, anxiety, asthenia, irritability, cognitive impairment, depression, dizziness, headache, mania, psychosis, sedation, insomnia, seizures, suicidal ideas/behaviors/attempts); nutritional and metabolic (anorexia, binge eating/increased appetite, increased cholesterol, increased triglycerides, metabolic syndrome, glucose dysregulation/diabetes, insulin resistance, increased waist circumference, weight gain/increased body mass index, weight loss); cardiovascular (arrhythmias/tachycardia, cardiomyopathy, cerebrovascular disease, coronary heart disease, hypertension, hypotension, myocarditis, QT prolongation, sudden cardiac death); gastrointestinal (abdominal pain, constipation, diarrhea, gastrointestinal symptoms, liver damage, nausea/vomiting); genitourinary (enuresis, kidney disease/failure, menstrual cycle alterations, polycystic ovarian syndrome, sexual dysfunction); movement disorders (akathisia, any extrapyramidal side effect, tremor, dystonia, tardive dyskinesia); impulse dyscontrol and risky behavior (criminal behavior, gambling, substance abuse, non-suicidal self-injury behaviors); endocrine (gynecomastia/galactorrhea, hypo/hyperprolactinemia, hypo/hyperthyroidism); hematologic (anemia, leukocytopenia, thrombocytopenia); mouth (dental caries, dry mouth, sialorrhea); respiratory (acute respiratory failure, asthma, nasopharyngitis/upper respiratory tract infection/pneumonia); venous thromboembolism (deep vein thrombosis, pulmonary embolism); bone health (osteopenia/osteoporosis, fractures); accidents (any accident, fall); neuroleptic malignant syndrome (neuroleptic malignant syndrome/fever/creatine phosphokinase elevation); any cancer; discontinuation due to adverse event; serious adverse events; and mortality (all-cause, due to natural causes, due to suicide).

The 80 psychotropic medications were subdivided into the four categories of antidepressants, antipsychotics, anti-ADHD medications, and mood stabilizers. The category of antidepressants included nine classes: monoamine oxidase inhibitors (IMAOs) (bifemelane, hydracarbazine, isocarboxazid, moclobemide,

nialamide, phenelzine, pirlindole, rasagiline, safinamide, selegiline, toloxatane and tranylcypromine); tricyclics (TCAs) and tetracyclics (TeCAs) (amitriptyline, amoxapine, clomipramine, desipramine, doxepine, imipramine, maprotiline, nortriptyline, protriptyline and trimipramine); selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline); serotonin-noradrenaline reuptake inhibitors (SNRIs) (desvenlafaxine, duloxetine, levomilnacipran, milnacipran and venlafaxine); serotonin partial agonist and reuptake inhibitors (SPARIs) (nefazodone, trazodone and milazodone); noradrenergic and specific serotoninergic antidepressants (NASSAs) (mianserin and mirtazapine); noradrenaline reuptake inhibitors (NRIs) (reboxetine); noradrenaline and dopamine reuptake inhibitors (NDRIs) (buproprion); others (agomelatine, esketamine, S-adenosyl-methionine and vortioxetine). The category of antipsychotics included two classes: first-generation antipsychotics (FGAs) (chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, promazine and trifluoperazine) and second-generation antipsychotics (SGAs) (amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone). Anti-ADHD medications included psychostimulants (d-amphetamine, lisdexamphetamine and methylphenidate) and medications with other mechanisms (atomoxetine, clonidine, guanfacine and modafinil). Mood stabilizers included antiepileptics (carbamazepine, gabapentin, lamotrigine, pregabalin, oxcarbazepine, topiramate and valproate) and lithium.

Primary and secondary outcomes

The primary outcome was the safety/coverage ratio (i.e., the number of adverse events significantly worse than placebo/no treatment over the number of adverse events covered by literature) for those psychotropic medications for which ≥20% of the 78 *a priori* selected events were covered by the literature. The secondary outcomes were the list of adverse events associated with each medication, their effect size ± 95% CI, and the study quality.

The magnitude of associations of each medication with the main adverse events was classified as small (≤0.5), medium (between >0.5 and <0.8) and large (≥0.8) for continuous outcomes (effect sizes >0) and inverse thresholds for effect sizes <0. For categorical outcomes, the magnitude of associations was classified as small (<3), medium (between ≥3 and <5) and large (≥5) for equivalent odds ratios (eORs) >1, and reciprocal thresholds for eORs <1[43].

Quality of evidence

The quality of MAs and NMAs was measured with a modified version of the A Measurement Tool for the Assessment of Multiple Systematic Reviews (AMSTAR)-PLUS[44], which allows to measure both the quality of the methodology of (N)MAs, and the quality of the studies included in (N)MAs (AMSTAR-Content). AMSTAR quality was considered low when the final score was <4, medium when it was 4-7, and high when >7[45]. For AMSTAR-Content, quality was considered low when the final score was <4, medium when it was 4-6, and high when >6. The overall quality of (N)MAs was rated choosing the lower score of either AMSTAR or AMSTAR-Content.

The quality of RCTs was assessed with the Risk of Bias tool 2[46], assigning high risk, low risk, or some concerns. The quality of cohort studies was measured with the Newcastle-Ottawa Scale (NOS)[47], and high quality was assigned when the NOS score was ≥7.

Statistical analysis

We extracted random effects effect sizes ± 95% CIs for the difference in the incidence of specific adverse events between individual medications and placebo (RTCs), or between treated vs. untreated youth with mental disorders (cohort studies). We considered ORs, log ORs or risk ratios (RRs) with respective numbers-needed-to-harm (NNH) for categorical outcomes, and standardized mean differences (SMDs) or mean differences (MDs) for continuous outcomes.

We calculated the overall proportional coverage of the *a priori* selected adverse events for each of the individual psychotropic medications using descriptive statistics, and divided the covered adverse events into those with and without significantly higher frequencies vs. placebo or matched subjects. Furthermore, we identified medications with the best or worst safety/coverage ratio among those that had results for ≥20% of the adverse events.

RESULTS

Search results

The flow chart of the search process for the three systematic searches is presented in Figure 1. At title and abstract level, we screened 1,309 hits for NMAs and MAs, 5,716 hits for individual RCTs and 8,518 hits for cohort studies. We assessed full texts of 292 articles for NMAs and MAs, 519 for individual RCTs, and 173 for cohort studies. We ultimately extracted data from nine NMAs, 39 MAs, 90 individual RCTs, and eight cohort studies, including 337,686 children and adolescents (120,637 for antidepressants, 66,764 for antipsychotics, 148,664 for anti-ADHD medications, and 1,621 for mood stabilizers).

For antidepressants, we included four NMAs[40,48-50], 15 MAs[36,51-64], 27 individual RCTs[65-91] also covered in those NMA/MAs, six additional RCTs[92-97], and three cohort studies[98-100]. There were 120,637 youth on antidepressants, including 24,659 across 139 RCTs after eliminating duplicated RCTs in multiple NMA/MAs (22,704 in NMA/MAs, 1,955 in additional RCTs), and 95,978 in three cohort studies.

For antipsychotics, we included three NMAs[101-103], 11 MAs[104-114],

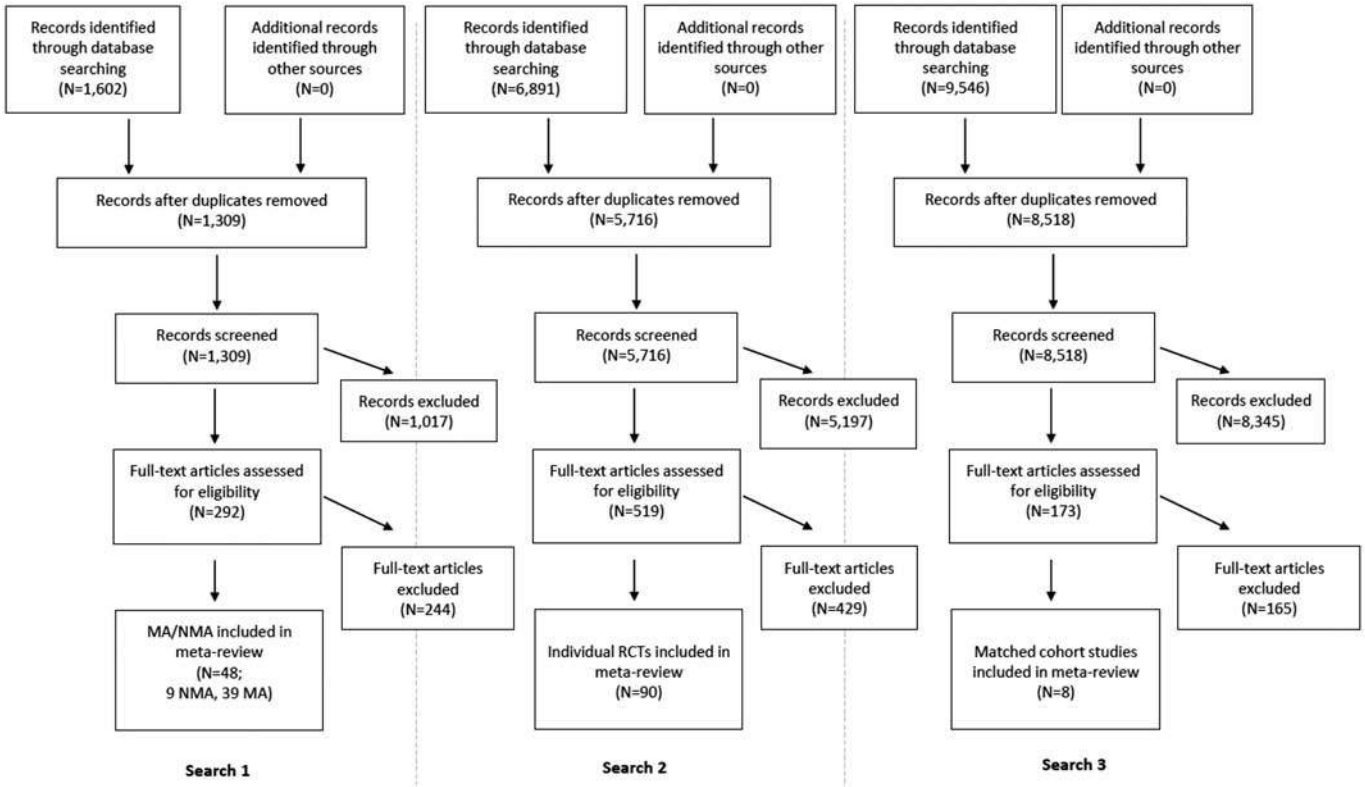

Figure 1 PRISMA flow chart for inclusion of studies. Search 1: network meta-analyses (NMA) and meta-analyses (MA); Search 2: individual randomized controlled trials (RCTs); Search 3: cohort studies controlling for confounding by indication

25 individual RCTs[115-139] also included in those NMA/MAs, three additional RCTs[140-142], and two cohort studies[99,143]. There were 66,764 youth on antipsychotics, including 7,712 across 53 RCTs after eliminating duplicated RCTs in multiple NMA/MAs (6,725 in NMA/MAs, 987 in additional RCTs), and 59,052 in two cohort studies.

For anti-ADHD medications, we included three NMAs[49,144,145], 11 MAs[146-156], 12 RCTs[157-168] also included in those NMA/MAs, five additional RCTs[169-173], and five cohort studies[99,174-177]. There were 148,664 youth on anti-ADHD medications, including 28,834 across 298 RCTs after eliminating duplicated RCTs in multiple NMA/MAs (27,188 in NMA/MAs, 1,646 in additional RCTs), and 119,830 in five cohort studies.

For mood stabilizers, we included four MAs[107,112,178,179], seven RCTs[180-186] also included in those NMA/MAs, and five additional RCTs[187-191]. There were 1,621 youth across 23 RCTs after eliminating duplicated RCTs in multiple NMA/MAs (1,244 in NMA/MA, 377 in additional RCTs).

Quality of included evidence

Among nine NMAs, the median AMSTAR score was 10 (interquartile range, IQR=9-11) and the median AMSTAR-Content score was 5 (IQR=5-7). The quality was moderate in two (22.2%) NMAs, and high in the remaining seven NMAs (77.8%). The RCTs included in NMAs had moderate quality in six (66.7%) NMAs, and high quality in three (33.3%). The overall quality of the evidence from included NMAs was moderate in six (66.7%) and high in three (33.3%).

Among 39 MAs, the median AMSTAR score was 9 (IQR=7-10) and the median AMSTAR-Content was 5 (IQR=4-6). The quality was moderate in 11 MAs (28.2%), and high in the remaining 28 (71.8%). The RCTs included in MAs had low quality in nine (23.1%) MAs, moderate quality in 23 (59.0%), and high in seven (17.9%). The overall quality of the evidence from included MAs was low in nine (23.1%), moderate in 25 (64.1%) and high in five (12.8%).

Among 90 individual RCTs, 26 (28.6%) had high risk of bias, 43 (47.3%) raised some concerns, and 22 (24.2%) had low risk of bias.

Among eight cohort studies, six (75%) had a high quality according to the Newcastle-Ottawa scale, and the median quality score was 7 (IQR=7-8).

Overall safety of classes of psychotropic medications in children and adolescents with mental disorders

Antidepressants

Out of 44 antidepressants, 18 (40.9%) had adverse event data covered in the literature. The available antidepressant literature covered 0-24.4% (mean: 5.6%, median: 0%) of the reviewed adverse events. Details on the proportion of the 78 adverse events covered in the literature and of the adverse events that were sig-

nificantly worse with individual antidepressants vs. placebo/controls are reported in Table 1 and Figure 2.

Among antidepressants with ≥20% of adverse events covered, the safety/coverage ratio was the best for escitalopram (1/17 adverse events covered significantly worse) and fluoxetine (1/16), progressively decreasing through vilazodone (2/16), paroxetine (3/16), sertraline (4/19), to venlafaxine, which had the worst safety/coverage ratio (7/16).

Five antidepressants were associated with significantly worse nausea/vomiting (duloxetine, nefazodone, paroxetine, sertraline, vilazodone), four with discontinuation due to adverse event (duloxetine, imipramine, venlafaxine, vilazodone), three with any extrapyramidal side effect (clomipramine, imipramine, paroxetine), two each with sedation (imipramine, nefazodone), diarrhea (duloxetine, sertraline), headache (nefazodone, venlafaxine), anorexia (amitriptyline, venlafaxine), and weight gain/increased body mass index (escitalopram, sertraline), and one each with weight loss (fluoxetine), and suicidality (venlafaxine).

Antipsychotics

Out of 21 antipsychotics, 15 (71.4%) had adverse event data covered in literature. The antipsychotic literature covered a range of 0-56.4% (mean: 16.6%, median: 2.6%) of the reviewed adverse events. Details of the proportion of the 78 adverse events covered in the literature and of adverse events that were significantly worse with individual antipsychotics vs. placebo/controls are reported in Table 2 and Figure 2.

Among antipsychotics with ≥20% of adverse events covered, lurasidone had the best safety/coverage ratio (1/33 covered adverse events significantly worse), progressively decreasing through asenapine (2/22), quetiapine (5/37), ziprasidone (4/25), paliperidone (5/26), risperidone (12/44), aripiprazole (10/35), to olanzapine, which had the worst safety/coverage ratio (13/25).

Ten antipsychotics were associated with significantly worse sedation (aripiprazole, clozapine, haloperidol, loxapine, molindone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone), nine with any extrapyramidal side effect (amisulpride, aripiprazole, haloperidol, loxapine, molindone, olanzapine, paliperidone, risperidone, ziprasidone), seven with weight gain/increased body mass index (aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, risperidone), five with hyperprolactinemia (haloperidol, olanzapine, paliperidone, quetiapine, risperidone), and three each with increased cholesterol (aripiprazole, olanzapine, quetiapine) and glucose increase/diabetes (asenapine, olanzapine, risperidone).

Anti-ADHD medications

All seven anti-ADHD medications had adverse event data covered in the literature. The available literature covered 7.7-32.1% (mean: 19.0%, median: 17.9%) of the reviewed adverse events. Details of the proportion of the 78 adverse events covered in the literature and of adverse events that were significantly worse with individual anti-ADHD medications vs. placebo/controls are reported in Table 3 and Figure 2.

Among anti-ADHD medications with ≥20% of adverse events covered, methylphenidate had the best safety/coverage ratio (5/25 adverse events covered significantly worse), while guanfacine and atomoxetine had the worst safety/coverage ratio (4/16 and 5/20, respectively).

Five anti-ADHD medications were associated with significantly worse anorexia (atomoxetine, d-amphetamine, lisdexamphetamine, methylphenidate, modafinil), four with insomnia (d-amphetamine, lisdexamphetamine, methylphenidate, modafinil), three with weight loss (atomoxetine, methylphenidate, modafinil), two each with abdominal pain (methylphenidate, guanfacine), discontinuation due to adverse event (lisdexamphetamine, guanfacine), hypertension (atomoxetine, lisdexamphetamine), and sedation (clonidine, guanfacine), and one with QT prolongation (guanfacine).

Mood stabilizers

Out of eight mood stabilizers, six (75.0%) had adverse event data covered in the literature. The mood stabilizer literature covered 0-24.4% (mean: 12.7%, median: 14.1%) of the reviewed adverse events. Details on the proportion of the 78 adverse events covered in the literature and of adverse events that were worse with individual mood stabilizers vs. placebo/controls are reported in Table 4 and Figure 2.

Among mood stabilizers with ≥20% of adverse events covered, the best safety/coverage ratio emerged for lithium (0/16 adverse events covered significantly worse), while valproate showed the worst safety/coverage ratio (4/19).

Two mood stabilizers were associated with significantly worse sedation (oxcarbazepine, valproate), and weight gain/increased body mass index (oxcarbazepine, valproate), and one each with weight loss or anorexia (topiramate), thrombocytopenia and leucocytopenia (valproate), and nausea/vomiting (oxcarbazepine).

Evidence from studies lasting ≥6 months

For antidepressants, no RCT lasted ≥6 months, while one cohort studies lasted 6 to 12 months[100], and two ≥12 months (range: 12-130 months)[98,99]. Significant associations emerged between current mixed antidepressants and fractures (small effect size, ≥12 months), but this association became non-significant when considering past exposure to antidepressants. Also, while antidepressants had a small association (≥12 months) with increased risk of any cancer in the first version of the analyses from a large cohort study, additional analyses from the same database did not confirm such association when removing mixed medications[99].

For antipsychotics, no RCT lasted ≥6 months, no cohort study lasted 6-12 months, while two cohort studies lasted ≥12 months (range: 84-130 months)[99,143]. A large association was found be-

Table 1 Safety of antidepressants in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls)

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Mixed antidepressants	12 (15.4%)	6 (7.7%)	Anorexia[48]	OR	4.01	1.63-10.17	NMA	M	26,114
			Discontinuation due to adverse event[59]	RR	1.66	1.20-2.28	MA	M	6,778
			Fractures[98]	HR	1.03	1.00-1.06	C	H	50,673
			Insomnia[63]	RR	2.16	1.42-3.27	MA	M	1,500
			Nausea/vomiting[63]	RR	1.88	1.44-2.45	MA	M	2,101
			Suicidality[56]	RR	1.95	1.28-2.98	MA	M	3,930
Mixed serotonin-noradrenaline reuptake inhibitors	9 (11.5%)	3 (3.8%)	Headache[63]	RR	1.52	1.09-2.13	MA	M	688
			Nausea/vomiting[63]	RR	1.97	1.36-2.87	MA	M	688
			Serious adverse events[59]	RR	2.10	1.19-3.69	MA	M	NA
Mixed selective serotonin reuptake inhibitors	14 (17.9%)	4 (5.1%)	Discontinuation due to adverse event[49]	Log OR	–1.8	–3.4 to –0.4	NMA	H	2,623
			Headache[63]	RR	1.27	1.03-1.56	MA	M	2,297
			Nausea/vomiting[63]	OR	1.89	1.42-2.52	MA	M	831
			Serious adverse events[59]	RR	1.72	1.12-2.63	MA	M	NA
Mixed tricyclics	12 (15.4%)	4 (5.1%)	Dry mouth[63]	RR	3.28	1.82-5.90	MA	M	232
			Hypotension[64]	OR	6.78	2.06-22.26	MA	L	324
			Tremor[64]	OR	6.29	1.78-22.17	MA	L	308
			Suicidality[49]	Log OR	25.1	4.5-57.4	NMA	H	2,623
Amitriptiyline	2 (2.6%)	1 (1.3%)	Anorexia[65]	NA	Sig	Sig	RCT	M	31
Bupropion	8 (10.3%)	0 (0.0%)							
Citalopram	8 (10.3%)	0 (0.0%)							
Clomipramine	8 (10.3%)	1 (1.3%)	Any extrapyramidal side effects[97]	RR	9.35	1.28-68.6	RCT	M	60
Desipramine	6 (7.7%)	0 (0.0%)							
Desvenlafaxine	9 (11.5%)	0 (0.0%)							
Duloxetine	13 (16.7%)	3 (3.8%)	Diarrhea[93]	OR	3.26	1.09-9.71	RCT	H	556
			Discontinuation due to adverse event[40]	OR	2.80	1.20-9.42	NMA	H	5,260
			Nausea/vomiting[93]	OR	1.93	1.15-3.25	RCT	H	556
Escitalopram	17 (21.8%)	1 (1.3%)	Weight gain[87]	OR	2.30	1.01-5.25	RCT	L	312
Fluoxetine	16 (20.5%)	1 (1.3%)	Weight loss[79]	MD	–1.2	–1.85 to –0.55	RCT	M	103

Table 1 Safety of antidepressants in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls) *(continued)*

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Fluvoxamine	11 (14.1%)	1 (1.3%)	Abdominal pain[89]	RR	1.70	1.06-2.71	RCT	M	128
Imipramine	15 (19.2%)	5 (6.4%)	Any extrapyramidal side effects[90]	OR	7.35	1.62-33.3	RCT	M	182
			Discontinuation due to adverse event[40]	OR	5.49	1.96-20.9	NMA	H	5,260
			Dry mouth[62]	RR	3.81	1.25-11.6	MA	M	56
			Hypotension[90]	OR	13.6	1.74-107	RCT	M	182
			Sedation[90]	OR	4.44	1.22-16.2	RCT	M	182
Mirtazapine	2 (2.6%)	0 (0.0%)							
Nefazodone	8 (10.3%)	3 (3.8%)	Headache[91]	NA	Sig	Sig	RCT	L	528
			Nausea/vomiting[91]	NA	Sig	Sig	RCT	L	528
			Sedation[91]	NA	Sig	Sig	RCT	L	528
Nortriptyline	3 (3.8%)	1 (1.3%)	Hypertension[67]	NA	Sig	Sig	RCT	M	50
Paroxetine	16 (20.5%)	3 (3.8%)	Any extrapyramidal side effects[90]	OR	5.12	1.09-24.1	RCT	M	180
			Insomnia[82]	OR	2.68	1.20-6.00	RCT	M	319
			Nausea/vomiting[69]	OR	3.69	1.01-13.5	RCT	L	319
Sertraline	19 (24.4%)	4 (5.1%)	Diarrhea[68]	OR	3.04	1.25-7.38	RCT	H	376
			Insomnia[84]	OR	4.05	1.94-8.49	RCT	L	189
			Nausea/vomiting[68]	OR	2.65	1.03-6.77	RCT	H	189
			Weight gain[68]	NA	Sig	Sig	RCT	H	376
Venlafaxine	16 (20.5%)	7 (9.0%)	Abdominal pain[70]	OR	2.36	1.29-4.32	RCT	M	367
			Anorexia[72]	OR	4.25	1.55-11.63	RCT	M	323
			Discontinuation due to adverse event[40]	OR	3.19	1.01-18.70	NMA	H	5,260
			Headache[72]	OR	0.56	0.35-0.92	RCT	M	313
			Hypertension[70]	NA	Sig	Sig	RCT	M	367
			Serious adverse events[70]	OR	4.14	1.15-14.9	RCT	M	367
			Suicidality[40]	OR	0.13	0.00-0.55	NMA	H	5,260
Vilazodone	16 (20.5%)	2 (2.6%)	Discontinuation due to adverse event[94]	OR	8.55	1.13-64.8	RCT	H	526
			Nausea/vomiting[94]	OR	4.40	2.43-9.76	RCT	H	526

OR – odds ratio, RR – risk ratio, Log OR – log odds ratio, HR – hazard ratio, MD – mean difference, NMA – network meta-analysis, MA – meta-analysis, RCT – randomized controlled trial, C – cohort study, NA – not available, H – high quality, M – medium quality, L – low quality (lower score of either AMSTAR or AMSTAR-Content), Sig – significant difference between medication and placebo without effect size available

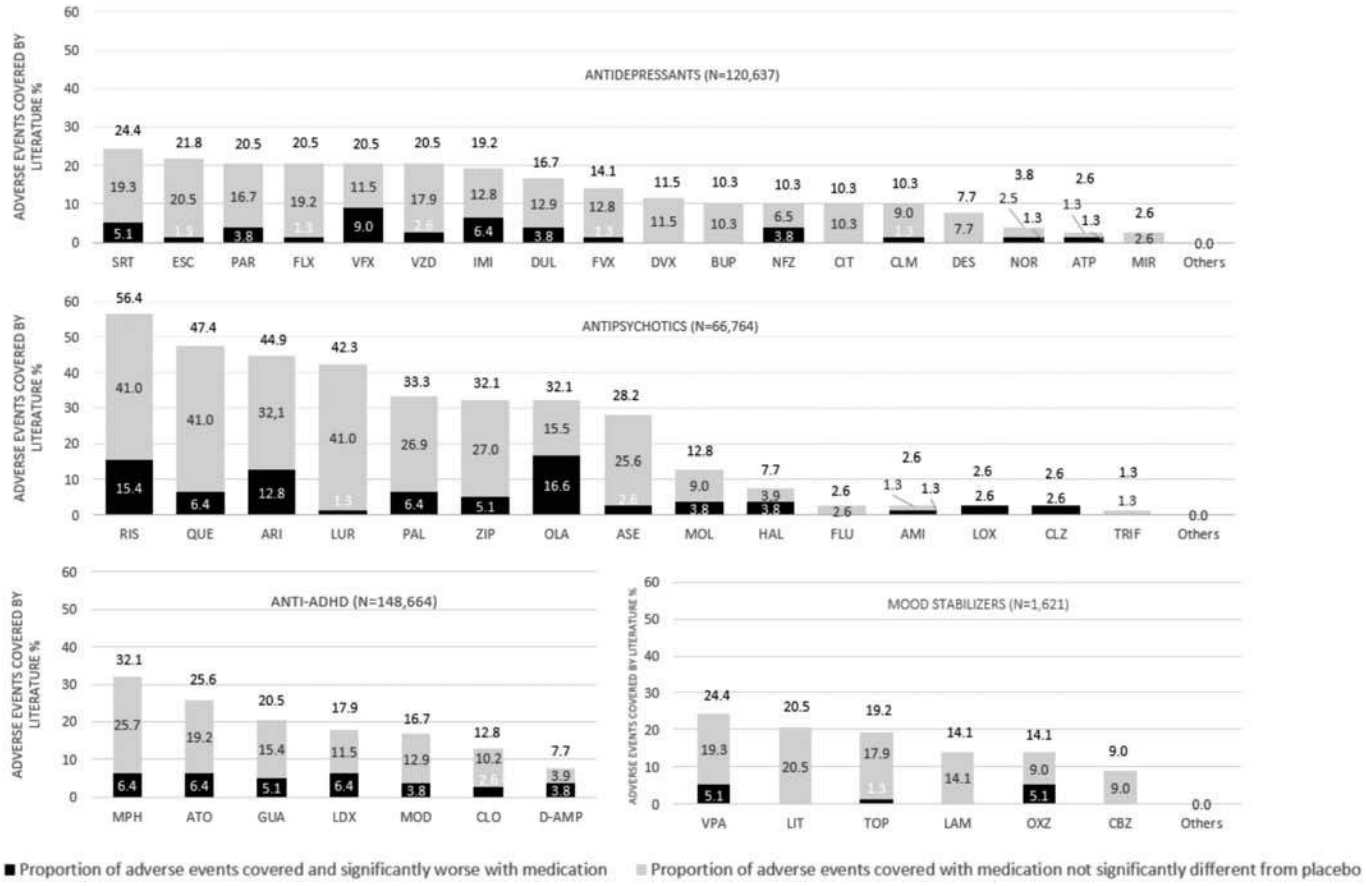

Figure 2 Proportion of adverse events covered by the literature that were significantly worse or non-significantly different from placebo, for antidepressants, antipsychotics, anti-attention-deficit/hyperactivity (ADHD) medications, and mood stabilizers in children and adolescents with mental illness. AMI – amisulpride, ATP – amitriptyline, ARI – aripiprazole, ASE – asenapine, ATO – atomoxetine, BUP – bupropion, CBZ – carbamazepine, CIT – citalopram, CLM – clomipramine, CLO – clonidine, CLZ – clozapine, DES – desipramine, DVX – desvenlafaxine, D-AMP – d-amphetamine, DUL – duloxetine, ESC – escitalopram, FLX – fluoxetine, FLU – fluphenazine, FVX – fluvoxamine, GUA – guanfacine, HAL – haloperidol, IMI – imipramine, LAM – lamotrigine, LIT – lithium, LDX – lisdexamphetamine, LOX – loxapine, LUR – lurasidone, MPH – methylphenidate, MIR – mirtazapine, MOD – modafinil, MOL – molindone, NFZ – nefazodone, NOR – nortriptyline, OLA – olanzapine, OXZ – oxcarbazepine, PAL – paliperidone, PAR – paroxetine, QUE – quetiapine, RIS – risperidone, SRT – sertraline, TOP – topiramate, TRIF – trifluoperazine, VPA – valproate, VFX – venlafaxine, VZD – vilazodone, ZIP – ziprasidone

tween mixed SGAs and diabetes (≥12 months).

For anti-ADHD medications, no RCT lasted ≥6 months, no cohort study 6-12 months, while five cohort studies lasted ≥12 months (range: 12-130 months)[99,174-177]. A large protective association was found between methylphenidate and any cancer (≥12 months), which survived after additional analyses from the same database removing mixed medications[99].

For mood stabilizers, no RCT lasted ≥6 months and no cohort studies were identified, so there was no long-term data on adverse events for any mood stabilizer.

DISCUSSION

This meta-review of 80 psychotropic medications summarized data on 78 preselected adverse events in children and adolescents with mental illness, quantifying data for 18 antidepressants (N=120,637), 15 antipsychotics (N=66,764), seven anti-ADHD medications (N=148,664) and six mood stabilizers (N=1,621).

Overall, the amount of coverage of the preselected adverse events was 0-24.4% for antidepressants (no data for 26 antidepressants), 0-56.4% for antipsychotics (no data for six antipsychotics), 7.7-32.1% for anti-ADHD medications (data for all anti-ADHD medications), and 0-24.4% for mood stabilizers (no data for two mood stabilizers).

Data were reported on ≥20% of the preselected adverse events for only six antidepressants (sertraline, escitalopram, paroxetine, fluoxetine, venlafaxine, vilazodone), eight antipsychotics (risperidone, quetiapine, aripiprazole, lurasidone, paliperidone, ziprasidone, olanzapine, asenapine), three anti-ADHD medications (methylphenidate, atomoxetine, guanfacine), and two mood stabilizers (valproic acid, lithium).

Thus, the present meta-review shows that the evidence on ad-

Table 2 Safety of antipsychotics in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls)

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Mixed antipsychotics	3 (3.8%)	2 (2.6%)	Discontinuation due to adverse event[104]	RR	2.40	1.10-5.30	MA	M	942
			Weight gain[104]	SMD	0.60	0.30-0.90	MA	M	625
Mixed second-generation antipsychotics	17 (21.8%)	10 (12.8%)	Akathisia[107]	NNH	20.4	14.1-36.5	MA	M	1,118
			Any extrapyramidal side effects[107]	NNH	7.5	5.7-11.0	MA	M	1,118
			Diabetes[143]	IRR	10.5	2.06-33.2	C	H	37,866
			Discontinuation due to adverse event[107]	NNH	20.4	13.4-47.5	MA	M	1,118
			Dystonia[105]	OR	3.90	1.70-8.40	MA	M	666
			Hyperprolactinemia[107]	NNH	7.9	6.10-11.1	MA	M	1,118
			Sedation[107]	NNH	4.7	3.90-6.0	MA	M	1,118
			Tardive dyskinesia[105]	OR	3.90	1.10-14.1	MA	M	666
			Tremor[105]	OR	3.49	1.50-8.0	MA	M	666
			Weight gain[107]	NNH	10.0	7.50-14.8	MA	M	1,118
Amisulpride	2 (2.6%)	1 (1.3%)	Any extrapyramidal side effects[124]	OR	9.60	1.48-62	RCT	L	27
Aripiprazole	35 (44.9%)	10 (12.8%)	Akathisia[102]	OR	3.10	1.0-9.0	NMA	M	2,158
			Any extrapyramidal side effects[103]	OR	3.80	2.20-6.20	NMA	M	3,258
				NNH	4.1	3.1-6.2	MA	M	296
			Asthenia[109]	OR	8.54	2.59-28.1	MA	M	405
			Anorexia[109]	OR	5.11	1.14-23.0	MA	M	308
			Increased cholesterol[108]	RR	2.50	1.40-4.40	MA	L	120
			Fever[109]	OR	5.89	1.23-28.2	MA	M	308
			Sedation[103]	OR	6.10	2.80-12.2	NMA	M	3,348
			Sialorrhea[109]	OR	10.5	1.30-84.2	MA	M	314
			Tremor[109]	OR	11.5	1.40-91.6	MA	M	313
			Weight gain[103]	OR	4.40	2.0-8.90	NMA	M	3,401
Asenapine	22 (28.2%)	2 (2.6%)	Increased body mass index[136]	NA	Sig	Sig	RCT	M	306
			Increased glucose[141]	NA	Sig	Sig	RCT	M	403
Clozapine	2 (2.6%)	2 (2.6%)	Sedation[103]	OR	54.8	3.9-260	NMA	M	3,348
			Weight gain[101,103]	OR	13.8	2.20-49.2	NMA	M	3,401
				SMD	–0.92	–1.61 to –0.22	NMA	M	3,003

Table 2 Safety of antipsychotics in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls) *(continued)*

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Fluphenazine	2 (2.6%)	0 (0.0%)							
Haloperidol	6 (7.7%)	3 (3.8%)	Any extrapyramidal side effects[131]	OR	59.1	6.66-525	RCT	L	50
			Hyperprolactinemia[101]	SMD	1.0	0.2-1.8	NMA	M	3,003
			Sedation[101]	Log OR	–1.3	–2.3 to –0.3	NMA	M	3,003
Loxapine	2 (2.6%)	2 (2.6%)	Any extrapyramidal side effects[131]	OR	62.4	7.05-553	RCT	L	50
			Sedation[101]	Log OR	–1.9	–3.1 to – 0.7	NMA	M	3,003
Lurasidone	33 (42.3%)	1 (1.3%)	Nausea/vomiting[142]	OR	3.1	1.50-6.60	RCT	M	343
Molindone	10 (12.8%)	3 (3.8%)	Akathisia[102]	OR	24.1	5.70-102	NMA	M	2,158
			Any extrapyramidal side effects[102]	OR	10.4	3.0-35.6	NMA	M	2,158
			Sedation[102]	OR	10.9	2.40-50.2	NMA	M	2,158
Olanzapine	25 (32.1%)	13 (16.6%)	Akathisia[102]	OR	3.70	1.10-12.7	NMA	M	2,158
			Anemia[119]	NA	Sig	Sig	RCT	L	107
			Any extrapyramidal side effects[103]	OR	6.40	2.40-13.8	NMA	M	3,258
			Increased cholesterol[103]	MD	4.5	1.2-7.7	NMA	M	1,784
			Increased creatine phosphokinase[119]	NA	Sig	Sig	RCT	L	107
			Increased glucose[103]	MD	2.1	0.1-4.3	NMA	M	1,784
			Hyperprolactinemia[101,103]	OR	15.6	4.40-41.1	NMA	M	3,348
				SMD	0.7	0.3-1.1	NMA	M	3,003
			Hypertension[130]	NA	Sig	Sig	RCT	L	107
			Liver damage[113]	OR	18.7	3.60-96.4	MA	H	265
			Sexual adverse events[108]	MD	11.5	8.80-14.1	MA	L	241
			Sedation[103]	OR	8.50	4.0-16.6	NMA	M	3,348
			Increased triglycerides[103,113]	OR	5.10	2.80-9.40	MA	M	268
				MD	20.2	9.8-30.5	NMA	H	1,655
			Weight gain[103]	OR	15.1	6.60-31.1	NMA	M	3,401
Paliperidone	26 (33.3%)	5 (6.4%)	Akathisia[102]	OR	5.60	1.80-17.7	NMA	M	2,158
			Any extrapyramidal side effects[102]	OR	6.30	2.30-16.8	NMA	M	2,158
			Hyperprolactinemia[101]	SMD	0.61	0.35-0.86	NMA	M	3,003
			Sedation[101]	Log OR	–2.4	–4.4 to –0.3	NMA	M	3,003
			Weight gain[101]	SMD	–0.7	–1.0 to –0.5	NMA	M	3,003

Table 2 Safety of antipsychotics in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls) *(continued)*

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Quetiapine	37 (47.4%)	5 (6.4%)	Increased cholesterol[103]	MD	10.8	6.6-145	NMA	M	1,784
			Hyperprolactinemia[101]	SMD	0.4	0.1-0.7	NMA	M	3,003
			Sedation[103]	OR	5.40	2.90-9.30	NMA	M	3,348
			Increased triglycerides[103]	MD	19.5	11.8-27.2	NMA	M	1,655
			Weight gain[101,103]	OR	6.20	2.60-13.6	NMA	M	3,401
				SMD	–0.85	–1.09 to –0.61	NMA	M	3,003
Risperidone	44 (56.4%)	12 (15.4%)	Akathisia[102]	OR	4.0	1.40-10.9	NMA	M	2,158
			Any extrapyramidal side effects[103]	OR	3.70	2.20-6.0	NMA	M	3,258
			Asthenia[109]	OR	3.89	1.77-8.53	MA	M	179
			Constipation[109]	OR	3.42	1.33-8.80	MA	M	179
			Gastrointestinal symptoms[115]	OR	3.74	1.15-12.2	RCT	H	168
			Increased glucose[103]	MD	3.70	1.10-6.40	NMA	M	1,784
			Hyperprolactinemia[101,103]	OR	38.6	8.60-126	NMA	M	1,180
				SMD	1.40	0.80-2.0	NMA	M	3,003
			Increased appetite[109]	OR	4.82	2.35-9.88	MA	M	179
			Nasopharyngitis/upper respiratory tract infection[109]	OR	3.14	1.26-7.80	MA	M	179
			Sedation[103]	OR	7.30	4.60-11.2	NMA	M	3,348
			Tachycardia[109]	OR	6.87	1.49-31.7	MA	M	179
			Weight gain[101,103]	OR	6.0	3.0-11.0	NMA	M	3,401
				SMD	–0.61	–0.89 to –0.32	NMA	M	3,003
Trifluoperazine	1 (1.3%)	0 (0.0%)							
Ziprasidone	25 (32.1%)	4 (5.1%)	Any extrapyramidal side effects[103]	OR	20.6	3.50-69.0	NMA	M	3,258
			Dizziness[135]	OR	9.15	1.20-69.7	RCT	L	283
			Nausea/vomiting[135]	OR	4.80	1.10-21.1	RCT	L	283
			Sedation[103]	OR	8.70	2.70 -22.0	NMA	M	3,348

OR – odds ratio, RR – risk ratio, Log OR – log odds ratio, SMD – standardized mean difference, IRR – incidence rate ratio, NNH – number needed to harm, NMA – network meta-analysis, MA – meta-analysis, RCT – randomized controlled trial, C – cohort study, NA – not available, H – high quality, M – medium quality, L – low quality (lower score of either AMSTAR or AMSTAR-Content), Sig – significant difference between medication and placebo without effect size available

Table 3 Safety of anti-attention-deficit/hyperactivity (ADHD) medications in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls)

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Mixed anti-ADHD medications	19 (24.4%)	7 (9.0%)	Abdominal pain[155]	RR	1.44	1.03-2.00	MA	H	2,155
			Anorexia[155]	RR	6.31	2.58-15.5	MA	H	2,467
			Discontinuation due to adverse event[144]	OR	2.30	1.36-3.89	NMA	H	14,346
			Hypertension[144]	SMD	0.09	0.01-0.18	NMA	H	14,346
			Insomnia[155]	RR	3.80	2.12-6.83	MA	H	2,429
			Nausea/vomiting[155]	RR	1.63	1.04-2.56	MA	H	1,579
			Weight loss[144]	SMD	–0.71	–1.15 to –0.27	NMA	H	14,346
Mixed α-2 agonists	5 (6.4%)	1 (1.3%)	Discontinuation due to adverse event[49]	Log OR	–29.6	–95.5 to –2.6	NMA	M	2,623
Atomoxetine	20 (25.6%)	5 (6.4%)	Anorexia[147]	RR	2.51	1.77-3.57	MA	M	2,179
			Gastrointestinal symptoms[147]	RR	1.76	1.51-2.07	MA	M	3,712
			Hypertension[144]	SMD	0.12	0.02-0.22	NMA	H	14,346
			Nausea/vomiting[156]	RR	1.91	1.24-2.94	MA	L	193
			Weight loss[144]	SMD	–0.84	–1.16 to –0.52	NMA	H	14,346
Clonidine	10 (12.8%)	2 (2.6%)	Hypotension[149]	Hedges' g	0.52	0.15-0.89	MA	M	119
			Sedation[164]	OR	7.67	2.92-20.1	RCT	M	230
d-amphetamine	6 (7.7%)	3 (3.8%)	Anorexia[170]	NA	Sig	Sig	RCT	L	81
			Insomnia[170]	NA	Sig	Sig	RCT	L	81
			Irritability[170]	NA	Sig	Sig	RCT	L	81
Guanfacine	16 (20.5%)	4 (5.1%)	Abdominal pain[166]	OR	4.51	1.34-15.2	RCT	M	455
			Discontinuation due to adverse event[144]	OR	2.64	1.20-5.81	NMA	H	14,346
			QT prolongation[149]	Hedges' g	0.33	0.12-0.54	MA	M	785
			Sedation[149]	RR	2.43	1.06-5.58	MA	M	1,059
Lisdexamphetamine	14 (17.9%)	5 (6.4%)	Anorexia[155]	RR	9.83	5.08-19.0	MA	H	1,081
			Discontinuation due to adverse event[145]	RR	3.11	1.20-3.76	NMA	M	6,931
			Dry mouth[169]	OR	8.63	1.13-66.0	RCT	H	547
			Hypertension[144]	SMD	0.14	0.03-0.25	NMA	H	14,346
			Insomnia[155]	RR	5.91	2.84-12.3	MA	H	1,081
Methylphenidate	25 (32.1%)	5 (6.4%)	Abdominal pain[154]	RR	1.50	1.26-1.79	MA	M	5,983
			Anorexia[154]	RR	3.21	2.61-3.94	MA	M	5,983
			Insomnia[148]	OR	4.66	1.99-10.9	MA	M	749
			Nausea/vomiting[154]	RR	1.38	1.04-1.84	MA	M	2,630
			Weight loss[144]	SMD	–0.77	–1.09 to –0.45	NMA	H	14,346
Modafinil	13 (16.7%)	3 (3.8%)	Anorexia[153]	RR	5.02	2.55-9.89	MA	M	921
			Insomnia[153]	RR	6.16	3.40-11.2	MA	M	921
			Weight loss[144]	SMD	–0.93	–1.59 to –0.26	NMA	H	14,346

OR – odds ratio, RR – risk ratio, Log OR – log odds ratio, SMD – standardized mean difference, NMA – network meta-analysis, MA – meta-analysis, RCT – randomized controlled trial, NA – not available, H – high quality, M – medium quality, L – low quality (lower score of either AMSTAR or AMSTAR-Content), Sig – significant difference between medication and placebo without effect size available

Table 4 Safety of mood stabilizers in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls)

Medication	Adverse events covered by literature	Adverse events worse than placebo	Adverse event	Type of effect size	Effect size	95% CI	Source	Quality	N
Mixed mood stabilizers	4 (5.1%)	1 (1.3%)	Sedation[107]	NNH	9.5	6.3-23.5	MA	L	469
Carbamazepine	7 (9.0%)	0 (0.0%)							
Lamotrigine	11 (14.1%)	0 (0.0%)							
Lithium	16 (20.5%)	0 (0.0%)							
Oxcarbazepine	11 (14.1%)	4 (5.1%)	Discontinuation due to adverse event[181]	OR	6.19	1.31-29.3	RCT	M	116
			Nausea/vomiting[181]	OR	3.66	1.33-10.1	RCT	M	116
			Sedation[181]	OR	6.89	1.47-32.4	RCT	M	116
			Weight gain[181]	NA	Sig	Sig	RCT	M	116
Topiramate	15 (19.2%)	1 (1.3%)	Anorexia[182]	OR	21.7	1.19-398	RCT	M	56
Valproate	19 (24.4%)	4 (5.1%)	Leukocytopenia[180]	NA	Sig	Sig	RCT	H	150
			Sedation[107]	NNH	7.8	5.3-15.0	MA	L	231
			Thrombocytopenia[180]	NA	Sig	Sig	RCT	H	150
			Weight gain[107]	Effect size	0.4	0.07-0.73	MA	L	231

OR – odds ratio, RR – risk ratio, NNH – number needed to harm, MA – meta-analysis, RCT – randomized controlled trial, NA – not available, H – high quality, M – medium quality, L – low quality (lower score of either AMSTAR or AMSTAR-Content), Sig – significant difference between medication and placebo without effect size available

verse events of psychotropic medications in children and adolescents is modest overall, and that psychostimulants are the drugs which have been most studied up to now.

The main adverse events for antidepressants were (in descending order of number of medications associated with the specific event): nausea/vomiting, discontinuation due to adverse event, extrapyramidal side effects, weight gain, sedation, diarrhea, headache and anorexia. Based on the safety/coverage ratio among agents with ≥20% adverse event coverage, the safest profile emerged for escitalopram and fluoxetine, and the worst for venlafaxine. These data confirm, and put in a more comprehensive framework, the findings of a previous NMA on antidepressants in children and adolescents[40] (focusing, however, on efficacy as its primary outcome), which showed that both fluoxetine and escitalopram were not associated with more drop-outs than placebo, while venlafaxine was, with a moderate effect size (OR=3.19). In the same NMA, fluoxetine was found to be the only antidepressant significantly superior to placebo with respect to its impact on depressive symptoms (SMD=–0.51). Merging the safety results of the present meta-review with the available evidence on efficacy from that NMA[40], fluoxetine probably has the best harm-benefit ratio among all antidepressants for youth, and might be proposed as the first-line treatment for depressive disorders in children and adolescents.

The main adverse events for antipsychotics were (in descending order of number of medications associated with the specific event): sedation, extrapyramidal side effects, weight gain, hyperprolactinemia, increased cholesterol, and glucose increase. Based on the safety/coverage ratio among agents with ≥20% adverse event coverage, the safest profile emerged for lurasidone, and the worst for olanzapine. These data confirm in part, and put in a more comprehensive framework, the findings of the largest NMA of antipsychotics in children and adolescents with schizophrenia[101] (which, however, focused on efficacy as primary outcome). In the same NMA, the only antipsychotic superior to all others in terms of efficacy was clozapine, and no further difference emerged among other antipsychotics, except for ziprasidone being inferior to molindone, olanzapine and risperidone, and fluphenazine being inferior to all other antipsychotics.

Merging the safety results of the present meta-review with available evidence on efficacy[101], lurasidone might be proposed as the first-line treatment for schizophrenia spectrum disorders in children and adolescents. Less tolerable yet effective medications can be used as second-line treatments, tailoring the choice to each individual patient's expectations and safety priorities (e.g., sexually active subjects might prefer agents not increasing prolactin). Importantly, clozapine should be considered only for treatment-resistant cases, given the lack of evidence regarding its safety in children and adolescents, and its poor safety profile in adults[192], which can be expected to be similar in children and adolescents, if not worse.

The main adverse events for anti-ADHD medications were (in descending order of number of medications associated with the specific event): anorexia, insomnia, weight loss, abdominal pain, hypertension, and sedation. Based on safety/coverage ratio among agents with ≥20% adverse event coverage, the safest pro-

file emerged for methylphenidate, and the worst for atomoxetine and guanfacine. Our comprehensive meta-review provides a finer-grained insight into the adverse events of anti-ADHD medications, while the largest NMA to date[144] did not reveal differences among these drugs concerning tolerability. Somewhat surprisingly, methylphenidate was also protective against cancer when long follow-up was considered, with such protective association surviving additional analyses excluding mixed medications[99]. Further research is warranted on this protective effect.

Our meta-review shows that both atomoxetine and methylphenidate induce weight loss, consistent with previous findings[144]. Sedation was only observed with the alpha-2 agonists clonidine and guanfacine. Clinically, this effect can sometimes be exploited to counter insomnia, but residual daytime sedation may impair cognitive performance in subjects with ADHD. In terms of efficacy, in the above-mentioned NMA[144], only methylphenidate outperformed placebo (SMD=–0.82) according to teachers' ratings. Moreover, methylphenidate was superior to atomoxetine (SMD=0.22). Considering the available safety and efficacy data, methylphenidate might be considered the first-line treatment for ADHD in children and adolescents.

The main adverse events for mood stabilizers were (with the same number of medications associated with the specific event) sedation and weight gain. Based on the safety/coverage ratio among agents with ≥20% adverse event coverage, the safest event profile emerged for lithium, and the worst for valproate. While the lack of any association between lithium and thyroid/kidney damage[188] as well as weight gain[190] is likely due to the small sample size of the included RCTs (N=124 and N=31, respectively), and the short duration of one RCT (3 months)[188], significant lithium-induced weight gain would have emerged during the six-month RCT[190]. Considering the well-established efficacy of lithium, which is the first-line treatment in adolescent bipolar disorder according to international guidelines[193], currently available data on the harm-benefit ratio favor the choice of lithium among mood stabilizers in youth. However, long-term cohort studies in this age group are clearly warranted. All antipsychotics have more adverse events than lithium according to this meta-review, except for lurasidone, which seems to have a comparably safe profile and could be preferred to lithium for the treatment of bipolar depression[193,194].

The results of this meta-review need to be interpreted considering some limitations. First, data for adverse events are lacking for some, and limited for many of the reviewed psychotropic medications. Absence of evidence for certain adverse events cannot be taken as evidence of their absence. Therefore, a more comprehensive reporting of adverse events is strongly recommended in studies concerning the use of psychotropic medications in children and adolescents.

Second, information on adverse events is mostly based on spontaneous reports. While these will underestimate the frequency of such events, the use of rating scales might increase the level of noise. Interviews and/or self-report scales would assure a more comprehensive capturing of adverse events, and applying appropriate thresholds for severity and frequency could enhance the signal-to-noise ratio.

Third, long-term and rare adverse events are likely underrepresented in the reviewed data, that are based mostly on short- and medium-term RCTs, with only eight cohort studies of sufficient methodological quality providing longer-term data. Fourth, we did not differentiate the adverse events based on dose effects due to limited data. Fifth, we took a transdiagnostic approach in order to capture all available information. Although certain adverse events could possibly differ across the various mental disorders, no clear evidence exists for this possibility, and other patient- and medication-related factors that are transdiagnostic (e.g., age, treatment-naiveté, dose, co-medications) are likely much more important than diagnosis.

Of course, safety of medications needs to be considered along with their efficacy. This was not a focus of this large-scale meta-review, but we discussed our findings in the context of efficacy data from the largest and most recent NMA or MA for the respective medication class for its main indication. Finally, this meta-review does not include data on strategies to prevent or mitigate adverse events of psychotropic medications in youth. While this is clearly an important area, this topic is beyond the scope of the present review and needs to be considered on the basis of targeted reviews and studies focusing on specific adverse events of individual medications[195-201].

In summary, the results of this meta-review have several clinical implications, which can guide the use of psychotropic medications in children and adolescents. First, for some medications, there are no or very insufficient high-quality adverse event data in this age group, which should caution their use. Second, within each of the four major classes, we provide a hierarchy of medications on the basis of the available safety evidence: the preferred agents are likely to be fluoxetine and escitalopram among antidepressants, lurasidone among antipsychotics, methylphenidate among anti-ADHD medications, and lithium among mood stabilizers. By contrast, potentially least preferred agents based on safety are likely to be venlafaxine among antidepressants, olanzapine among antipsychotics, atomoxetine and guanfacine among anti-ADHD medications, and valproate among mood stabilizers.

Together with the efficacy data for these medications, the results of this comprehensive and updated meta-review of top-tier evidence regarding the safety of antidepressants, antipsychotics, anti-ADHD medications and mood stabilizers in children and adolescents can inform clinical practice, research and treatment guidelines.

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Transdiagnostic clinical staging in youth mental health: a first international consensus statement

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Recognizing that current frameworks for classification and treatment in psychiatry are inadequate, particularly for use in young people and early intervention services, transdiagnostic clinical staging models have gained prominence. These models aim to identify where individuals lie along a continuum of illness, to improve treatment selection and to better understand patterns of illness continuity, discontinuity and aetiopathogenesis. All of these factors are particularly relevant to help-seeking and mental health needs experienced during the peak age range of onset, namely the adolescent and young adult developmental periods (i.e., ages 12-25 years). To date, progressive stages in transdiagnostic models have typically been defined by traditional symptom sets that distinguish "sub-threshold" from "threshold-level" disorders, even though both require clinical assessment and potential interventions. Here, we argue that staging models must go beyond illness progression to capture additional dimensions of illness extension as evidenced by emergence of mental or physical comorbidity/complexity or a marked change in a linked biological construct. To develop further consensus in this nascent field, we articulate principles and assumptions underpinning transdiagnostic clinical staging in youth mental health, how these models can be operationalized, and the implications of these arguments for research and development of new service systems. We then propose an agenda for the coming decade, including knowledge gaps, the need for multi-stakeholder input, and a collaborative international process for advancing both science and implementation.

Key words: Clinical staging, youth mental health, transdiagnostic, progression, extension, heterotypy, homotypy, health services, service transformation

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In clinical practice, health professionals respond to presentations for care by individuals at variable points along an illness course. Even with careful history-taking, assessments are frequently conducted without a consistent approach that allows incorporation of risk factors, earlier presentations, individual trajectories or projected illness course into initial treatment selection or secondary prevention strategies[1]. Among other things, current approaches generally lack predictive validity for future course of illness[2].

The goal of understanding how initial symptoms, syndromes, physical and mental health comorbidities[3], and related social and occupational impairment remit or evolve over time thus requires the development of more innovative clinical frameworks[4]. Critically, these frameworks need to integrate prior and ongoing risk factors and individual illness course into new models for personalized treatment selection and organization of ongoing health care[5].

This goal is especially crucial for conditions that have their onset during times of major neurobiological and socio-developmental transition, such as adolescence to young adulthood[6,7]. In this developmental period, there is a need to delineate the patterns of continuity and discontinuity (at the individual level) between the earlier mental phenomena or overt disorders that emerge in childhood[8-10] (dominated by fundamental cognitive, attentional and behavioural features) and the more adult-like conditions that manifest during adolescence and young adulthood. The latter largely consist of mood, perceptual and complex cognitive features, which have an increased probability of becoming persistent, recurrent or chronically impairing[11,12].

Recent epidemiological studies[13] have vividly demonstrated complex patterns of emergence of psychopathology, along with their homotypic and heterotypic continuity[14,15] and the appearance of diagnostic instability[13] and artefactual comorbidity[16] at the individual level. This underscores the need to adopt a broad "transdiagnostic" approach – one that views the individual as located along a multidimensional and evolving continuum of illness – rather than a traditional narrow view based on the historical concept of risk for development of a single and categorically discrete adult-type "disorder"[15,17].

Traditional clinical frameworks have prioritized the identification of discrete mental disorders, largely as the basis for proceeding to evidence-based treatment decisions. Such "discrete" disorders, however, typically represent the fully-formed, prototypical and relatively late-stage syndromes that are managed in adult specialized or secondary mental health service systems internationally[18]. These disorders dominate the international clas-

sification systems, that are used not only for clinical practice but also for aetiological, pathophysiological, prediction and intervention research[19,20]. Ironically, despite being framed as "pure" cases, these individuals often present with complex and comorbid conditions, requiring multiple and/or intensive therapeutic interventions.

There is thus an urgent need to generate clinical definitions that both recognize the fluid developmental course of mental illness and are suitable for use in services aiming to intervene "early", during the initial phases of illness[21]. Such a shift also needs to differentiate earlier risk factors (e.g., childhood maltreatment, childhood-onset neurodevelopmental disorder) – some of which may be addressed by broad population-based health measures – from mild clinical states (with low probability of illness progression) that benefit from supportive but nonspecific interventions, and from attenuated syndromes (with higher probabilities of progression) that may require immediate active intervention or secondary prevention[22].

In our view, clearer definitions of each of these stages and the clinical or pathophysiological boundaries between them requires a concurrent understanding of principles that underpin clinical staging, an agreed-upon framework for operationalizing staging and its implications, and a clinical research agenda to advance the field. We hope that, by articulating these elements and creating a roadmap for international research and collaboration, a solid empirical basis for enhanced youth-focused clinical practice and research can be provided that in turn galvanizes stakeholders and generates further momentum.

CURRENT AND FUTURE FRAMEWORKS

Traditional psychiatric taxonomies have been unable to capture the complexities of emerging and early illness, continuity and comorbidity, largely as a consequence of our limited understanding of underlying pathophysiology[23,24]. In other areas of medicine – such as oncology, rheumatology and cardiovascular medicine – clinical staging is routinely linked to disease progression (of the primary clinical syndrome or pathophysiology), disease extension (i.e., complications beyond the primary pathophysiology), prognosis, and stage-informed treatment selection[25].

In cancer, evolving understandings of disease progression have allowed the development of the tumor-node-metastasis (TNM) model of staging, that differentiates between pathological stages (pTNM, based on microscopic examination of tumors after surgical removal) and clinical stages (cTNM, based on all available clinical and investigatory information)[26]. Furthermore, recent advances regarding immunological mechanisms involved in cancer progression have led to increasingly refined treatment strategies[27]. Here the ability to link clinical presentation to pathophysiology is drawn from detailed knowledge of aetiology and longitudinal biomarkers.

Personalizing care is similarly the ultimate objective of clinical staging in psychiatry. Largely as a consequence of the early intervention movement, and beginning with early psychosis, transdiagnostic clinical staging in youth mental health has the overt aim of enhancing clinical care for young people entering our health service systems[28]. What is still lacking, however, is a consensus as to how best to define, test and then iteratively refine the key clinical boundaries of the concept.

Importantly, an individual's stage differs from his/her current clinical state. State-based measures such as symptoms and functioning frequently undergo partial or even full remission, making clinical state reversible. However, the achievement of an improved state (e.g., functional recovery or symptom remission) at any given stage does not guarantee that the underlying disease process(es) have been reversed. For this reason, the concept of clinical staging in mental disorders is unidirectional: that is, an individual's stage can move from solely having risk factors to nonspecific clinical syndromes and then on to earlier or later stages of active illness, but not in the reverse direction. Indeed, knowledge of a person's highest clinical stage incorporates salient details regarding his/her own personal history (longitudinal course), which in turn contains information that may be relevant for predicting future trajectory, treatment selection and prognosis. Operationalizing staging and clinical states in a manner that conveys both will be an essential aspect of a future clinical research agenda.

Despite the unidirectionality of staging, it is critical to note that progression from early to later stages is probabilistic rather than inevitable. In other words, individuals most likely to progress to a given stage are those currently proximal to that stage, while those least likely to progress are those currently at the earliest stages. Staging, therefore, assertively promotes prevention and treatment aimed at full recovery or remission from acute presentations (states), regardless of the clinical stage at presentation for care.

Consistent with the principles of early intervention[4], the ultimate goal of staging is clinical utility. Staging models in mental health have typically made a distinction between early clinical stages – which are assumed to have low rates of progression to severe, persistent or recurrent disorders, thereby making prevention a central focus – from later stages, which are characterized by higher rates of persistence, impairment and disease progression, thereby demanding intensive clinical intervention[22]. At all stages, the optimal choice, intensity and duration of active intervention or secondary prevention strategies needs to take account of the probability of progression to later stages. This implies that different intensity and duration of care packages may be required to achieve these goals, with more intensive, specialized and multimodal interventions (albeit with potentially greater risk and delivered over longer periods) more likely to be required at later stages.

Recent transdiagnostic, pluripotential staging models have also proposed dimensional boundaries for progressive stages, signified by changes or increases in the severity of primary clinical presentations (Table 1). Specifically, syndromes comprised of nonspecific (largely anxiety and depressive – stage 1a) symptoms, or more complex but still attenuated (stage 1b) symptom

Table 1 Examples of recent staging models in youth mental health

Stage	Definition		
	Symptoms	Functioning	Neurocognition
0	No current symptoms; increased risk of disorder	No historical change	Normal to mild deficits
1a	Mild or nonspecific symptoms (QIDS 0-11)	Mild functional change/decline; GAF 70-100	Mild neurocognitive deficits or relatively normal profile
1b	Moderate but sub-threshold symptoms (QIDS 11-20, YMRS >9, attenuated psychotic symptoms)	Functional decline to caseness (GAF <70)	Moderate neurocognitive changes, particularly in attention, learning, or executive function (e.g., 0.5-1.0 SD decrement relative to premorbid IQ)
2	Full-threshold disorder with moderate to severe symptoms (QIDS >20, YMRS >15, meets CAARMS/SIPS criteria)	Functional decline (GAF <50)	Neurocognitive deficits (1.0-1.5 SD decrements relative to premorbid IQ)
3	Incomplete remission or relapse	Persistent functional decline (GAF <40)	Persistent decrement in neurocognition (>1.5 SD relative to premorbid IQ), including social cognition
4	Severe, unremitting or refractory illness	Poor treatment effectiveness despite persistently intensive interventions (GAF <30)	Similar to stage 3, with poor treatment effectiveness despite persistently intensive interventions

QIDS – Quick Inventory of Depressive Symptomatology, YMRS – Young Mania Rating Scale, CAARMS – Comprehensive Assessment of At Risk Mental States, SIPS – Structured Interview of Psychosis-risk Syndromes, GAF – Global Assessment of Functioning

sets, are differentiated from syndromes that are characterized by more discrete and persisting phenomena (e.g., manic symptoms, perceptual disturbances, severe depressive symptoms – stage 2), recurrent/multi-episode (stage 3) or persistent/unremitting syndromes (stage 4), with corresponding thresholds for changes in functioning or neurocognition[2,18,29]. The specifics of each stage differ slightly across models.

This "transdiagnostic" approach implies that staging can be applied to clinical presentations both within and across traditional diagnostic boundaries, and capturing both homotypic and heterotypic progression[30,31]. Homotypic progression may be the development of a severe depression following a milder form, or development of a threshold-level psychosis following a prior attenuated syndrome characterized by brief and non-persistent psychotic-like experiences. In contrast, heterotypic shifts might typically include new-onset mania or new-onset psychotic syndrome in individuals who had previously only experienced unipolar depressive episodes. A key advantage of the transdiagnostic, pluripotential approach is that its broader scope may better facilitate the prediction of future course of illness than those approaches that are organized within or around diagnostic silos[2].

TRANSDIAGNOSTIC CLINICAL STAGING: THE ROAD AHEAD

We argue that the further development of clinical staging for young people now needs to accomplish two critical tasks. First, it requires frameworks that can better capture the complexity of emerging mental health syndromes, moving beyond classical notions of "sub-threshold" and "threshold" disorders[32]. The clinical features of "sub-threshold" presentations rarely sit within one major diagnostic category: they are more often protean and ill-defined, with admixtures of anxiety, depressive, sleep disturbance and other symptoms that frequently morph over time.

Notions of "threshold" are also inconsistent across the disorders that are most relevant to youth mental health. For example, rather than treating all "full-threshold" disorders as comparable, anxiety disorders are frequently considered "at-risk" states for depressive disorders. Depressive disorders are seen as at-risk states to psychotic disorders, while full-threshold unipolar depressive disorders have also been considered as at-risk states to bipolar disorders. In this way, current "threshold" concepts remain grounded within existing diagnostic systems, creating the artefactual notion of diagnostic purity once a supra-threshold "exit-disorder" has emerged – whereas the reality is often one of more rather than less complexity and comorbidity over time.

Second, any research programme on clinical staging must differentiate more clearly the concept of illness progression from illness extension. While the idea of *progression* inherently involves a shift from categorical diagnoses to dimensionality, it is also tied to notions of meaningful step-wise changes in clinical status (for example, from partial to full delusional conviction), not simple increases in symptom severity, intensity or duration. It implies that at any particular point along the illness path, further worsening is possible, especially if appropriate specific treatments or secondary prevention strategies are not provided.

Extension, by contrast, is fundamentally multidimensional and potentially independent of progression (Figure 1). Extension signifies that the illness process has taken on new and more complex features. This can be operationalized as one or more of: a)

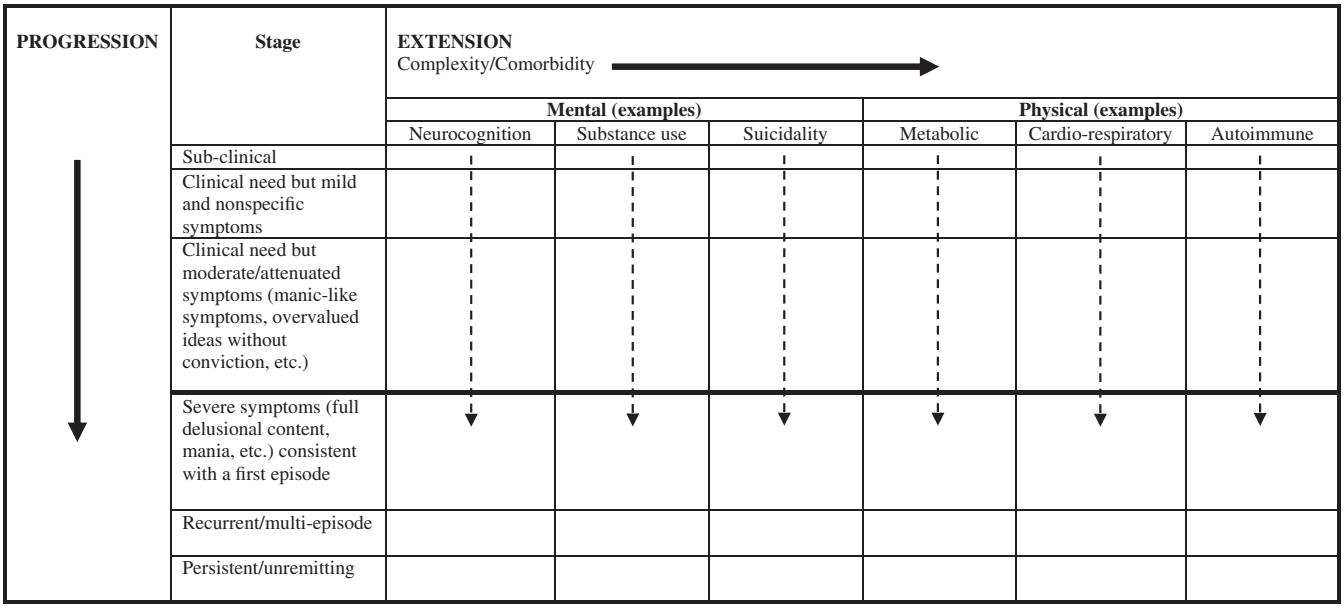

Figure 1 A revised multidimensional staging model for youth mental health incorporating elements of progression and extension

the emergence of mental or physical health comorbidities (e.g., onset of substance dependence alongside mental health symptoms or dysfunction; onset of metabolic or autoimmune complications); b) a marked change in a linked biological construct (e.g., emergence of an objective marker of circadian dysfunction in an individual with bipolar disorder[7]). Finally, previous staging models have lumped neurocognition together with symptoms and functioning[18,29]. While there may be some evidence for this in conditions such as psychosis[33,34] and bipolar disorder[35,36], this is unlikely to occur in synchronized decrements across all disorders[37]. Thus, extension may also be marked by c) an independent neuropsychological construct (e.g., marked deterioration in objective measures of cognitive function, such as verbal memory or executive function).

STAGING AND CLINICAL UTILITY

Since illness progression or extension implies a step-wise increase in severity or complexity, along with increased risk of persistence or recurrence, it should be accompanied by a corresponding need to instigate a categorical change in immediate treatment or indicated prevention strategies. The distinction between progression and extension means that interventions should become more intensive in the case of the former, or may need to broaden and expand in the case of the latter. Examples of response to progressive changes in core clinical symptoms and functioning would be the use of lithium following a first manic episode or the initiation of antipsychotic agents in association with a clear first-onset psychotic illness. Examples of response to the extension of illness would be dietary modifications and/or metformin for individuals whose illness now includes varying degrees of metabolic dysregulation, or addition of a psychosocial therapy targeting self-harm and suicidal ideation for individuals in which these elements develop.

For cardiovascular disease, staging is grounded in individually-focused reductions in known risk factors that can be clinically assessed (e.g., cessation of smoking, or reduction in blood pressure or cholesterol in individuals at high familial risk), followed by initiation of secondary prevention strategies or immediate intervention based on changes in clinical stage[23]. Similarly, preventive interventions aimed at addressing the earliest stages of mental health difficulties may be more effective at the population rather than the individual level. Further along, "indicated" prevention may take place at the individual level[38].

At still higher stages, the emphasis should first be on examining which novel, combined or alternative treatment strategies are required to improve immediate outcomes or prevent progression or extension of illness – and "reverse translating" this to identify the critical transitions, junctures or step-wise discontinuities in illness course (which might distinguish between putative stages) that such interventions address. The extent to which clinical transitions correspond to objective or neurobiological "markers" is also the subject of active clinical research[6,37]; maintaining a central focus on clinical utility may allow staging to address recent critiques regarding psychiatry's thus far futile search for disorder-specific biomarkers[39-41].

Finally, we recognize that there are other models either under development or articulated that also appreciate the transdiagnostic nature of mental illness, especially for research purposes[41-44]. We do not see these as competing approaches: clinical staging is designed principally to enhance the delivery of highly personalized care, with its appeal being that it is explicitly meant for clinical practice. And staging is particularly well poised to

contribute to youth mental health, given that it is in synchrony with the momentum already established towards broader early intervention and services development[2,4,45].

INTERNATIONAL CONSENSUS STATEMENT

Despite much promise[46], clinical staging has yet to be embraced widely in clinical practice, mental health services or health systems research. In order to accelerate its study and refinement, and following input from international experts in youth mental health, we propose a coordinated approach that: a) focuses on transdiagnostic clinical staging in youth mental health (onset age 12-25 years); b) draws from principles underlying the utility of clinical staging in general medicine; and c) sets a proposed agenda for coordinating future collaborative and comparative work in this area.

Principles and assumptions

Transdiagnostic clinical staging in youth mental health:

- relates to those mental health problems that typically have their onset at ages 12-25, and their putative resolution, progression or extension (which may continue through to the adult years);
- is an approach to *clinical* staging; that is, it is most relevant for individuals entering health service systems. As such, it should draw from and be applied to broadly defined help-seekers rather than non-clinical, community or other population-based samples. While important, the application of the model to the latter groups presents many other challenges and is beyond the scope of this consensus statement;
- is not only about redefining illness course or trajectory within or across traditional diagnoses such as major depression, bipolar disorder or psychotic disorder, but also about characterizing these *beyond* diagnostic silos;
- is not simply a way of arranging our existing narrow categorical diagnoses in a sequential manner based on conventional features of severity, duration, persistence or recurrence: earlier stages of the common anxiety, mood or psychotic disorders are not equivalent to current criteria for sub-threshold or threshold-level DSM or ICD common (anxiety or depressive) disorders, and later stages are not simply equivalent to threshold-level severe (mood, bipolar, psychotic or personality) disorders;
- acknowledges the fluid, heterotypic nature of the evolution of emerging mental disorders, and the pluripotentiality of later outcomes for those who present at earlier stages. Thus, transdiagnostic clinical staging for young people includes the broader admixture of clinical syndromes and associated complexities that dominate attenuated and full-threshold, as well as highly comorbid, mental health and substance misuse disorders;
- offers advantages over current nosology, diagnostic systems and cross-sectional clinical practice (including treatment selection, prognostic statements and secondary prevention) in youth mental health, that are increasingly acknowledged as inadequate[47];
- is fundamentally based on the idea, consistent with staging in other areas of health care, that any transition from an earlier to a later stage (disease progression or extension) is associated with a step-wise or meaningful deterioration in a relevant clinical, health, neurobiological or social factor, or leads to consideration of a new specific treatment or secondary prevention intervention;
- is tied to clinical interventions whose goals at each stage are to relieve current symptoms, reduce risk and prevent progression to later stages. In other words, it aims to both address the illness at the stage at which the individual is presenting (reducing prevalence), and to arrest its clinical and pathophysiological progression or elaboration (reducing future incidence);
- carries with it the concept that transitions across stages are probabilistic, not inevitable. Those who are at stage 0 have risk factors, but are not presenting for care: the goal through community or population-based interventions is to prevent transition to "a need for care". For those at subsequent clinical stages, it is to prevent transition to the next downward step in illness course;
- posits that likelihood of progression to a given stage is associated with prior proximity to that stage, meaning that those at later stages are at greater risk of progression to further stages. Similarly, illness progression (severity, persistence, recurrence, functioning) or extension (involvement of other physical/mental systems or comorbidity) within a stage may also predict increased risk of transition to a later stage. In both cases, these individuals are also at higher risk of illness extension to other poor health or social outcomes than those who are at earlier stages;
- should have the capacity to evolve iteratively based on emerging evidence. Specifically, a well-operationalized staging approach should generate testable clinical, neurobiological and psychosocial hypotheses. In turn, these can be studied systematically, and refined or refuted, on the basis of relevant data;
- can be used in an iterative manner to complement other formal diagnostic systems. Initially, the aim is to use staging for improved clinical prediction of risk and selection of the most personalized and appropriate treatments early in the course of illness;
- recognizes, as its archetypal methodological approach, longitudinal and multidimensional data collection from broad clinical cohorts, beginning at the earliest stages of illness and need for care. This may be complemented by a range of analytic techniques;
- must embody (and assemble knowledge with) the values of hope, optimism, respect and transparency that have served as cornerstones for the youth mental health community.

Operationalization of staging

Fully operationalized, transdiagnostic clinical staging in youth mental health:

- should be based on systems that operate across the full course of illness(es) or syndrome(s). As such, these systems need to specify distinctions – based on clear criteria and independent validation – between:
  a. population-based, but individually-applicable, risk factors (e.g., family history of bipolar disorder; exposure to childhood trauma; persistent cannabis use);
  b. non-specific symptom sets, where the individual already displays relevant emotional, cognitive or behavioural symptoms, but has no clearly persisting syndrome;
  c. onset of illness syndromes (i.e., persisting and associated with functional impairment), whether these are "sub- "or supra "threshold" according to current diagnostic systems;
  d. need for care, where local context may strongly influence both presentations to, and willingness to provide, appropriate health care;
- envisions a multi-stage system, from risk factors (non-symptomatic, non-impaired) to early symptomatic states (symptoms but minimal impairment) to those with more overt clinical syndromes with significant impairment and on to more severe and persistent illness. However, it is based on help-seeking and corresponding clinical case identification. Its applicability in wider population-based and epidemiological studies, where the base rate of specific disorders varies and differentiation from normal deviations in development remains unclear, is problematic;
- must fundamentally integrate the course of clinical presentation (including disease progression and extension) into comprehensive assessments, which would in turn facilitate an assignment of stage. Multidimensional assessments should take into account core presenting phenomena (symptom type, severity and frequency, along with functioning) as well as components of extension: severity of distress, substance use, neurocognition, physical and mental health comorbidities, and other clinically apparent features;
- is based on a convention that, while clinical state is reversible, staging itself is unidirectional. Thus, while an individual may remit or recover fully at any stage, he/she still retains the original stage classification – but can be assigned a further designation regarding current state, such as "in remission" or "responded to treatment". This convention recognizes that individuals who have made these step-wise stage progressions may have key differences compared to those who never progressed to the same stage, are at substantive increased lifetime risk of recurrence or future illness progression, and may benefit from additional interventions or different combination of them. For example:
  a. stages can be used concurrently with detailed modifiers of longitudinal clinical course to indicate grades of response to treatment, degrees of remission from an episode, number and frequency of relapses, and short or longer-term functional recovery;
  b. stages can contain indices of within-stage stratification based on key clinical, neurobiological, neuropsychological or psychosocial features, or response to treatment. A key consideration is whether such factors predict response to treatment or prognosis (notably transition rates to later stages);
- recognizes earlier or concurrent risk exposures (e.g., exposure to cannabis misuse, psychosocial trauma) known to increase risk for a staging transition, and risk indicators (e.g., traits that may suggest higher risk for a stage transition but may not themselves have a causal relationship), both of which may provide valuable information regarding prognosis and treatment response;
- begins with an initial stage (stage 0) comprised of known risk factors (e.g., prior history of childhood trauma, central nervous system infection, remitted childhood-onset mental or neurodevelopmental disorder, significant family history) for a new adolescent-onset mental disorder (i.e., syndrome) or impairment, but not currently help-seeking;
- requires the creation of an ongoing, collaborative and international clinical research process to create, refine and test the validity of criteria used to define stages and to distinguish between successive stages;
- acknowledges that those with youth presentations of mental disorders may have had childhood-onset disorders that may have persisted or remitted, or are associated with increased risk of new-onset adolescent disorders – e.g., childhood anxiety increasing the risk of adolescent-onset depression, childhood-onset attention-deficit/hyperactivity disorder (ADHD) increasing the risk of other adolescent-onset mood, cognitive or behavioural syndromes. Childhood-onset anxiety or depression that persists into adolescence needs to be assessed appropriately in terms of adult-type disease progression or extension;
- should be designed to assist the earliest provision of specific early intervention and secondary prevention efforts that not only offer a better risk/benefit ratio, but also target the underlying pathophysiology. Consequently, this approach has the potential to prevent the development of chronic illness states (neurobiologically and psychosocially);
- proposes specific clinical or clinicopathological[18] "cut-points" that may represent thresholds for major changes in treatment strategies – particularly where there are no specific independent markers available to guide such clinical decision-making. Typically, the benefit-risk ratio is anticipated to shift towards more intensive and higher-risk interventions in later stages;
- is designed to be dynamic, in that understanding of an individual's clinical trajectory should change as more clinical and neurobiological information is acquired. Thus, the adoption and application of staging should itself encourage more indi-

vidualized assessment and systematic longitudinal tracking over time;
- promotes the measurement-based tracking of individual trajectories. However, individual trajectories need to be differentiated from the broader concept of clinical stages, with the step-wise nature of the latter being quite distinct.

Implications for research and service systems

Transdiagnostic staging in youth mental health:

- needs to formally test the assumption that multidimensional staging models are an advance over simpler unidimensional models of illness course (which track severity, duration, persistence or recurrence);
- is best developed in naturalistic clinical cohorts that are recruited from services with broad (non-exclusive) entry criteria, in order to ensure inclusion of subjects with typically variable clinical courses, complex comorbidities, mixed risk factors, and multiple underlying pathophysiologies;
- is not simply focused on preventing one DSM/ICD-defined exit disorder[18,48]. As illness processes develop, they rarely result in one simple or single outcome. In fact, disorders often gain complexity, due to secondary complications of the initial illness processes (biologically and socially), and comorbidities with other conditions. Studies should, therefore, be designed to measure and record outcomes against a multidimensional framework that includes multiple forms of potential disease extension. These factors should be captured and documented independently of the primary diagnosis assigned by clinicians[1];
- does not simply identify a threshold at which "discrete", traditionally diagnosed disorders appear (see Figure 1, thick horizontal line). Instead, this stage signals the developed need for intensive clinical care (based on severity and functional impairment) in addition to secondary prevention measures. Over time, improved data quality and analyses will better indicate the clinical profiles, and neurobiological characteristics, of transdiagnostic illnesses at this stage and later;
- is likely to be of more limited utility in narrow cohorts that are pre-selected based on:
  a. specific symptomatic or syndromal characteristics that are used to define current illness outcomes (e.g., psychotic or manic-like experiences);
  b. risk factors that are likely to limit the breadth of outcomes (i.e., family history of major psychotic or mood disorder, offspring of parent with major psychotic or mood disorder);
  c. prior childhood-onset neurodevelopmental disorders;
  d. specific patterns of comorbidity (e.g., alcohol or other substance misuse).
- should attempt to validate hypothesized boundaries (i.e., pathophysiologically, neurobiologically, socially) independently of the clinical criteria (symptoms and signs) used to define membership of any specified clinical syndrome. For example, specific brain imaging, circadian, immune, metabolic or objective neuropsychological tests may differentiate one stage from another;
- can be used to assist in health system developments, particularly in early intervention and youth mental health. Here, the concept is clearly designed to assist with the process of appropriate allocation of care intensity, matched to current need and potential for progression to later stages;
- also needs to explore whether cohorts of young people, and their families and carers, experience higher quality, satisfaction and safety of care provision as a result of its application;
- requires a multidisciplinary youth mental health workforce to undertake clinical training and professional development in the understanding of the clinical staging framework, and its skill-based implications for assessment, intervention and care delivery.

KNOWLEDGE GAPS AND A FUTURE RESEARCH AGENDA

In the preceding text, we have provided background justification for the study and application of transdiagnostic clinical staging in youth mental health; described a multidimensional matrix including progression and extension that could catalyze further advances in this area; outlined principles and core operational parameters around which transdiagnostic staging can be organized; and argued for the close collaboration between research, service design and provision, and implementation science.

Indeed, this articulation of an approach to clinical staging that captures the key dimensions of disease progression and extension emerges alongside a new wave of clinical research infrastructures that combine reduced-barrier services[49], an appreciation of the transdiagnostic course of mental illness in youth[5], and acknowledgment of the need for both traditional research projects[50] as well as attempts at implementation[51,52]. We now chart key issues that a coordinated agenda for transdiagnostic clinical staging in youth mental health can tackle over the coming decade, and how the community can work together to achieve this (Table 2).

First, other frameworks, including emerging empirically-derived or research systems[53,54], have also recognized challenges with prevailing diagnostic systems (DSM-5 and ICD-10/11, with their accepted course specifiers). Advances commonly promoted by these frameworks (in addition to staging) include: a) recognition of the dimensional and/or transdiagnostic nature of characteristic (e.g., psychotic, manic or depressive) symptoms; b) use of agnostic clustering methods; or c) testing and subsequent inclusion of specific pathophysiological hypotheses (e.g., neurodevelopmental disorders, circadian-based disorders, immune-metabolic disorders).

Moving forward, the focus for staging models should be to demonstrate that this framework can produce genuine advances in clinical practice and service organization: specifically, its ability to identify and promote improved clinical outcomes, en-

Table 2 Cross-cutting issues in transdiagnostic clinical staging for youth mental health

	Principle/Assumption	Operationalization	Implications
Service infrastructures	Transdiagnostic clinical staging does not simply aim to stage within or across traditional, symptom- or impairment-based diagnoses.	Clinical infrastructures undertaking transdiagnostic staging need to have broad intake and exit points and provide continuity of care for those with ongoing need.	Research and service systems need the ability to follow individuals longitudinally and across current diagnostic silos. This may also require the ability to reach across service silos in more complex systems of care with multiple layers.
Cohort design	Clinical staging is based on the tracking of help-seeking rather than community-based cohorts.	Non-help seeking (i.e., community- or population-based) subjects may not experience or receive clinical interventions and are unlikely to reflect actual help-seeking populations.	Studies of staging need to be tightly linked with functioning clinical services and systems.
Stage assessment and review	Assignment of stage is linked to disease progression and extension.	Infrastructures that purport to undertake transdiagnostic clinical staging need to capture multidimensional outcome measures in order to determine stage at the point of assessment and at regular points throughout care.	Youth mental health service structures must more effectively embed routine outcome monitoring using standard assessments and apparatus within their infrastructures.
Defining stages	Transitions from one stage to another are associated with a step-wise deterioration in a relevant indicator.	Agreement must be established as to what constitutes a sufficient change or threshold for deterioration that is recognizable as a change in stage or a cut-point.	For alignment and (ideally) collaborative research studies to be undertaken, a process is required to generate and agree on clear criteria and validation.

hanced choice of treatments, personalization of care and prognostic predictions. We also believe that this further development of clinical staging in young people can eventually be extended to other developmental stages along the life course (e.g., early childhood, late-life emotional and cognitive disorders). In doing so, this elaboration would need to incorporate other key features, such as age and developmentally-dependent cognitive capacities. In children, these would include neural, social and communication development, while in older adults this would include classical neurocognitive abilities.

Second, even while some degree of predictive validity for clinical staging exists for illness paths such as early phases of psychosis[55], the evidence relevant to other possible paths remains limited. Additionally, while various cohorts have generally been followed for illness progression (measured by symptom severity, persistence or impairment), only rarely have they included elements of illness extension (within or across stages). New studies need to incorporate a multi-dimensional framework that captures additional outcomes of interest, including neurocognition, social and occupational functioning, and neurobiological measures (see Figure 1).

A longer-term goal is to develop methods for studying staging models that have the capacity to evolve and to integrate emerging evidence from across these many dimensions. If staging is to have utility for treatment selection, data collection regarding the effectiveness of interventions and secondary prevention should include information regarding both the population being studied as well as indicators of relative risk and benefit.

Third, the complex relationships between mental health conditions that emerge in youth (adolescence or young adulthood) and those that emerge in childhood remain open to further examination. For example, it is still unclear whether childhood-onset disorders (e.g., separation anxiety, ADHD, conduct disorder, autism spectrum disorder, or childhood-onset bipolar disorder) should be treated as a separate track of early life neurodevelopmental conditions in their own right, whether they are better thought of as risk states for youth-onset conditions, or both. Studies that aim to demonstrate advantages and disadvantages of such approaches are urgently required.

Fourth, staging and its application in research settings and service systems will undoubtedly benefit from the perspectives of multiple stakeholders – particularly those who are directly affected, such as youth and their families and carers. Such input could range from issues as broad as diagnostic terminology (e.g., the impact of telling individuals that they are experiencing "non-specific symptom sets", "risk states" or "risk syndromes") to the effectiveness and tolerability of specific interventions or service platforms. This will enable researchers and practitioners to better understand and adapt the acceptability of this approach to the needs of people with lived experience, including awareness of relevant factors such as gender, age and ethnicity. Given the early stage of development of clinical staging, and the goal of accelerating its integration into real-world practice settings and overarching clinical infrastructures, the involvement of such stakeholders, as well as research and implementation evaluation in this area, is critically needed.

Fifth, the rapid spread of digital (mobile and communications) technologies in mental health can be harnessed. These technologies now include a wide range of highly-personalized (passive and active) mobile sensors and apps that can capture

subjective and objective data on repeated occasions. Along with relevant e-assessments, these technologies can now be integrated within more sophisticated clinical research infrastructures[56-58]. International collaboration around definitions and nomenclature involved in staging is urgently needed in order to design studies that capture such data (using novel technologies and sensors) that can facilitate comparing and contrasting findings[59-61].

Sixth, it is highly likely that data from prior, ongoing or completed studies can be used to address priority areas or research questions around clinical staging. Funding agencies may choose to support this as a short-term goal, while attempting to organize the research community around the longer-term agenda described above.

Finally, building on this first international consensus statement, we propose the creation of an International Working Group on Transdiagnostic Clinical Staging in Youth Mental Health. In an effort to promote clinical staging, to determine clear criteria for transitions from one stage to another, to ensure consistency in their application, and to facilitate a base of research-service collaboration around transdiagnostic clinical staging, this Working Group will convene – beginning in 2021 – workshops and satellite meetings at the International Association of Youth Mental Health and Intervention in Early Psychosis Association conferences, which run in alternating years. The development of staging models will also require the continuing engagement of young people and their families and carers.

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The role of countertransference in contemporary psychiatric treatment

The concept of countertransference has undergone considerable change since Freud first proposed it in 1910. At that time, he conceptualized it as an obstacle to be overcome. In essence, it was viewed as the doctor's transference to the patient. The doctor unconsciously experienced the patient as someone from his/her past.

However, as the term evolved in clinical usage, its meaning was broadened. The implication suggested by P. Heimann in 1950[1] was that the doctor's total emotional response to the patient is not simply an obstacle or hindrance based on his/her own past, but rather an important tool in understanding the patient's unconscious world.

D.W. Winnicott[2], writing at about the same time as Heimann, also argued for the usefulness of countertransference. He noted that therapists often react to patients in the same way that others do. Certain patients can be so contemptuous that everyone with whom they come in contact, including the therapist, may respond with negative or even hateful feelings. He made the point that this hateful reaction had much less to do with the therapist's own personal past or intrapsychic conflicts. Rather, it reflected the patient's behavioral strategies and the need to evoke specific reactions in others.

Clinicians of all persuasions accept today the idea that countertransference can be a useful source of information about the patient. However, at the same time, the therapist's own subjectivity is involved in the way the patient's behavior is experienced. Hence, there has been a movement in the direction of regarding countertransference as a *jointly created* phenomenon that involves contributions from both patient and clinician. The patient draws a therapist into playing a role that reflects the patient's internal world, but the specific dimensions of that role are colored by the therapist's own personality[3].

The implications are that the patient may project some aspects of his/her internal world into the therapist, and the therapist may react as though he/she has been "taken over" by the patient. Generally known as projective identification[3,4], this mechanism is pervasive in clinical practice, whether the clinician is a psychotherapist or not. It can be understood in three steps: a) an aspect of the patient's self (or an internal representation of others) is projectively disavowed by the patient and unconsciously placed in the therapist; b) the patient exerts interpersonal pressure that coerces the therapist to experience or unconsciously identify with what has been projected; and c) the recipient of the projection processes and contains the projected contents and helps the patient take back, in modified form, what has been projected.

A simplified clinical example of this phenomenon is the following: the patient may have had a harsh and critical father and carries an internal representation of that father within. If he has a male therapist, he may experience him as having similar characteristics when the therapist asks him to say whatever comes into his mind. The patient, who may hear the therapist's request as an order, may become defiant and say that he is not going to talk about what is in his mind. The therapist may at first be calm, but over time grow irritated with the patient's refusal to cooperate with the process. At some point, he may say: "You are not doing what I have asked you to do!". In this second step of projective identification, the therapist has become very similar to the patient's own father and produces a reaction in the patient, who might reply: "I feel you are scolding me. I don't think you are behaving very professionally". In this third step of the process, the patient himself takes back the hostile internal representation of his father after the therapist has expressed his irritation.

The most important point in this example is that projective identification and countertransference often reflect the patient's attempt to evoke feelings in the therapist that the patient cannot tolerate. The patient attempts to nudge the therapist into behaving in a manner that corresponds to what the patient is projecting. Most clinicians would argue that the therapist is inevitably influenced to some degree by whatever the patient is projecting. There is an ever-present risk that the therapist may confuse his/her own feelings with those of the patient. It is important to clarify in this context that the countertransference jointly created by patient and doctor will vary from one clinician to the next. The therapist's experience of important people in his/her life has also been internalized and interacts with whatever is projected into him/her by the patient. Hence, there are variations from one therapist to another depending on how the combination of the patient's projection and the therapist's internal world interact.

When the therapist responds in a way that reflects influence by the patient's projection, this is often referred to as a countertransference enactment. In other words, the therapist is enacting something that originated in the internal world of the patient. It is generally accepted that the countertransference enactment may have valuable aspects that can be discussed between patient and therapist.

In the Menninger Treatment Intervention Project[5], audiotaped transcripts of psychotherapy with patients who had borderline personality disorder were studied by a team of researchers, revealing numerous examples of these enactments. For example, in one case, the patient repeatedly threatened to quit the therapy. The therapist responded by verbally pursuing the patient and insisting that he felt she was not ready to terminate. So, there was a partial transference gratification produced by the countertransference enactment by the therapist: the patient experienced it as a sign that the therapist cared about her and was engaged in trying to help her find a way to continue treatment. The countertransference enactment also sent the message that the patient was treatable and could be helped by the process. The patient ultimately stayed for two years of therapy and was rated by independent assessors as considerably improved.

In recent years, with the demise of the "blank screen" stereotype, virtually all clinicians acknowledge that occasionally mak-

ing self-disclosures of what they are feeling can be helpful to the treatment process. It is common knowledge that therapists are disclosing things about themselves whenever they are choosing to comment on a particular aspect of what the patient is saying. However, these inadvertent self-disclosures are not the same as specific technical interventions designed to allow one to use the countertransference constructively.

In *some* treatments with *some* patients, self-disclosures may be constructive. Therapist's feelings are often apparent to the patient and to deny them would be disingenuous. If the patient sees that the therapist is upset and asks "Are you angry?", the therapist might, for example, say "I think you are accurately detecting some of my feelings, and I hope we can understand what is happening here to make me irritated". Direct self-disclosure of countertransference feelings is often contrasted with containment of those feelings that ultimately lead to interpretation and understanding. In the reality of clinical practice, containment and self-disclosure are by no means mutually exclusive and often work together synergistically.

Countertransference has moved to the heart of psychodynamic technique. It has evolved from a narrow conceptualization of the therapist's transference to the patient to a complex and jointly created phenomenon that is pervasive in the treatment process. Much has been made about the "fit" between patient and therapist, and countertransference is largely determined by that fit.

A clinician must remember that enactments involving countertransference provide valuable information about what is being re-created in the therapeutic setting. In this regard, therapists are wise to recognize that they will be drawn into various roles in the course of the therapy, and that maintaining an artificial aloofness is neither desirable nor helpful.

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Psychotherapy supervision: an ever-evolving signature pedagogy

Psychotherapy supervision has been rightly recognized as one of the key signature pedagogies of psychiatry and other mental health disciplines[1]. Signature pedagogies refer to those characteristic forms of teaching and instruction that organize how future practitioners are educated with regard to three dimensions of professional work: to think, perform, and act with integrity[2].

Psychotherapy supervisors foster development of treatment-facilitative habits of head (knowledge), habits of hand (skills), and habits of heart (attitude/values). Much as clinical rounds serve as the signature pedagogy for medical education, psychotherapy supervision serves as the signature pedagogy for psychotherapy education.

Since its formal inception nearly a century ago, supervision has been increasingly recognized as highly important for, even *sine qua non* to, the optimal learning of psychotherapy. Nagging, inhibiting myths about its practice (e.g., "If I have experienced supervision as a supervisee, then I am qualified to be a supervisor") have been exposed as erroneous, and a guiding ethos of supervision as a competency-based, evidence-based area of practice in its own right has emerged prominently[3]. Perhaps supervision's current status and future directions might best be captured by means of the following ten points.

First, although a host of supervision definitions has been put forth, they all converge on some core features. Psychotherapy supervision typically involves senior, professionally approved supervisors formally providing relationship-based, treatment-focused psychotherapy education and training to junior colleagues/trainees about their ongoing therapeutic work[4,5].

Second, supervision's primary purposes are: developing and enhancing supervisee conceptual/treatment skills; developing and crystallizing the supervisee's sense of identity as a psychotherapist; developing the supervisee's conviction about the meaningfulness of psychotherapy itself; and monitoring supervisee treatment efforts and safeguarding patient care[1,4,5]. Thus, supervision is fundamentally normative (assuring quality control), formative (facilitating supervisee development), and restorative (encouraging supervisee emotional processing and attending to supervisee well-being).

Third, the primary perspectives of supervision practice are psychotherapy-focused, developmental, and social role/process[1,4,5]. Psychotherapy-focused supervision perspectives are oriented around a particular form of psychotherapy and its learning; the supervision process is uniquely stamped by the psychotherapy being learned. Developmental supervision perspectives give focus to the developmental stages and issues that define the growth experience of the evolving therapist and the supervisor's facilitative responsiveness to the developing supervisee. Social role/process perspectives place focus on supervisees' evolving learning needs and the supervisor roles that most responsively match those evolving needs.

Fourth, the chain of change in psychotherapy supervision follows a logical progression. Through meeting and melding of their person/personhood, supervisor and supervisee build a constructive supervisory relationship, that makes supervisor intervention possible, that then contributes to supervisee development, that then accordingly contributes to patient development[6,7]. Each variable in the chain builds on and is made a more likely reality by its predecessor's realization.

Fifth, all supervision perspectives have come to increasingly grant primacy of place to the supervision relationship. This is now

roundly recognized as a robust contributor to, and potential potentiator of, supervision's unfolding process and outcome[7,8].

Sixth, the primary trans-theoretically applicable components of psychotherapy supervision are case conceptualization, teaching/instruction, modeling, providing feedback, asking reflection-purposed stimulus questions, and discussion[8].

Seventh, conceptual contributions and empirical study identify the earliest period of therapist development as being the most troubling, a time of particularly heightened supervisee vulnerability[9]. Beginning therapists tend to have limited skills, lack a sense of therapist identity, feel like an impostor, and can question their very fitness to serve. Heightened supervisor sensitivity to and support of the vulnerable supervisee may be most crucial at this pivotal juncture. According to the International Study of Development of Psychotherapists, a beginning supervision experience characterized by *healing involvement* is developmentally critical[9].

Eighth, supervision has increasingly become a multi-culturally minded endeavor. All supervision in some respects is a triadic multicultural relationship. Thus, such variables as gender, race/ethnicity, sexual orientation and religion/spirituality, readily affecting the treatment experience, also readily affect the supervision experience. Supervisors ideally strive to understand the myriad ways in which that is so and make the multicultural an integral part of the supervision process[1,4].

Ninth, supervision research has advanced considerably since its inception in the late 1950s. Data across a host of studies indicate that supervision works, at least for supervisees, contributing to such positive outcomes as enhanced treatment knowledge, skill development/enhancement, and heightened self-awareness[9]. But supervision's impact on patients, referred to as the real effectiveness acid test, has yet to be definitively investigated and remains a most pressing accountability issue. Other identified limitations of supervision research (e.g., small sample sizes, over-reliance on self-report measures) also require redress going forward[9].

Tenth, psychotherapy supervision's significance as a vital educational practice is internationally recognized more so now than at any time in its 100 year history[4]. Supervision has gone global, a reality that seemingly will become even more heartily evident in the years and decades ahead.

No longer viewed as an ancillary, expendable practice, psychotherapy supervision's time has come. It is now rightly recognized as one of the key signature pedagogies of the mental health disciplines, educational *sine qua non* for, and grand facilitator of the psychotherapist development process. Just as "there is nothing so practical as a good theory", there is nothing so positively practice affecting as a good psychotherapy supervisor.

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The unified protocol for transdiagnostic treatment of emotional disorders

Broadly defined, the fields of psychotherapy and psychopathology have been with us for well over 100 years, but in recent decades substantial paradigm shifts have occurred. In particular, classification of mental disorders shifted from a global set of descriptors based almost entirely on theoretical conceptions to a more atheoretical empirically derived and more narrowly construed set of criteria, resulting in a substantial increase in the total number of disorders.

Paradigm shifts such as this often produce a substantial surge in research, which was indeed soon evident. In addition to ramping up research on neurobiological and cognitive bases of various disorders, these new more precise descriptions of psychopathology led to operational definitions of disorders as dependent variables. This development resulted in well-defined clinical trials typically evaluating either drugs or very specific psychological treatments targeted to the main features of each disorder[1].

These outcomes were seen as positive by most clinical scientists and, in the years following, enabled a closer look at commonalities among disorders, differences that define the disorders, and response to treatment. This was particularly true for a class of disorders we have come to refer to as "emotional disorders"[2], comprising anxiety, depressive, and related disorders that constitute what used to be called the "neurotic spectrum". Clinical scientists came to discover common neurobiological mechanisms underlying emotional disorders, and a hierarchical structure with dimensions of temperament at the top of the hierarchy, specifically neuroticism or negative affect and extraversion or positive affect[3].

Based on this research, we developed a single "transdiagnostic" treatment that no longer focuses directly on what we now regard as trivial symptomatic differences among disorders such as panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, and depression, but rather targets their shared temperamental core[4]. Thus, the term "transdiagnostic" does not, in our view, simply refer to a treatment thought to be applicable across a wide range of psychopathology, as was true for old "schools" of psychotherapy, but rather to an intervention that tar-

gets specific psychopathological mechanisms (e.g., neuroticism) shared across a defined class of disorders[2].

The unified protocol for transdiagnostic treatment of emotional disorders (UP) is an emotion focused cognitive-behavioral intervention consisting of five "core" modules or components based on cognitive behavior therapy (CBT) elements of proven effectiveness that target negative emotionality and aversive reactions to emotions when they occur. These modules are preceded by an introductory session that reviews the patient's presenting symptoms and provides a therapeutic rationale, a module on motivational enhancement, and a module focusing on psychoeducation about emotions. A final module consists of relapse prevention[5].

As the treatment proceeds, the domains of thoughts, physical sensations, and behaviors are each explored in detail, focusing specifically on elucidating dysfunctional emotion regulation strategies that the patient has developed over time within each of these domains, and teaching patients more adaptive emotion regulation skills.

The UP has accrued substantial support for its efficacy in the treatment of anxiety and depression. In fact, a recent systematic review and meta-analysis examined 15 studies with a total of 1,244 participants and found large effect sizes across studies for symptoms of anxiety and depression when UP was delivered in both individual and group format[6].

Following two small open trials and an initial randomized controlled trial comparing the UP to a waitlist control condition, our group conducted a large randomized controlled equivalence trial (N=223) comparing the efficacy of the UP to established single-disorder protocols (SDPs) and a waitlist control condition. The UP was equally effective as SDPs in reducing symptom severity ratings across disorders, as well as decreasing symptoms of anxiety and depression, both at the end of treatment and at 6-month follow-up[7]. In addition, the UP condition exhibited lower rates of attrition over the course of the study.

Meanwhile, other researchers have examined the efficacy of the UP in both individual and group contexts globally, including countries in South America, Asia and Europe. In general, these studies have also found the UP to be efficacious in the treatment of emotional disorders. While all humans experience emotions, culture can impact the messages one receives about the experience and expression of emotions, and the relevance of emotion regulation. Given that the majority of research has been conducted in Europe and the US to date, further research in other global contexts is warranted.

As with any CBT, cultural competence is critical when using the UP. A promising recent pilot study conducted in Japan with the UP found significant reductions in symptoms of anxiety and depression that were large in magnitude[8]. The authors did not find any difference in emotion suppression from pre- to post-treatment, which they state is consistent with existing literature showing a lack of association between suppression and psychopathology in Japan, and may represent an important cultural difference to consider when delivering the UP. In another example, the UP has been adapted to fit the uniquely broad spectrum of cultures, education levels and backgrounds of victims of Colombia's armed conflict[9].

The UP has been translated into numerous languages, including Chinese, Dutch, German, Japanese, Korean and Spanish. An Internet-delivered version of the protocol has recently been developed.

In summary, the UP provides a transdiagnostic psychological treatment that targets shared underlying mechanisms of all emotional disorders, thereby offering a single treatment that can be used across the most common clinical presentations. This treatment is equally effective as gold-standard SDPs, but may confer additional benefits with regard to efficiency, dropout, and training therapists.

Given the unmet global demand for mental health care, combined with the lack of clinicians trained in evidence-based treatments, we believe that transdiagnostic treatments are the future of mental health care, and represent one approach to increasing access to evidence-based care and impacting global mental health.

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Can we help more?

Before you read this essay, you need the benefit of informed consent. Reading it could make you anxious, somewhat uncomfortable, and perhaps a bit provoked – in the sense of activating your intellect and triggering your social conscience. If acceptable, please read on.

If possible, ask someone to read this piece to you. Settle in to a relaxed, seated, upright position. If comfortable for you, close your eyes. Clear your mind. Focus on your breath… breathe in and out… breathe deeply. Settle down and get ready to imagine something important to the fields of medicine, psychiatry, be-

havioral and public health.

Imagine that you suffer from a potentially fatal, often chronic, mostly recurrent disease that affects your health, interpersonal relationships, job, finances, and overall well-being, including your ability to identify, think through, and solve problems. Picture several of your family members and friends also suffering with this disease. Realize that 322 million people worldwide live with this disease[1]. Grasp that this illness is the most significant contributor to non-fatal loss of health worldwide[1]. Appreciate that annually the disease results in 50 million years of living with disability and contributes to 788 thousand deaths[1].

Envision that you engage in a treatment for three to four months with about a 50% chance of improving your symptoms and your functioning[2]. Imagine that, if this treatment worked well for you, the chance that your symptoms would recur is significantly reduced, compared to the alternative treatment most often prescribed to adults with your symptoms[3]. Note that, in fact, if most of your symptoms are absent (i.e., remitted) for the final six of the 12 to 14 weeks of therapy, then you are not likely to experience a recurrence for about a year[4].

Is this a treatment that you would seek and want readily available for others (like you) throughout your local community? If you fund research, would you want to understand the parameters of this treatment? If you work in the scientific industry, would you want to know how to "assay" this treatment, learn how to package it? If you are the lead executive of a university technology transfer office, would you be interested in working with a knowledgeable researcher on products with the potential to disseminate this resource? If you are chairperson of the board of a start-up company, would you be seeking investors to brand, market and disseminate this treatment based on what people will really use? If you run a health system, would you want to assure that this treatment was accessible to all your providers and patients? If you are responsible for educating the next generations of clinical providers, would you assure that your graduates could provide this therapy at an optimal level with the ability to personalize it for each individual in need? If you work in global health, would you be looking for technologies to improve access for such treatment?

What is this disease? What is this therapy? The disease is major depressive disorder. The depression-specific treatment is cognitive-behavioral therapy (CBT). With your eyes closed, continue to breathe in and out, with repetition, as your visualization may become clearer, perhaps more embellished and full now that you have a context for your images.

Appreciate that most depressed adults, especially those who are female or young, prefer psychotherapy to antidepressant medications[5]. Despite their preference, most adults instead receive prescriptions for those medications[6]. Not surprisingly, less than half of adults adhere to these prescriptions[6]. Even fewer adults seek any treatment for depression[7]. Those who prefer psychotherapy often have difficulty overcoming practical and perceived barriers to accessing CBT and other evidence-based psychotherapies[7].

As you continue to breathe deeply, understand that, currently, the mechanisms through which CBT achieves reductions in depressive symptoms and depressive relapse, and (perhaps) recurrence are not well understood. Consider that one possible mechanism is the extent to which patients comprehend and use the compensatory skills that they learn in therapy[8]. So, in order to achieve the full effect of CBT you will need to: have the critical skills presented, understand these skills, and use them whenever your mood becomes dysregulated and/or you have a significant problem or re-emergence of the symptoms comprising major depressive disorder.

Realize that there are several related forms of CBT that have been shown to prevent relapse after antidepressants or CBT in combination or alone reduce symptoms[9]. Picture, in your mind's eye, that high quality CBT can be readily available to any person with or at risk for major depressive disorder and related syndromes. How many depressive episodes would be prevented? In doing so, how much human suffering would be alleviated? How much money would health systems and taxpayers save? Would suicides and other deaths be prevented alongside depressive relapse and recurrence, as well as the associated disease burden to families?

What would happen if psychiatry, psychology, and related disciplines propelled a world-wide vision to recognize what is known today about psychological treatments that prevent depressive relapse, and ensure that the public (including patients, providers, and public health systems) could benefit? Picture a global vision to create new knowledge about mechanisms, parameters and dissemination that matches what is known and can be learned about effective psychological intervention to prevent first onset, relapse and recurrence using the approach that the people affected want. What if there is also access to such benefits? Suppose that we, as a field, have not only such a vision but, most importantly, also have the will to carry it forward. What are the next critical steps?

Count backward in your mind from five to one. Open your eyes. Return to your daily work, perhaps more alert, open, and committed to new opportunities.

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Developing competencies for the WHO mhGAP Intervention Guide Version 2.0 training package

Mental, neurological and substance use (MNS) conditions contribute significantly to global burden of disease, accounting for 10.4% of total all-cause disability adjusted life years (DALYs), and being the third leading cause worldwide[1]. The World Health Organization (WHO) has developed the mental health Gap Action Programme (mhGAP) to help close the treatment gap that exists in low- and middle-income countries (LMIC), through task-shifting care for MNS conditions to non-specialist health care providers[2].

The mhGAP Intervention Guide Version 2.0 (mhGAP-IG V2.0) includes evidence-based interventions for depression, psychoses, epilepsy, child and adolescent mental and behavioural disorders, dementia, substance use disorders, suicide and self-harm, and other disorders[2].

Training in the first version of mhGAP-IG demonstrated improvements in pre- and post-training knowledge testing, but with the need for ongoing supervision[3,4]. Feedback collected by the WHO requested more experiential learning; a focus on building skills; easier access to training materials; shorter training of six days maximum with post-training supervision, and the addition of clinician competencies.

This feedback has been incorporated into the updated mhGAP-IG V2.0 training package[5], which for the first time includes core competencies. Competency-based education uses outcomes to inform curriculum and assessment, involving the consideration of knowledge, skills and attitudes needed to perform a task[6,7]. For mhGAP-IG V2.0, these competencies tell us what non-specialist health care providers should be able to do in their clinical practice after training and supervision.

Competency development in health education is often a multi-step process involving literature review, looking for repetitive themes or ideas, and review by key stakeholders, before incorporation into curriculum and assessment[7]. The evidence-based mhGAP-IG V2.0 identified key aspects of practice, supplemented by recent literature on competency development for non-specialist health care providers treating MNS conditions in LMIC.

As a next step, core competencies were broadly identified. These included an attitude of respect and dignity towards those with an MNS condition, knowledge around identifying and managing priority MNS conditions, and accompanying skills to assess and deliver psychosocial (psychoeducation and basic supportive counselling skills) and pharmacological interventions. Additionally, mhGAP-IG V2.0 included the assessment and management of emergency presentations, performing follow-up, assessment and management of physical health, and referral and linkage to specialists and other sectors such as employment, education and social services. Each competency was then broken down to outline the exact tasks it requires, and standardized and mapped to each module of mhGAP-IG V2.0.

A common theme in competency development is achieving stakeholder consensus[7]. Initially, we reviewed the draft competencies with our mhGAP expert team, reaching consensus on these and adding the skill of effective communication. The skills of self-care and reflection were raised, but deferred for coverage in supervision. The competencies were then distributed for broader stakeholder feedback, including thought-leaders, partner organizations, and field experts. Once complete, the competencies fed into curriculum development and instructional methods in the training package.

Training to improve knowledge will be through group lectures and persons' stories of lived experience. Training to develop skills will be through interactive methods, including videos and multiple role-plays across assessment, management and follow-up scenarios. Attitude will be developed through the use of persons' stories, class discussion, and time for reflection and feedback.

Assessment can be defined as either formative, used to guide and motivate future learning, or summative, providing a potential barrier to practice if competency is not demonstrated[8]. In LMIC, summative assessment may exclude non-specialist health care providers who, with ongoing supervision, can improve their skills and treat large numbers of patients with MNS conditions, who would otherwise remain untreated. For this reason, the mhGAP-IG V2.0 assessment is only formative. Accordingly, instead of grading competency through traditional stages of novice through to expert[7], a more pragmatic approach was taken to focus on areas of strength and areas for improvement.

For ease and simplicity, all twelve mhGAP-IG V2.0 core competencies can be assessed using the same standardized form. The form outlines the exact tasks needed for each competency, is intuitive to use, suited to multiple settings, and can be kept by the trainee for future reference.

Competencies should be assessed by methods that are tailored for their specific purpose, with sound psychometric properties, practicality and acceptability[8]. The multiple methods across mhGAP-IG V2.0 training enhance competency assessment.

For knowledge assessment, multiple-choice questions show high reliability and easy administration[8], and familiarity to LMIC. A bank of questions has been developed, utilizing techniques to improve validity.

Skills can be assessed by using the multiple role-play scenarios available in the training package. These lack the formality and resource-intensiveness of observed structured clinical examinations, which have high reliability and validity in clinical skill assessment[8], but share similarities, such as instructions on discrete clinical scenarios, timing, checklists for candidate demonstration, and capacity for multiple role-plays to improve reliability and cover various skills. Role-plays also have the advantage of established acceptability in LMIC training settings[3,4], and can utilize peer assessment to manage limited assessor availability[8].

Finally, attitudes can be assessed using multi-method and longitudinal formats[8], involving role-plays, some multiple-choice

questions, and direct observation throughout the training program and supervision.

This variety of teaching and assessment methods ensures a truly blended training package that is more interactive and experiential. As competencies are a new addition to the mhGAP-IG training, principles of competency-based education for future trainers and supervisors are taught in the "training of trainers and supervisors" package[5]. The importance of ongoing supervision has not been overlooked, with inclusion of a participant logbook and multiple supervision options in the training package, to account for all resource settings[5].

The training package is now freely available online, to begin up-skilling the non-specialist health care workforce in LMIC[5]. Early feedback confirms usability of these resources. More rigorous field-testing may include improvements and retention seen on pre- and post-testing, and a review of validity and reliability, by correlating test results for participants, or between peer and trainer assessments. Such information will help future development of mhGAP-IG training material.

Developing core competencies for the mhGAP-IG V2.0 training package clearly outlines what non-specialist health care providers should be able to do after the training, with ongoing supervision. Core competencies break down the individual steps needed to be able to assess and manage priority MNS conditions, providing a framework for training and assessment. These are supplemented by the WHO's EQUIP: Ensuring Quality in Psychological Support, an initiative to develop and disseminate resources that support trained non-specialist health care providers to reach a standard of competency to be able to deliver manualized psychological interventions[9].

We hope that these materials will be valuable tools in the ongoing training of non-specialist health care providers in delivering care for MNS conditions.

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Anxiety and depression among general population in China at the peak of the COVID-19 epidemic

An epidemic of coronavirus pneumonia (COVID-19) throughout China has been occurring between 2019 and 2020. To combat the contagion, the Chinese government has implemented community-wide containment strategies such as home quarantine, business and public transportation shutdown, and class suspension for all schools. Psychological assistance has been offered to patients with COVID-19 infection and health professionals in Wuhan[1].

The effects of the COVID-19 epidemic and state-imposed massive quarantine on public mental health at the general population level have not been evaluated systematically. Our study aimed to examine the prevalence of anxiety and depression among China's adult population at the peak of the COVID-19 epidemic and identify the stressors associated with these disorders.

We performed a nationally representative online survey of Chinese residents aged ≥18 years through Wenjuanxing, a web-based survey company. A stratified sampling method was used, and the sample population was randomly distributed in all China's provinces and municipalities. Subjects with pre-existing psychiatric disorders were excluded.

A standardized questionnaire collected information on socio-demographic characteristics, time spent on news related to COVID-19 per day, and perceived sources of stress. The severity of anxiety and depression was assessed using the Generalized Anxiety Disorder-7 (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9), respectively. A cut-off total score of 8 was used for both GAD-7 and PHQ-9 to obtain the optimal sensitivity and specificity[2,3]. The protocols were approved by the Ethical Committee of Changzhi Medical College.

The sample size was calculated by assuming that the prevalence of anxiety and depression would be 4% in China[4]. This would require the sample size to be roughly 4,100 to achieve the margin of error of 15%. The survey was conducted between February 9 and February 16, 2020. We used descriptive statistics and Mann-Whitney tests or χ^2 tests for bivariate analysis. The associations between the above-mentioned variables and the occurrence of anxiety and depression were determined by multinomial logistic regression. All analyses were performed in Prism 8.3.

A total of 5,033 individuals (1,676 men and 3,357 women; 40.9% living in provinces with at least 220 coronavirus cases) completed the questionnaire (response rate: 78.1%). The prevalence of anxiety or depression or both was 20.4% (1,029 of 5,033). The median total score on GAD-7 was 10 (interquartile range, IQR: 9-14). The median total score on PHQ-9 was 9 (IQR: 8-13).

The occurrence of anxiety and/or depression was significantly associated with time spent on COVID-19 related news per day (odds ratio, OR=1.61, 95% CI: 1.42-1.84, p<0.001). The prevalence of depression and/or anxiety was 17.8% among those spending less than 5 min per day on COVID-19 related news, and 27.9% among those who spent more than one hour.

Three psychosocial stressors were significantly associated with the development of both anxiety and depression: "I worry about myself and my loved ones being infected by COVID-19" (OR=1.95, 95% CI: 1.54-2.49 for anxiety; OR=1.24, 95% CI: 1.04-1.50 for depression), "I worry about my income, job, study or ability to pay the loan being affected" (OR=1.38, 95% CI: 1.13-1.68 for anxiety; OR=1.58, 95% CI: 1.35-1.86 for depression), and "Home quarantine causes great inconvenience to my daily life" (OR=1.31, 95% CI: 1.04-1.64 for anxiety; OR=1.42, 95% CI: 1.18-1.70 for depression).

In summary, our study revealed that the COVID-19 epidemic caused a sharp increase in the prevalence of anxiety and depression among the general adult population in China, compared to the prevalence of 4% in 2019[4]. The amount of time spent on news related to COVID-19 was significantly associated with the occurrence of these mental health problems, which is likely explained by excessive media coverage[5].

The financial burden caused by massive quarantine was one of the primary stressors related to both anxiety and depression. Besides psychological interventions, financial aid such as wage subsidy, tax exemption, and extended loan repayment may help reduce the anxiety and depression in the general population.

Our study was conducted around the peak of the COVID-19 epidemic[6]. A longitudinal follow-up would be helpful to track the changes in anxiety and depression levels at different stages of the epidemic.

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Preventing suicide in the context of the COVID-19 pandemic

The impact of the COVID-19 pandemic on the labour market, as well as the government's response to mitigate risk via social isolation and quarantine, has resulted in the greatest and most rapid change in the employment sector ever recorded in the US. Notwithstanding emergency government financial response, it is anticipated that a significant percentage of the labour market will contract[1]. Moreover, the predicted increase in unemployment is expected to approximate, and perhaps exceed, that reported during the Great Depression lasting from 1929 to 1939 (i.e., 24.9%)[2]. The foregoing rapid rise in unemployment and associated economic insecurity is likely to significantly increase the risk for suicide.

In fact, during the most recent economic recession, a 1% rise in unemployment was associated with a rise in the suicide rate of 0.99% in the US (95% CI: 0.60-1.38, p<0.0001)[3]. Similarly, each percentage point increase in unemployment was accompanied by a 0.79% rise in suicide (95% CI: 0.16-1.42, p=0.016) in individuals 65 years of age or younger in Europe (e.g., Spain, Greece)[4]. During the 1997-1998 Asian economic recession, unemployment was a critical determinant mediating the increase in suicides in Japan, Hong Kong, and South Korea[5].

We used time-trend regression models to assess and forecast excess suicides attributable to the economic downturn following the COVID-19 pandemic. Suicide mortality was estimated for three possible scenarios: a) no significant change in unemployment rate (i.e., 3.6% for 2020, 3.7% for 2021); b) moderate increase in projected unemployment rate (i.e., 5.8% for 2020, 9.3% for 2021), mirroring unemployment rates in 2008-2009; and c) extreme increase in projected unemployment rate (i.e., 24% for 2020, 18% for 2021).

The annual suicide mortality rate accelerated in the US by 1.85% (95% CI: 1.70-2.00, p<0.0001) between 1999 and 2018. We found that a percentage point increase in unemployment was associated with an increase in suicide rates of 1.00% (95% CI: 1.02-1.06, p<0.0001) between 1999 and 2018. The suicide rate was 14.8 per 100,000 in 2018 (N=48,432).

In the first above-mentioned scenario (i.e., unemployment rate remains relatively consistent), the predicted suicide rates per 100,000 are 15.7 (95% CI: 15.3-16.1) in 2020 and 16.2 (95% CI: 15.7-16.8) in 2021. The foregoing suicide rates would result in 51,657 suicides in 2020 and 53,480 in 2021 (assuming 2019 population size of 329,158,518). In the second scenario (i.e., moderate increase in projected unemployment rate), suicide rates per 100,000 will increase to 16.9 in 2020 (95% CI: 16.4-17.5; N=52,728) and 17.5 in 2021 (95% CI: 16.8-18.2; N=55,644). This second scenario would result in a total of 3,235 excess suicides over the 2020-2021 period, representing a 3.3% increase in suicides per year (when compared to the 2018 rate of 48,432). In the third scenario (i.e., extreme increase in projected unemployment rate), suicide rates per 100,000 are projected to increase to 17.0 in 2020 (95% CI: 16.6-17.5; N=56,052) and 17.4 in 2021 (95% CI: 16.8-18.0; N=57,249). This rise in suicide rate would result in 8,164 excess

suicides over the two-year period, representing an 8.4% increase in suicides (when compared to the 2018 rate of 48,432).

What is especially concerning about our projections is the genuine uncertainty with respect to the labour market post-COVID-19, as well as the tremendous financial uncertainty and decrease in consumer sentiment, all of which are independent and additional contributors to suicide[6]. Moreover, social isolation and quarantine, which are critical viral transmission risk mitigation strategies, are recommended nation-wide. Social isolation is well established as a significant risk factor for suicidality[7].

Multiple studies have reported that government policy response can significantly mitigate the increased risk of suicide due to economic hardship and unfavourable labour market dynamics. For example, in Japan, a 1% per capita increase in local government expenditures was associated with a 0.2% decrease in suicide in the years following the 2008 recession[8]. The Japanese experience was replicated in Europe, wherein government spending, especially on social programs intended to mitigate suicide risk, significantly reduced projected suicides in Denmark[9].

Preventing suicide in the context of the COVID-19-related unemployment and financial insecurity is a critical public health priority. In addition to financial provisions (e.g., tax deferral, wage subsidy), investing in labour market programs that intend to retrain workers is warranted. Furthermore, government support for employers is critical to reduce the massive increase in unemployment and contraction of the labour market.

Proactive public-private partnerships that aim to provide psychological first-aid and psychiatric emergency services to persons at imminent risk of suicide are essential. Individual resilience enhancement strategies should be implemented (e.g., exercise, sleep hygiene, structured daily schedule, better diet). Approximately half of suicides in the US are committed with a gun; recommendations surrounding appropriate gun and ammunition storage are warranted. For persons with clinically significant depressive/anxiety symptoms or persons experiencing features of post-traumatic stress disorder or drug/alcohol abuse, timely access to comprehensive treatment should be part of the COVID-19 management strategy.

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Open access of psychological intervention manuals

Open science is a movement aimed at making research methodologies, protocols, tools, data, analyses and reports accessible as early as possible, to facilitate further research[1]. Open science of psychological treatments is an area that warrants special attention.

Psychological treatments for mental disorders are increasingly being investigated globally, with promising results[2,3]. This body of research has resulted in recommendations by the World Health Organization (WHO) on a range of psychological interventions, such as cognitive-behaviour and interpersonal psychotherapies, as first line treatment options for depression[4]. There is also substantial evidence that psychological interventions can be delivered effectively not only by specialist mental health providers, but also by general health staff and community workers, who are more easily available[5]. One would then expect that psychological treatment manuals underpinning these findings be readily accessible.

The psychological treatment manual is a key element of the research methodology, because it outlines the various aspects of the intervention, including the psychological techniques used, the number and duration of sessions, and the specific content details. The manual is usually carefully designed, revised after piloting, and possibly adapted to local context, before being used in randomized controlled trials (RCTs).

Papers on RCTs typically include a paragraph describing the treatment provided. However, such a brief description – in the absence of a manual – is insufficient for readers to implement the intervention or replicate the study. Also, the limited details often make it difficult to accurately understand the intervention and interpret the results of the study, which becomes a major challenge when conducting and interpreting meta-analyses of psychological interventions.

We reviewed a database of 27 trials investigating psychological treatments for common mental disorders delivered by non-specialist providers in low and middle income countries (LMICs)[3], in order to explore how many treatment manuals used in the studies were cited and how many were open access.

We defined a psychological treatment manual as a structured form of guidance (written material and instructions to be followed). Manuals were coded as being either generic (i.e., the manual was developed for a non-specific context and had to be adapted before use) or exact (i.e., the manual is exactly the one used). From an open science perspective, the exact manual needs to be accessible.

We operationalized open access of a psychological treatment manual as one of the following: a) the weblink to the exact man-

ual is included in the trial report; b) there is an explicit offer to make the exact manual available from the authors (with their e-mail address included), or c) the manual is available online so that it can be found without difficulties by searching its name. With respect to the last option, a search was undertaken by entering the name of the programme or the reference in Google search engine. A full version of the manual had to come up within the first 30 hits.

In 19 of the 27 trials, a manual was mentioned in the text of the report, while in the remaining eight there was no mention of the existence of a manual.

Focusing on the 19 trials for which a manual was mentioned, there were eight manuals that were referenced in the paper's bibliography. Six of the references were for the generic manual adapted for the study, while only two were citations of the exact manual used. Of the remaining 11 studies in which a manual was not referenced in the bibliography, six cited another paper as source for the manual but, when searched, that paper did not cite the manual. Four of 11 cited another paper that, when searched, cited a generic manual in the bibliography. Finally, one study cited another paper that, when searched, cited in turn a further paper that, when searched, revealed no citation for the manual. A flow chart summarizing these findings is available upon request.

When we investigated open access to psychological treatment manuals, no study was found to provide a direct weblink. Seven manuals could be found when using a Google search (of which six were generic and only one[6] was the exact manual used). Only in one study[7], access to the exact manual was offered via e-mail from the authors. Thus, out of 27 trials, a total of only two (7%) exact treatment manuals could be identified that met our definition of open access.

In summary, only two studies (7%) reporting results of a psychological treatment for common mental disorders in LMICs provided citations to the exact manual used in the study, and only two (7%) provided open access to the manual.

Access to treatment manuals for psychological interventions is important for the replication and independent scrutiny of study results and for the dissemination of effective interventions.

Change is not only needed but also feasible. For example, two relevant RCTs of psychological treatments were released around the same time of the systematic review[3] and were thus not included in our analyses. One included a reference to an online version of the exact manual used[8], and the other offered access to a linked training programme to learn the intervention[9].

Accessibility to treatment manuals is a key aspect of open science of psychological treatments. Mental health journals and research funders should consider setting up mechanisms that require authors of RCTs to make the psychological treatment manuals they used open access.

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Three questions to consider before developing a mental health app

Most people with mental health problems do not access treatment, and the world does not have enough mental health clinicians to fill this treatment gap. Recently, many scholars have argued that technology-based interventions have the potential to reduce the treatment gap[1].

As smartphone ownership is becoming nearly ubiquitous around the world, interventions delivered through smartphone applications have received particular attention. Additionally, recent meta-analytic findings suggest that smartphone-based interventions are effective for a variety of common mental health problems[2]. This growing enthusiasm has led many academic researchers, non-profit organizations, and companies to create their own mental health applications (MH apps). Indeed, there are over 10,000 commercially available MH apps, and new apps are being released at an increasing rate[3].

Given the clear potential of MH apps, it is not surprising that many teams are investing substantial time and resources to develop new ones. However, it is important to consider recent evidence suggesting that the reach and impact of most new MH apps is limited, with most engaging few users[4,5].

Here, we propose that the proliferation of new MH apps is often unnecessary, sometimes counterproductive, and often redundant with apps that already exist. We pose three questions that people should consider prior to developing a new MH app. We also present alternative options that can often meet the needs that new MH apps are meant to address.

The first question calls for a thorough examination of alternatives that are already available. In many cases, it is likely that existing apps are sufficient to meet the needs of users. Recent evidence shows that many publicly available apps include a variety of evidence-based practices – for instance, in the case of depression and anxiety apps, cognitive restructuring, behavioral activation,

self-monitoring, and mindfulness[6].

In many cases, researchers may benefit from using these publicly available apps rather than spending time and money "reinventing the wheel". In addition, several of these apps have demonstrated that they are able to attract users and keep them engaged, a significant accomplishment that a new app might have difficulty matching.

Many options exist to help investigators identify existing apps efficiently. These include analyses of the treatment content within publicly available apps[6], expert reviews of publicly available apps[7], and evaluation tools from professional societies such as the Anxiety and Depression Association of America (https://adaa.org/finding-help/mobile-apps) and the American Psychiatric Association (https://www.psychiatry.org/psychiatrists/practice/mental-health-apps).

To supplement these resources, investigators can conduct their own searches of app stores. Generally, the most engaging apps in a given category will appear in the first few search hits. Given that engagement is one of the greatest challenges in digital mental health, using apps that are already known to engage users is an advantage that cannot be overstated.

With this in mind, there are some specific cases in which new apps would be valuable. For example, in a recent review of publicly available apps for depression and anxiety, many apps included relaxation and meditation, yet only two apps included exposure, and none included problem solving[6]. Thus, while creating new MH apps may not be necessary for the majority of treatment elements, there are some important evidence-based techniques for which developing new MH apps is warranted.

In the event that available MH apps do not provide a suitable alternative, the next consideration involves thinking critically about an engagement plan. One takeaway from digital mental health research is that engaging users is extremely difficult. Dropout rates reported in trials of digital interventions tend to be high, and engagement outcomes are even worse outside the context of controlled trials[4]. For instance, over 90% of users discontinue using MH apps within a week of installation[4].

Furthermore, MH app developers often need to compete in a highly saturated market. Recent research suggests that the top three MH apps account for about 90% of active users, leaving most apps with zero active users[5]. These top apps generally have large teams of product designers, human-computer interaction specialists, programmers, marketers and advertisers. Indeed, performing adequate user testing often involves years of work by large interdisciplinary teams, requiring substantial financial resources[8].

Additionally, as a practical consideration, commercial apps must be regularly updated in order to maintain usability after updates to iOS and Android platforms, not to mention upgrading to maintain user appeal in a crowded market. This means that app developers need to plan and budget for regular updates and upgrades in order to stay competitive.

In many cases, investigators will lack sufficient resources or expertise to attract and retain users simply by releasing an app on the app store. Instead, alternative strategies (e.g., receiving referrals from medical centers) may be necessary to attract and retain users. In the absence of these plans, releasing a new MH app may be an unnecessary addition to an already crowded marketplace.

The third consideration is whether a smartphone app is the best digital platform to implement an idea. Sometimes, the purpose of app development is not to attract and retain thousands of users but rather to study a research question involving technology.

Developing a smartphone app may be unnecessary in these instances. Several online platforms (e.g., Qualtrics, jsPsych) can help people develop and disseminate web-based surveys and interventions. Web-based alternatives are generally cheaper to develop, easier to adapt, and more useful for prototyping. Additionally, tools and interventions created on such platforms are often sufficient to engage participants in the context of lab-based experiments and even interventions. As an example, a single-session (30 min) web-based intervention developed on Qualtrics was shown to reduce youth depressive and anxiety symptoms[9].

With this in mind, mobile apps have some important advantages over web-based platforms in specific circumstances. For instance, mobile apps may be useful for studies involving real-time sampling, the collection of passive smartphone data, reminders or notifications, and research designs that require instant communication with participants. However, outside the context of these specific cases, web-based platforms offer cheaper options that are easier to refine.

In conclusion, the perceived advantages of MH apps have led to enormous enthusiasm and considerable funding for the creation of new apps. However, given the wide array of competing MH apps, the challenge of attracting and retaining users, and the utility of web-based alternatives, we advise caution. A thorough consideration of the above-mentioned questions will lead many to conclude that a new MH app is not a worthwhile investment. Resources may be better spent to advance other key priorities in digital mental health, such as evaluating the effectiveness of existing interventions, determining for whom these interventions are helpful, and experimentally testing strategies to improve engagement.

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Neurocognitive deficits in schizophrenia are likely to be less severe and less related to the disorder than previously thought

Even according to Kraepelin's observations more than one hundred years ago[1], the term *dementia praecox* was an exaggeration, if not a misnomer. Not all of his patients showed signs of dementia, and a subgroup even recovered. Kraepelin also acknowledged that memory impairment, the core symptom of dementia, at times reflected lack of interest rather than faulty "impressibility of memory".

While the term was soon replaced by that of schizophrenia(s), the claim that the disorder is marked by global neurocognitive impairment lingers on. In fact, all major meta-analyses and reviews converge on the conclusion that patients with schizophrenia display large and global neurocognitive impairment, which many experts view as a core vulnerability factor for the disorder. Yet, the magnitude of these deficits – usually one standard deviation below the mean[2] – is far less than the extent of impairments seen in patients with primary dementia, which is inconsistent with the idea that schizophrenia is a (praecox) form of dementia.

We do not dispute that a large subgroup of patients show deficits on neurocognitive tests. Yet, we would like to emphasize that the degree to which these deficits can be attributed to schizophrenia itself is likely overestimated, whereas the degree to which they are due to medical and psychological factors that are often associated with schizophrenia, but that do not form part of the syndrome itself, has not been fully appreciated.

These two classes of bias at times overlap, but should be distinguished for heuristic purposes. Importantly, this distinction is not just an academic issue. It has significant implications for: a) understanding why many people with schizophrenia appear to be cognitively impaired; b) understanding why the extent of observable cognitive impairment in people with schizophrenia can fluctuate widely depending on the environmental and interpersonal context; and c) choosing interventions to address the impairment.

With respect to overestimation, an emerging literature indicates that poor performance is partly due to confounds during neurocognitive assessment. Most obviously, disorganization and derailed thinking, frequent symptoms in the disorder – especially under stress – may prevent proper understanding of task instructions and/or lead to avoidance of full engagement, with subsequent failure in more difficult tests.

Patients may also experience interference from symptoms such as hallucinations, rumination and delusional ideas during assessment, further distracting them from the task at hand[3].

Moreover, patients' motivation for assessment is often lowered, while anxiety and stress are higher compared to controls, and both of these factors are known to compromise performance[3]. According to Beck and colleagues[4,5], poor effort can explain one-quarter to one-third of the variance in test results.

So far, the role of stigma related to diagnosis remains elusive. However, defeatist beliefs, which are a common consequence of being labelled with the diagnosis of schizophrenia, are associated with poor performance[4,5].

Another potential source of bias that may contribute to an overestimation of deficits is the lack of representativeness of control participants. In some studies where psychiatric patients performed significantly worse than non-clinical controls, despite non-significant baseline differences on age or years of education, the performance of controls was in fact above average, rather than patients performing below average according to norm scores[6].

Apart from the aforementioned *state* factors compromising neurocognitive assessment, there are some conditions that can cause real and more lasting impairment, but do not reflect pathogenetic factors of schizophrenia. Perhaps most importantly, patients more often than controls suffer from obesity and diabetes (which can be independent of and/or related to treatment with antipsychotic medication) as well as cardiovascular disease (e.g., hypertension), and these factors compromise neurocognitive performance in both schizophrenia patients and the general population. In addition, hospitalization and loneliness have also been associated with poor neurocognitive performance[7].

One may argue that neurocognitive deficits were observed also in the pre-neuroleptic era and have been found even in at-risk individuals. However, the effects of, for example, defeatist beliefs (which are high in at-risk subjects, too) and hospitalization (at least in manifest patients) may have contributed to this.

Poor neurocognitive performance may also represent an epiphenomenon of perceptual problems[8]. Furthermore, patients are often prescribed anticholinergic medications (clozapine or drugs aimed to reduce extrapyramidal symptoms) that compromise attention and memory. Finally, motor side effects, which are common with first-generation antipsychotics but can also occur with second-generation medications, can reduce performance on timed tests.

Experienced neuropsychologists will be well aware of the aforementioned biases and confounds. In written individual reports, these may be acknowledged and perhaps even adjusted for. In group comparisons, however, these influences are traditionally ignored, as they are hard (e.g., motivation) or even impossible to control for (e.g., medication when the control group is not medicated at all).

We advise researchers to either control/adjust for these factors where possible, for example through mediation analyses[3], or to acknowledge possible sources of exaggeration of deficits in the abstract and discussion of their manuscripts. We also advise researchers not only to report mean values, but also the percentage of patients performing one and two standard deviations below the norm, to more fully describe the level of impairment in the sample. Often, only a minority of patients drives group differences that are then extrapolated to the entire population.

Some aforementioned biases resulting in overestimation of

deficits can be mitigated through creating a kind and motivating atmosphere during assessment[9]. In addition, it would help to test patients when distracting symptoms (e.g., hallucinations) are at a minimum. Change in medication might be sought, especially lower doses and minimization of drugs with anticholinergic properties.

Addressing lifestyle factors related to hypertension, obesity and diabetes (e.g., weight loss, physical exercise) may reduce neurocognitive-relevant somatic risk factors, and there is tentative evidence that such interventions indeed enhance neurocognition[10]. Future consideration of these factors may open new windows for therapy beyond cognitive remediation, the traditional way to enhance neurocognition.

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The practice of psychiatry in health care and sustainable development: progress on the WPA Action Plan 2017-2020

The founding of the WPA 70 years ago marked a movement towards an internationally valued professional identity and the description of a broad purpose for the Association: the advancement of mental health and psychiatry across the world.

Based on this remarkably modern statement of purpose that is elaborated in the statutes of the Association and evident in the work accomplished in its 70-year history, the WPA vision is "a world in which people live in conditions that promote mental health and have access to mental health treatment and care that meet appropriate professional and ethical standards, integrate public health principles and respect human rights"[1].

How the practice of psychiatry contributes to realizing this vision is the focus now: psychiatry as a discipline central to medicine and health care and vital to sustainable development in each country. We are working with Member Societies and partners to demonstrate how psychiatry can contribute to strengthening communities to meet mental health needs, especially for people living in adversity.

In common with a number of its Member Societies, the WPA now recognizes that advancement of mental health and the provision of appropriate and acceptable mental health services cannot be truly achieved without the involvement of service users and family carers. Their advice is needed on the actions proposed, including the development, implementation and evaluation of the care services, and advocacy at national and international levels.

The WPA has given priority in this triennium to best practice in engaging with service users and family carers. This builds on earlier work, when the Association established a taskforce on best practices in working with service users and family carers, which developed a set of ten recommendations for good practice[2]. This became the basis for a worldwide consultation of stakeholders, including the WPA officers and over 200 national and international civil society organizations. Several of the recommendations were included as a new paragraph in the Declaration of Madrid in 2011.

A service user and family carer advisory group to the President is now established. The purpose of this group is to revive and refresh the conversation with the range of people involved. M. Amering has agreed to coordinate the group, that includes four people with lived experience of service use and four people with experience as family carers.

The WPA Congress programs are an opportunity to bring this advisory group together to start a new phase of practical work, as at the World Congress of Psychiatry in Lisbon in 2019, and the forthcoming World Congress of Psychiatry in Bangkok.

As well as advising WPA on organizational and scientific aspects of its congresses, the initial focus of this work is participation in and advice to the WPA taskforce on minimizing coercion in mental health care[3]. This taskforce has been appointed and begun work. A workshop supported by the Royal Australian and New Zealand College of Psychiatrists was held in Melbourne in February 2020. It brought together the chairs of the taskforce, S. Galderisi and J. Allan, a representative from the service user and family care advisory group, and research and project consultants.

The workshop considered comments from the taskforce on a discussion paper developed over preceding months, and the design of case studies on programs that have supported alternatives to coercion and quality rights in various parts of the world. The taskforce will next ask Member Societies for comments on the discussion paper and develop the case studies.

The plan before the end of the triennium is to prepare a position paper with recommendations for action and an optional protocol designed to support Member Societies to engage with this work in ways that suit their local circumstances. The aim is to promote continuing work critical to the quality of mental health care for patients and their families, and support psychiatrists to contribute to practical ways of implementing the positive provisions of the United Nations Convention on the Rights of People with Disabilities.

The Lancet-WPA Commission on Depression[4] is finalizing its report and plans for dissemination of the messages and recommendations. The Wellcome Trust in London is continuing its support for the Commission and combining with the United Nations Children's Fund (UNICEF) to engage young people with lived experience of depression in the development of recommendations and the dissemination of the findings. The WPA is well positioned to have an important role in the afterlife of this Commission.

The program of work with young women and men in cities, especially those living with adversity, continues actively. The WPA, along with citiesRISE[5], has engaged in Chennai and Nairobi with local communities and professional groups – including the WPA Member Societies and their branches – to prepare psychiatrists and other practitioners for mental health work in schools and gathering places in informal community settings.

The WPA is actively engaged in planning and providing materials for these programs of work, especially support for psychiatrists and other practitioners to use their expertise to promote participatory approaches to health across these settings. In January 2020, the Association participated in a practice workshop for mental health professionals in Chennai, together with the Schizophrenia Research Foundation and citiesRISE, that demonstrated the eagerness of psychiatrists and other practitioners for this work. The workshop was over-subscribed, with local psychiatrists on a waiting list for the next edition. Strengthening perinatal mental health systems is an important related area of work with partners.

The use of technology and mental health is another important theme for the triennium, both in this program with young people in cities[6] and with the World Economic Forum (WEF), as well as through activities of the WPA Scientific Sections. As President of the WPA, I co-chair the WEF Global Future Council on Technology for Mental

Health, that convened at the Annual Meeting of the Global Future Councils in Dubai in November 2019.

Quickly developing technology will change industries, governments and societies in the future. The Council's mandate is to address the potential and pitfalls of these developments for mental health, particularly concentrating on youth suicide prevention. Its program for 2020 follows the report of its predecessor in 2018-19, which emphasized the need to outline ethical principles in using data and technology for early diagnostics and prevention of mental illness[7]. The WPA is positioned to contribute to constructive debate on these topics with Member Societies, service user and family care advisors, as well as other partners.

A range of other programs and projects that contribute to progress on the Action Plan is underway with support from WPA officers and components. These include our education, publications and scientific programs[8-11], and the meetings program, with the Regional Congress in St. Petersburg and the 20th World Congress of Psychiatry in Bangkok. The active work of many of the Scientific Sections, and the early career psychiatrists, is a tribute to the power of collective action[12-14].

Collaborative work with the World Organization of Family Doctors (WONCA) on competencies in mental health for family doctors, and a survey of the demography and training of psychiatrists worldwide are in progress through Member Societies and with the work of Secretary for Education R. Ng, the WPA Secretariat, and WPA consultants Community Works.

My colleagues and I in the WPA Executive Committee welcome the suggestions and engagement of our Member Societies as we endeavour to support psychiatry and its positive impact on mental health globally.

Helen Herrman
WPA President

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WPA educational initiatives: where are we after three years?

In the past three years, the goal of the WPA educational work has been to "promote education for all, no matter who you are, where you are and how you are". The targets of the educational work are service users and carers, medical students, primary care doctors, early career and experienced psychiatrists, mental health professionals, and WPA Member Societies[1].

The WPA has set up an advisory group of service users and carers[2], one of its roles being providing user-focused advice on the educational content of the upcoming WPA congresses and participating in various taskforces with an aim to enrich educational materials with service users' perspectives. Working with our service users and carers is extremely important for service quality improvement and also for creating a united voice to lobby national governments and fundholders to invest in mental health.

In order to enhance psychiatric education on recovery-based care, the WPA is working with several institutions in promulgating evidence-based educational materials for different stakeholders of mental health care[3,4].

Given the scope of mental health problems and the constraints of resources in training psychiatrists in most parts of the world, the WPA strategically focuses on enhancing psychiatric education for medical students and primary care doctors, both of which playing pivotal roles in increasing accessibility and acceptability of mental health care in most parts of the world.

The WPA collaborated with the International Federation of Medical Students (IFMSA), conducting a global survey on students' perspectives about the quality of undergraduate psychiatric education in their respective countries. The survey was published in *World Psychiatry*[5] and is freely available online for a wide readership. It enables the WPA to identify regions with pressing needs of undergraduate psychiatric education.

As a complement to this survey, another global endeavour was made which canvassed the wisdom of over 20 educational experts around the world to depict the current landscape of global psychiatric education. This collective wisdom will be crystallized in a publication to be freely available online.

Based on the findings of these academic activities, the WPA is now working closely with several Member Societies as pilot sites to conduct medical students' workshops to enhance their awareness of public and personal mental health. There will be an ongoing study to evaluate how these workshops can have an impact on the students' attitudes towards psychiatry and their stigma towards mental health issues.

As aforementioned, primary care doctors are our important partners of mental health care and shoulder key responsibilities in preventing and managing mental health problems in many parts of the world. The WPA is working closely with the World Organization of Family Doctors (WONCA) to identify possible areas of collaboration. A global survey was conducted to understand how senior psychiatrists viewed the primary mental health competencies developed by the WONCA for primary care doctors around the world. Based on the survey findings, the WPA and WONCA are

planning to develop mental health educational initiatives for medical students, medical schools and primary care doctors globally.

While recognizing the important roles of primary care doctors and other health professionals in providing mental health care, the WPA is fully aware that psychiatrists are key mental health service providers, trainers of other professionals, academic mental health researchers, as well as leaders and advocates of public mental health care.

In order to set a minimum global training standard that meets the above strategic role requirements, the WPA released a set of key recommendations on the postgraduate psychiatric curriculum. The Association is now conducting a global survey on whether national training curricula offered by Member Societies are meeting these recommendation standards.

Furthermore, the WPA is conducting a global survey on the demographic landscape of psychiatrists. These data will inform the Association on how to advise Member Societies on the national strategy for building up mental health capacity. They are also highlighting the shortage of training and education for many early career psychiatrists in different parts of the world. As such, pre-congress workshops with a focus on skill acquisition are now regularly offered hand in hand with WPA conference lectures and symposia providing updates in knowledge[6].

While conferences are ideal for intensive learning within a short period of time, many early career and trained psychiatrists in resource-constrained regions cannot afford the time and money to attend these academic events. Recognizing their learning needs, some of these educational materials will soon be available on the WPA website[7].

Besides, the WPA is now working actively with potential funding bodies to support and study the impact of early career psychiatrists after undergoing the one-year diploma course on international psychiatry developed jointly by the WPA and the University of Melbourne.

Apart from knowledge and skill acquisition, the WPA has also formed an international taskforce to develop a new volunteering programme to encourage early career and experienced psychiatrists joining hands to provide in-reach training to professionals working in under-served areas around the world. This programme also hopes to mobilize national experts from high-income countries to address national training and educational needs of WPA Member Societies in regions with underserved populations. Further work is now ongoing to delineate the relative functional and legal roles of the volunteers, the volunteer Member Societies, the host Societies and the WPA in the programme.

While these endeavours might sound promising and meaningful, they will not be beneficial to our stakeholders if they are not user-friendly, acceptable and accessible to them. In order to enable learners from different countries, especially those from underserved populations, to receive high-quality education, it is important to have a user-friendly and stable online platform for supporting these educational activities.

The WPA is now seeking educational grants from potential donors to set up a new learning management system. With such an online platform in place, high-quality teaching materials such as powerpoint slides with voices, webinars, and live video streams could be readily available[8]. Real-time training and supervision in the form of virtual classrooms and chat rooms can be set up to connect trainers and learners living in far end corners of the world.

In order to achieve our mission of providing education regardless of location, training experiences and professional backgrounds, the WPA needs the support of all Member Societies in responding to global surveys, nominating colleagues into different taskforces, participating in different educational initiatives, as well as giving feedback on the experience of participating in the development and the use of these educational resources.

Let us join hands to make the WPA a global learning organization, so as to equip our stakeholders with the proper attitudes, skills and knowledge to enhance global mental health.

Roger M.K. Ng
WPA Secretary for Education

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Mental health economics: bridging research, practice and policy

The WPA Section on Mental Health Economics focuses on economic factors in the provision, organization and use of services for mental and addictive disorders in countries across the world.

The Section was founded in 1998 and given permanent status approval by the WPA in 1999. By that time, a group of health economists had established the field of mental health economics, with substantial research knowledge about psychiatric practice and mental health policy.

Two primary aims of the Section are to encourage interdisciplinary research among psychiatrists, health economists and other mental health professionals, and to facilitate communication among those who finance, organize, provide and use mental health services.

Over the last three decades, clinicians have felt it increasingly necessary to become familiar with the conceptual frameworks of health economics and its applied research. This was considered necessary because economic analysis is an important part of how policy-makers and payers assess the recommendations of clinicians

regarding the need for more services or for funding research to develop new treatments. For example, in many countries, the government health system or commercial insurance decides whether to pay for certain types of pharmacological or psychosocial treatments based in part on economic evaluations of alternative treatment approaches such as cost-effectiveness analysis.

Over the years, several other issues have been addressed by the Section's official journal, *The Journal of Mental Health Policy and Economics* (www.icmpe.org); by its international biennial Workshops, and by its Symposia organized for WPA Meetings.

The first research topic in mental health economics has been to document the economic burden of mental disorders. Over time, the World Health Organization (WHO)'s Global Burden of Disease Study has refined the methodology, and identified mental disorders as a major contributor to the global burden of disease[1]. It has been also pointed out that, in the case of schizophrenia, a large portion of societal cost is due to lost worker productivity[2].

A further activity has been the assessment of the cost-effectiveness of different treatment approaches. For example, some economic analyses concluded that atypical antipsychotics delivered little or no additional health benefits, despite their substantial additional cost[3]. This work has involved adapting measurement and statistical approaches to some specific features of mental health system data.

Another research focus has been the lack of parity in how health systems finance mental health compared to other diseases. In the US, parity refers to attempts to equalize insurance coverage of mental disorders to coverage of other care, and many papers have examined these attempts[4]. These studies provided the evidence to policy-makers for supporting the economic feasibility of the Mental Health Parity and Addiction Equity Act (2008). Elsewhere, broader inequalities in resource allocation and related clinical outcomes have also been documented[5].

The role of financial incentives in influencing decision-making concerning mental health treatment has also been investigated. Examples include incentives around how providers are paid and what consumers are expected to pay themselves[6]. Currently, in the provider payment area, researchers and others are designing payment approaches that reward value, not just volume of inpatient and outpatient services, and developing performance measures appropriate to mental health treatment. For instance, the research paper that won the 2019 Willard Manning Award presented by the Section's journal focused on costs and performance of mental health providers[7].

Most recently, several studies are considering the determinants of individuals' mental health. Some projects examine how mental health treatment use is affected by government or commercial insurer policies[8]. More broadly, researchers are studying how individuals' mental health is influenced by several social determinants, including macroeconomic conditions[9].

Since 1999, the WPA Section on Mental Health Economics has organized Symposia at the World Congresses of Psychiatry and International WPA Meetings. The topics of these sessions concentrated on important policies and practices, such as the financial consequences of deinstitutionalization (Yokohama, 2002); the cost-effectiveness of depression interventions in developing countries (Cairo, 2005); the economic case for prevention strategies in mental health (Prague, 2008); the impact of national health reforms on adults with mental disorders (Buenos Aires, 2011); predictors of clinical treatment choice (Madrid, 2014); treatment choice in adolescent depression (Berlin, 2017); and hospital payment and inpatient psychiatric readmissions (Lisbon, 2019).

The Section also holds biennial Workshops on Costs and Assessment in Psychiatry. The next Workshop is scheduled for the Spring of 2021 in Venice, Italy. The topic is Mental Health Services, Economics, and Policy Research. Abstracts of papers presented at the Workshops are disseminated through supplements to *The Journal of Mental Health Policy and Economics*. This is a quarterly peer-reviewed indexed journal. It publishes applied research using advanced economic and policy analysis methodologies.

The Section's current international, interdisciplinary leadership builds upon the previous achievements in establishing research capacity and regional professional and social networks. The Section encourages research about disparities in financing of mental and medical health care, the economic burden of mental disorders on the non-medical sectors of society (including workplace, education, family), and the potential role of digital health and electronic health records in reducing the disparities in global mental health.

The Section strives for excellence in mental health economics research and education to promote the mission and fulfill the goals of the WPA.

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Intellectual developmental disorder and autism spectrum disorder in the WPA next triennium mainstream

Both intellectual developmental disorder (IDD) and autism spectrum disorder (ASD) are included in the section of neurodevelopmental disorders of the ICD-11 and DSM-5. They represent meta-syndromic groups including many different clinical conditions characterized by cognitive and relational impairment. The guiding syndromic pattern involves maladaptive cognitive impairment in IDD and severe limitation and restriction of complex interpersonal interactions in ASD[1]. The two conditions often co-occur, and their differentiation may be difficult, especially in the context of increasing severity of cognitive impairment. About 30-40% of persons with ID have pervasive features of ASD, and about 80% of persons with ASD have lower intellectual functioning compared to the general population[2,3].

Both IDD and ASD are associated with a broad vulnerability to concomitant health issues, especially psychiatric disorders, with a prevalence five or more times higher than in the general population[4]. The identification of concomitant psychiatric disorders in persons with IDD and ASD requires a specific knowledge and expertise. The symptomatology can in fact be mixed, intermittent, atypical, masked, and range from poorly defined to extremely rigid. Even key elements of some syndromes, such as delusions, hallucinations or suicidal ideation, are often very hard to recognize, especially in persons with low or absent verbal communication skills, who may only be able to express themselves through changes in behaviour[5].

IDD and ASD impose an enormous burden on families and caregivers, require high service provision, and have high health and societal costs[6].

Despite the above evidence, IDD and ASD have often been overlooked as mental health issues by the majority of national and international organizations worldwide. Even in those countries where specific care programs are available, significant gaps are usually reported between awareness, planning and delivery of services, especially for persons with higher severity of impairment in communication, conceptual and adaptive skills. Specific training for psychiatrists and other mental health professionals is also often lacking, at every level within the clinical education system, including undergraduate, graduate and postgraduate training as well as professional continuing education.

Around one half of the persons with ID and low-functioning ASD receive psychotropic medication, and in one-third of cases drugs are prescribed to manage problem behaviours such as aggression or self-injury, in the absence of a diagnosed psychiatric disorder[7].

These vulnerabilities and shortage of services to address them seem to extend to persons with borderline intellectual functioning (BIF), who present an IQ below the average (between one and two standard deviations), but not enough to be comprised within the upper limit of IDD. According to research findings, at least one-eighth of the world population has BIF and shows, compared to people with higher IQ, greater social disadvantage, higher rates of psychiatric disorders and substance use, and more frequent use of psychopharmacological therapies and health services, including emergency ones[8,9].

To address the above-mentioned issues, to raise awareness, and to provide some initial solutions, the WPA has just launched a specific program within its proposed Action Plan 2021-2024. During the 19th World Congress of Psychiatry, held in Lisbon in August 2019, two interrelated working groups on IDD and ASD have been established, comprising experts with long-standing contributions to WPA activities in the field.

In the next triennium, these groups will produce a set of collaborative documents on policies, services, as well as education and training. Within these documents, the diagnosis of concomitant psychiatric disorders, and the relevant treatment and outcome measures, will occupy a central place.

The WPA Action Plan 2021-2024 aims to address the mental health needs of persons with IDD and ASD, develop strategies for the collaboration of psychiatrists with other health professionals, and promote partnerships for joint collaborative work in capacity building among medical students, young psychiatrists and allied professionals.

The overarching objective is to strengthen the care of persons with IDD and ASD worldwide and to fulfil their right to mental health care, in accordance to the United Nations Convention on the Rights of Persons with Disabilities.

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The relevance of COVID-19 pandemic to psychiatry

The ongoing coronavirus disease 2019 (COVID-19) pandemic has several aspects of psychiatric interest and relevance.

It should be first noticed that a pandemic of such proportions was largely unexpected in Western countries, where people generally believe that modern health systems, available medications and healthy lifestyles should allow them to cope with any kind of aggressive agents. This event undermined the sense of safety of our societies, where progress is often considered relentless, life increasingly better and longer, epidemics just a waning memory of past centuries, and death is removed and generally considered a private event. The pandemic is promoting a mounting awareness of our intrinsic vulnerability.

Indeed, the progression of the pandemic has been facilitated by one of the most salient characteristics of our societies: the interconnections between countries and the easiness to travel with affordable budgets. This means that there is no barrier that cannot be overcome or pierced, and that a total isolation is impossible. Ironically, isolation has become the most effective strategy to slow the progression of the pandemic, as demonstrated by the China experience.

People have now to abruptly face significant changes in their everyday life, working models and social behaviours. It is not surprising that several individuals are showing acute fight-or-flight responses, such as increased anxiety levels, panic attacks, irrational fears up to paranoid-like convictions and related behaviours, or a quiet resignation[1]. Assaulting supermarkets to buy enormous amounts of food to be stored, like during war periods, as well as visceral reactions towards specific groups of people or individuals with symptoms of cold or cough, have become common during these months.

At least at the beginning of the pandemic, these reactions have also been fuelled by the ambiguity of politicians, who on the one hand tried to reassure their communities, while on the other organized too weak or too stringent countermeasures to limit the progression of the infection, that were sometimes inappropriate and had to be corrected. Even worst, in some countries such as Italy, politicians of different parties expressed strong personal opinions, sometimes with no scientific background, or "used" the pandemic to criticize the government and/or increase their consensus. In addition, the information provided by the media has been in several cases catastrophic and sensational rather than prudent and accurate, and generally too insistent (taking an excessive number of hours in TV programming and of pages in newspapers daily).

All these factors have been converging to increase people's sense of uncertainty and helplessness as well as distrust towards official information, while fuelling the conviction that nobody can do anything really effective to stop the pandemic.

Psychiatrists, in this emergency, can potentially play key roles. First, they can support front-line physicians, nurses and all involved personnel by dealing with their fears and those of affected individuals. These professionals are too often burdened by the workload of these months, with the mounting risk of burnout syndromes, and are exposed to the constant threat of being themselves infected (more than 30,000 doctors have been infected in China and more than 30 died). Furthermore, in some countries, due to the shortage of the appropriate equipments, front-line physicians are increasingly being faced with the ethical dilemma of selecting the affected patients who can be treated optimally, a situation that is always a personal tragedy[2].

Second, psychiatrists will have to be ready to face not only the acute reactions to the pandemic, that generally are self-limiting, but also its long-term consequences. We do expect an epidemic of post-traumatic stress disorder and depressive syndromes, due to the convergence of a variety of factors, such as the experience of being infected or witnessing the infection and perhaps the death of dear ones, the drastic changes of lifestyles, quarantine, and the profound economic recession that many countries are going to face[3,4].

In addition, we are well aware that all these factors may have a more significant impact on the most vulnerable subjects in our societies, among whom people with mental disorders are obviously included. We are already witnessing and should be prepared to increasingly see the incorporation of themes related to the infection into the fears and delusions of many of our patients.

Only a correct scientific information coupled with the management of the emergency by a range of specialists, including psychiatrists, in connection with governmental (or, even better, supranational) agencies[5], can be regarded as an appropriate strategy to enable people to cope with fears that are not unmotivated, but may be excessive and irrational[6]. If fear and anxiety are biologically rooted reactions that have promoted human survival and evolution, when within physiological limits, they may become, if they cross a certain border, a powerful obstacle to personal and public mental health.

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Pierre Pichot's 100th birthday

Pierre Pichot has been the fifth President of the WPA. He was elected during the World Congress of Psychiatry held in Honolulu in 1977. Having being one of his closest students, I had the privilege to spend exclusive time with him recently on his 100th birthday with his daughter, C. Simon-Pichot. Memories came back easily during about an hour.

Pichot was the first University intern to join in 1944 the team of J. Delay, who was going to become the very first President of the WPA (from 1950 to 1961). He had been trained in mathematics and in psychology and wanted at first to become a neurologist. Delay asked him to take care of patients with general paralysis in Bicêtre Hospital and after that of children with epilepsy in the Fondation Vallée in Gentilly, south of Paris. After that, he joined Delay at the Sainte Anne Hospital in Paris.

Pichot remained in the team of Delay until his early retirement in 1970 and replaced him as chair of the Clinique des Maladies Mentales et de l'Encéphale in Sainte Anne Hospital. At the same time, another chair was created for P. Deniker, who had discovered with Delay the antipsychotic properties of chlorpromazine.

In 1948 Pichot was appointed as first assistant of H. Ey, the Secretary General of the first World Congress of Psychiatry (named "International Congress of Psychiatry") that took place in Paris in 1950. He had a crucial role in the organization of that congress, and spent numerous days and nights typing letters himself in various foreign languages that he mastered (English, German, Spanish among others).

In 1960, he headed the team of collaborators and friends who offered the sword of academician to Delay when he was elected member of the Académie Française. During the ceremony Delay addressed Pichot with the following words: "I have been able to measure – but it is imprudent to use this term before an exacting specialist of psychometry – the rectitude of your character and the sureness of your judgement".

As a matter of fact, Pichot was also Professor at the Institute of Psychology of the René Descartes University in Paris. He published with Delay, who had also been trained in psychology during his early career, a book entitled *Abrégé de Psychologie*[1]. In the field of quantitative psychopathology and psychometrics, he produced the volume *Les Tests Mentaux*[2] and co-authored the book *Méthodes Psychométriques en Clinique – Tests Mentaux et Interprétation*[3].

Pichot introduced, translated and validated the Brief Psychiatric Rating Scale in French. He also introduced and promoted in the early 1970s behavioural therapy, later to become cognitive behavioural therapy. However, he kept a number of psychoanalysts in his team.

When he became President of the WPA in 1977, with P. Berner from Vienna as Secretary General, they had to deal with a very serious crisis: the political abuse of psychiatry in various countries of the world (South Africa, Cuba and especially Soviet Union). The cold war that darkened the political atmosphere worldwide at that time found a strong battlefield in psychiatry. This crisis led to the withdrawal of the Association of Psychiatrists and Narcologists of the Soviet Union from the WPA during the Athens World Congress of Psychiatry in 1989, and the trip of the WPA Commission that was sent in 1991 to the Soviet Union to assess the situation on this subject, of which I was a member.

After having left the presidency of the WPA at the end of the World Congress in Vienna, Pichot was instrumental in creating the European Psychiatric Association, with some French and German colleagues. He also wrote an important book on the history of psychiatry, *Un Siècle de Psychiatrie*[4], describing with many details classical psychiatry during the 19th and the 20th centuries. Among his most recent contributions are the papers on the origins of the concept of bipolar disorder[5] and on the reception of the DSM-III from a European perspective[6].

The fact that he was one of the organizers of the first World Congress of Psychiatry, that he was polyglot, his interests outside psychiatry and neurology, including history, led him to open windows from French psychiatry towards the rest of the world, making it known elsewhere, and from the world into French psychiatry, making it more international. For example, he organized in Paris a meeting between the Société Médico-Psychologique and the American Psychiatric Association, the two oldest psychiatric associations in the world, on the DSM-III project two years before it was published. This and other moves in his professional life come from a strong vision about psychiatry's future and about the role that must be played by the WPA.

P. Pichot has numerous pupils around the world, especially in Japan, where he received in the early 1990s a medal from the Emperor in recognition of his support to Japanese psychiatry.

Professor Pichot was my teacher since 1973, when he welcomed me in his department. I am proud to be one of his pupils. I never talked to him without learning something from him. A true mentor who honours French speaking, European and world psychiatry.

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ICD-11 sessions at the 19th World Congress of Psychiatry

At the 19th World Congress of Psychiatry, held in Lisbon, Portugal, from 21 to 24 August 2019, a plenary session, an educational course and several individual presentations were devoted to the Clinical Descriptions and Diagnostic Guidelines developed by the World Health Organization (WHO) Department of Mental Health and Substance Abuse for the chapter on Mental, Behavioural and Neurodevelopmental Disorders of the 11th revision of the International Classification of Diseases and Related Health Problems (ICD-11).

The ICD-11 has been adopted unanimously by the 72nd World Health Assembly in Geneva on May 25, 2019, although reporting of health statistics based on the new classification will only begin on January 1, 2022. Up to that date, the WHO Member States will keep on using the ICD-10 for reporting data[1].

The ICD-11 classification of mental disorders includes the following groupings: neurodevelopmental disorders, schizophrenia and other primary psychotic disorders, mood disorders, anxiety and fear-related disorders, obsessive-compulsive and related disorders, disorders specifically associated with stress, dissociative disorders, feeding and eating disorders, elimination disorders, disorders of bodily distress and bodily experience, impulse control disorders, disruptive behaviour and dissocial disorders, personality disorders, paraphilic disorders, factitious disorders, neurocognitive disorders, and mental and behavioural disorders syndromes due to disorders or diseases not classified under mental and behavioural disorders[2].

The Clinical Descriptions and Diagnostic Guidelines for the ICD-11 classification of mental disorders have been tested through Internet-based field studies and clinic-based field studies.

The Internet-based field studies, implemented through the Global Clinical Practice Network, including about 15,000 clinicians from 155 countries, reported that the diagnostic agreement for several groups of disorders (e.g., disorders specifically associated with stress, and feeding and eating disorders) was considerably higher for the ICD-11 compared with the corresponding ICD-10 categories[3].

The clinic-based field studies, conducted in clinical settings, found that the interrater reliability for the main groups of mental disorders ranged from moderate to almost perfect (.45 to .88) and was generally superior to that obtained for ICD-10[4]. Concerning clinical utility, the diagnostic guidelines were perceived as easy to use, corresponding accurately to patients' presentations, clear and understandable, providing an appropriate level of detail, taking about the same or less time than clinicians' usual practice, and providing useful guidance about distinguishing disorder from normality and from other disorders[5-7].

At the World Congress, the plenary session mostly dealt with the implementation of the new classification system, that will involve the interaction of the classification with each country's laws, policies, health systems and information infrastructure. G. Reed, the coordinator of the process of development of the new system, and K.M. Pike, from Columbia University, New York, illustrated the multiple modalities developed for training a vast array of international health professionals. D. Kestel, Director of the WHO Department of Mental Health and Substance Use, described how the new classification fits the most important plans and priorities for the Department going forward. M.E. Medina-Mora, O. Gureje, J. Huang, D.J. Stein, M. Pinto da Costa and N. Sartorius discussed various aspects of the implementation progress and provided recommendations for what the WHO should do in order to ensure that the ICD-11 achieves its potential around the world. M. Maj, who chaired the session with G. Reed, summarized some lessons that should be learnt from the process of implementation of previously developed classification systems.

The educational course of the Congress provided training on the use of the Clinical Descriptions and Diagnostic Guidelines for schizophrenia and other primary psychotic disorders, mood disorders, and obsessive-compulsive and related disorders. The course was based on the use of clinical vignettes describing real cases, followed by a discussion of diagnostic dilemmas, including some crucial differences between the ICD-11 and DSM-5[8,9], as well as the dimensional approach recently advocated by several experts[10-12] and partially implemented in the ICD-11.

Overall, the sessions emphasized the strong collaboration between the WHO and the WPA in all the steps of the development and testing of the ICD-11 chapter on Mental, Behavioural and Neurodevelopmental Disorders, and the long-term partnership that will now be established between the two organizations in the dissemination and implementation of the diagnostic system.

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Correction

It has been brought to our attention that in the Acknowledgements of the paper "Early intervention in psychosis in low- and middle-income countries: a WPA initiative", by Singh et al, published in the February 2020 issue of the journal, the name of one member of the International Advisory Panel, D. Das, was missing, while that of another member was mispelled (it should be J. Walters instead of J. Walter).

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