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SPECIAL ARTICLE

The S20 Brazilian Mental Health Report for building a just world and a sustainable planet: Part II

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This is the second part of the Brazilian S20 mental health report. The mental health working group is dedicated to leveraging scientific insights to foster innovation and propose actionable recommendations for implementation in Brazil and participating countries. In addressing the heightened mental health challenges in a post-pandemic world, strategies should encompass several key elements. This second part of the S20 Brazilian Mental Health Report will delve into some of these elements, including: the impact of climate change on mental health, the influence of environmental factors on neurodevelopmental disorders, the intersection of serious mental illness and precision psychiatry, the co-occurrence of physical and mental disorders, advancements in biomarkers for mental disorders, the use of digital health in mental health care, the implementation of interventional psychiatry, and the design of innovative mental health systems that integrate principles of innovation and human rights. Reassessing the treatment settings for psychiatric patients in general hospitals, where their mental health and physical needs are addressed, should be prioritized in mental health policy. As the S20 countries prepare for the future, we need principles that can advance innovation, uphold human rights, and strive for the highest standards in mental health care.

Keywords: Mental health policy; environmental factors; precision psychiatry; implementation science; innovation in mental health care

Introduction

The G20 can serve as a model for the collaborative use of science to achieve the shared objective of universal holistic health. This endeavor to enhance physical and emotional well-being could pave the way for global implementation. The physical dimension of health encompasses aspects such as diet, exercise, sleep patterns, stress levels, lifestyle choices, and one's relationship to the environment. Recent research underscores the profound link between physical health, psychological well-being, and the environment. Conversely, research has consistently shown that poor physical health can lead to adverse psychological effects, such as diminished self-esteem or feeling overwhelmed by daily responsibilities. A poor environment can also contribute to neuropsychiatric disorders.

Ideally, a universal holistic health policy would encompass physical, psychological, social, cultural, and environmental dimensions. It should consider diverse age

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groups, spanning from early childhood to adulthood, as well as different cultural backgrounds, tailoring interventions accordingly. Such a policy should be evidence-based, contextually relevant, resource-efficient, culturally sensitive, and equity-promoting.

About two-thirds of the world's population will live in large urban centers by 2050. Consistent floods, landslides, heat waves, and climate threats, accompanied by worsening social conditions, can increase feelings of insecurity, particularly for people living in urban centers, especially among youth and older adults.

Social media has revolutionized the way people create and consume information. Unlike traditional media broadcasts, which are passively consumed, social media depends on users to provide content for their social contacts.

Many individuals with mental health conditions, including common disorders like depression and anxiety, lack access to adequate public mental health care. Brazilian epidemiological studies estimate that the mental health gap is over 50% for adults and adolescents, which is important because individuals with mental illness often experience physical health problems that can lead to increased mortality, poorer health outcomes, and higher health system costs. The average life expectancy of those with severe mental illnesses (SMI), such as acute depression, bipolar disorder, and schizophrenia, is 20 years shorter than the general population. Because one-third of patients with severe depression or other SMI have difficult-to-treat conditions, new interventions are required, such as the emerging field of interventionist psychiatry.

As part of the ongoing effort to address developing challenges in global mental health, the second part of the S20 Brazilian Mental Health Report will delve into the following topics: the impact of climate change on mental health, the influence of environmental factors on neurodevelopmental disorders (NDD), the intersection of SMI and precision psychiatry, the comorbidity of physical and mental disorders, advancements in biomarkers for mental disorders, the integration of digital health in mental healthcare, the implementation of interventional psychiatry, and the design of innovative mental health systems that incorporate principles of innovation and human rights.

Climate change and mental health

The concept of climate insecurity is intricately linked to environmental aggression, which has multifaceted effects on the planet.[1] These effects include reduced agricultural productivity, which is curtailing food availability and increasing hunger and malnutrition among vulnerable populations.[2,3] Rising sea levels are contributing to a scarcity of both drinking water and agricultural irrigation water.[4] Climate change is also disrupting the economy by affecting supply chains, leading to financial losses for businesses and governments. Increasing air pollution and frequent heat waves are also exacerbating human health risks. Environmental aggression also poses a significant threat to biodiversity, resulting in habitat loss, species extinction, and ecosystem disruption, triggering migration and displacement. In summary, environmental changes are beginning to jeopardize human survival, creating a state in which basic needs, such as safety, provisions, and well-being, will not be met.

The impact of climate change on mental health is multifaceted, having both direct and indirect effects on affected populations. Extreme weather events, such as hurricanes, floods, wildfires,[5] and heatwaves,[6] directly contribute to psychological distress. The indirect effects of such events include chronic stressors like drought, food insecurity, displacement due to environmental degradation, and existential anxiety about the future amid escalating climatic changes.[7-9] Studies have demonstrated that extreme weather events increase the prevalence of post-traumatic stress disorder, depression, anxiety disorders,[6] and a wide range of psychological morbidities that can impair functioning and well-being long after the initial event.[5]

Awareness of the threat that climate change poses, referred to as eco-distress, climate anxiety, or climate grief, is significantly impacting mental health and psychological well-being on a global scale.[10] Young people worldwide are showing high levels of concern about climate change. This emotional state can manifest as feelings of helplessness, fear for the future, sadness over environmental loss, and guilt regarding their own ecological impact. Engaging in community actions and pro-environmental movements has shown potential benefits for youth.[9] In a recent survey of 10,000 youth (aged 16-25 years) from 10 countries, 60% expressed significant concern about climate change, with 45% reporting disruptions to their daily lives, including sleep patterns and daily functioning.[11] Young people, recognizing the future implications of climate change, feel that the government's response has been inadequate. While climate anxiety is not classified as a psychiatric illness, the reality of the climate crisis is undeniable, and the lack of substantial government action is evoking an overwhelming response, particularly among adolescents.[12] This trend is evolving into a moral injury for children and adolescents.[13]

Environmental factors in neurodevelopmental disorders

The human brain, the most complex system and most fascinating part of our organism, consists of 86 billion neurons and weighs about 1.5 kg. Neurons are the basic unit of the nervous system and are considered the main elements in the generation, transmission, and processing of cerebral information.[14] The brain is a flexible and adaptable organ, constantly changing throughout life. Neuroplasticity, i.e., the brain's ability to change its anatomy, connectivity, and networks in response to external and internal stimuli, allows neurons to structurally reorganize and form new cells, adjusting their number, morphology, and function in response to environmental changes.[15,16] Exposure to environmental toxins, whether natural or manmade, has been identified as a key factor in impaired neuroplasticity and disrupted brain

development, contributing to NDD.[17-19] Although NDD are highly heritable, a number of environmental risk factors have also been suggested.[20] Environmental factors commonly linked to NDD include diet (including food additives), lead contamination, tobacco and alcohol exposure during pregnancy, and low birth weight.[20] Current evidence indicates that exposure to pesticides during neurodevelopment increases susceptibility to many NDD.[20,21] Pesticide use may have been involved in the rapid increase of autism spectrum disorder in the last decade.[22] This relationship has been attested to by studies measuring a range of exposure types, from residential exposure to agricultural drift, whose methodologies have ranged from questionnaires on insecticide use to assessing biological specimens to detect metabolites and pesticides, such as organochlorine and organophosphate pesticides.[22] The serious effects of indiscriminate pesticide use on both the environment and human health are well known.[23] In 2019, global pesticide consumption was approximately 4.19 million metric tons, with China being the largest consumer (1.76 million metric tons), followed by the United States (408,000 tons), Brazil (377,000 tons), and Argentina (204,000 tons).[24] Pesticide contamination is a major environmental and health concern in Brazil, particularly among Indigenous communities.[25] Pesticide use in Brazil must be considered a public health emergency, given the number of people who live in agricultural areas and near pesticide factories, as well as the general population, who consume their residues in food.[26] Hence, new experimental, epidemiological, and clinical studies are needed to accurately determine the effects of environmental toxin exposure on human health.

Serious mental illness and precision psychiatry

SMI is characterized by significant functional impairment resulting from a mental disorder. Its prevalence is approximately 5%, with most cases manifesting before 18 years of age, significantly impeding educational and employment opportunities for affected individuals.[27,28] Beyond personal suffering, the social burden of SMI is substantial, given that it is one of the most prevalent causes of lifelong disability and requires significant resources from the health care system.[29,30] The prevalence of SMI tends to be higher among minorities and people in lower socio-economic strata, disproportionately affecting the most vulnerable segments of society.

SMI treatment faces significant challenges worldwide. A substantial portion of patients remains untreated[31] and, even among those who receive treatment, evidence-based interventions are not universally accessible.[32] Diagnostic delays are commonplace, particularly for conditions such as schizophrenia and bipolar disorder.[33,34] Rehabilitation programs have yielded only modest results, as evidenced by a recent meta-analysis indicating a persistent education gap between individuals with schizophrenia and the general population over the past few decades.[35] Urgent action is needed to transform this situation.

Precision medicine seeks to enhance the diagnostic accuracy and treatment efficacy by accounting for interindividual variability.[36,37] The novelty lies not so much in the objective itself, but in the use of cutting-edge technologies such as omics, big data, and ecological momentary assessment. These tools allow tailored treatments for individual patients at the opportune moment. In rapidly evolving fields like oncology and cardiology, novel findings are emerging swiftly. For SMI, precision psychiatry has the potential to spearhead a genuine scientific revolution. Some encouraging findings highlight this potential, including machine learning's ability to predict lithium[38] and antipsychotic[39] response. Genetic panels have been used to predict severe adverse effects, such as Steven-Johnson syndrome, which has been associated with carbamazepine use in Chinese patients.[40] Another noteworthy observation is that elevated C-reactive protein levels in depressed patients are linked to poor treatment response.[41] However, some of these promising results have been criticized. For instance, the association between C-reactive protein and depression in recent studies lost significance after adjustment for body mass index and potential confounders.[42,43] Thus, despite the promise of precision psychiatry, clinically relevant results are still elusive.

The scarcity of results for precision psychiatry can be attributed to several factors. While it may be argued that insufficient time is a factor, the rapid emergence of results in other medical fields raises legitimate concerns. However, instead of resorting to arguments about greater brain complexity, a more fundamental and intrinsic issue must be addressed: the definition of psychiatric disorders. In oncology, the search for tumor biomarkers involves identifying and genotyping specific cell types. But what cell type causes schizophrenia? What brain region is responsible for depression? Psychiatric diagnoses are for syndromes rather than etiological entities, representing states of brain function. Köhne & Van Os[44] elegantly outlined similar concerns. Although the diagnosis problem in psychiatry does not actually hinder the use of precision medicine, it must be taken into consideration.

Beyond this fundamental problem, two additional concerns warrant attention. First, most research on precision medicine has focused on genetics and has been conducted in high-income countries. This geographic bias may explain its low replicability, particularly among ethnic groups not covered by current studies. Consequently, the best existing algorithms may only be effective for White European populations, which underscores the need to include diverse ethnic groups.[45] As these tools advance and better predict clinical outcomes, a second concern emerges regarding accessibility: will these tools be available to all patients with SMI, or will they be limited to only those who can afford them? This ethically complex issue highlights the need for new studies in low- and middle-income countries to develop better algorithms. However, the irony of these advancements lies in their potential inaccessibility due to high costs. In general, precision psychiatry must consider the social and cultural context, since related factors

significantly influence mental disorders, serving as either risk factors or affecting prognosis/treatment response.

Although the promise of precision psychiatry is both clinically and scientifically relevant, the limitations of psychiatric nosology remain the primary barrier. Progress will require extensive translational datasets, larger and more representative international samples, and longitudinal studies. Validation and implementation studies, preferably with a commitment to making advancements accessible to those in need, are crucial. Otherwise, advancement will only further widen the social gap. Beyond these challenges, we must not lose sight of the centrality of human experience as the core of psychiatric practice. More than mere words, human experience is the emerging property of our brain and a focal point for neuroscience. In conclusion, establishing greater connections between disciplines will be essential to enhancing the lives of individuals with SMI. New technologies can be exceedingly beneficial, provided they do not lose sight of the essence of human care and its significance.

Physical and mental comorbidities

There is extensive evidence of a robust association between mental disorders and physical illness. A considerable proportion of the increased mortality associated with psychiatric disorders may be attributable to the high prevalence of comorbid physical conditions, including cardiovascular, respiratory, metabolic, and other diseases.[46] Studies have shown that mental illness exacerbates the effects of many physical conditions. For example, meta-analyses have shown that depression increases the risk of total stroke, fatal stroke, and ischemic stroke.[47] There is also an association between depression and an increased risk of myocardial infarction,[48] including a 22% higher risk of all-cause mortality after an ischemic coronary event.[49] This association has proven so important that the American Heart Association should consider elevating depression to the status of a risk factor for adverse medical outcomes in patients with acute coronary syndrome.[50] Higher risks of sudden cardiac death and recurrent atrial fibrillation have also been associated with depression.[51]

Numerous studies have demonstrated an association between diabetes and other clinical conditions. A 2019 meta-analysis found that, in individuals with diabetes, depression is associated with an increased risk of macrovascular and microvascular complications,[52] as well as increased diabetes-related mortality.[53] Data also indicate that depression increases the risk of obesity, which is closely associated with cardiovascular and cerebral complications.[54] Even more surprising findings from studies assessing depression both before and after cancer diagnosis indicate that higher levels of depressive symptoms predict increased cancer mortality.[55]

Biomarkers in mental disorders

Although the search for the biological substrate of mental disorders is necessary for more effective therapies and, above all, preventive strategies through early diagnosis, experimental attempts to identify specific markers for different disorders remain unsuccessful. Thus, current treatments are symptom-based, not disease modifiers, and have low response rates.[56] Such negative results may be related, at least in part, to non-specific global changes in brain biology in certain clinical conditions.[56] In fact, the symptoms and clinical manifestations themselves are non-specific in different disorders,[57] including a lack of phenotypic specificity observed in clinical practice. Hence, it is assumed that there may be a common genetic basis to brain structure and function abnormalities in these disorders.[58] For this reason, experimental strategies should consider both the biological differences and similarities of different diagnoses. The rationale for this is that a genetic basis would result in a common vulnerability to disturbances in brain maturation, plasticity, and function.[58] The interaction of such a genetic basis with non-genetic factors could determine the variety of clinical manifestations and influence pathoplasty.[58]

The detection and treatment of mental disorders is restricted by historically established procedures that are generally based on subjective observation of individuals suffering from a mental condition.[59] As a result, psychiatric diagnostic categories, as well as the complete lack of a reliable biological signature to guide diagnosis, have been criticized.[59] Indeed, one of the fundamental shortcomings of conventional, phenotype-based psychiatry is that diagnosis is based on a descriptive set of behaviors rather than objective markers.[59] Peripheral biomarker changes have now been confirmed in a wide range of mental health problems,[60] although they do not respect diagnostic boundaries and are quite variable between persons with the same phenotypic diagnosis.[60] As a result, no peripheral biomarkers have been identified that can assist in the differential diagnosis of mental disorders.[60,61]

For psychiatry to further develop, peripheral blood marker behavior must be determined on an individual level across nosological categories.[62] Given the complexities of mental disorders, a single or even several biomarkers related to the same unit of analysis within a biological system (i.e., a single domain) is unlikely to provide diagnostic criteria to adequately guide real-world therapeutic decisions.[61] However, investigation of many potential biomarkers in a wide range of illnesses may contribute to the understanding of micro-changes in the neurocircuitry of psychiatric disorders.[61]

The most investigated peripheral biomarkers are generally the same across psychiatric disorders. Compared to healthy controls, brain derived neurotrophic factor, interleukin-6, tumor necrosis factor-alpha, and C-reactive protein levels are frequently altered in people with psychiatric conditions.[63-65] Specifically, brain derived neurotrophic factor levels are lower in bipolar disorder, major depressive disorder, and schizophrenia and higher in autism spectrum disorder.[63-66] Inflammatory cytokines interleukin-6, TNF-alpha, and C-reactive protein are lower in post-traumatic stress disorder, bipolar disorder, schizophrenia, and major depressive disorder.[41,60,67,68] It is not surprising that similar compounds would attract attention across disorders based on publishing trends, but the fact

that the variation patterns have been consistent among mental disorders indicates biological commonalities in their peripheral characteristics.

In conclusion, we should be optimistic that biomarkers can lead to novel therapies and patient-tailored interventions, revolutionizing our capacity to delay disease onset and improve treatment for complex mental disorders. The most ambitious goals would be to identify novel pharmaceutical targets and justify the use of well-known medications, given the intricate interplay among genotype, lifestyle, nutrition, pharmacological therapy, environmental exposure, and gut bacteria. Ultimately, given the complexity of mental illnesses, a connection must be established between various biomarker types. Thus, a combination of biomarkers, rather than a single biomarker, may result in more personalized mental health care and better outcomes.

Digital mental health interventions

The World Health Organization refers to digital health as "The field of knowledge and practice associated with the development and use of digital technologies to improve health. Digital health expands the concept of eHealth to include digital consumers, with a wider range of smart-devices and connected equipment. It also encompasses other uses of digital technologies for health such as the Internet of things, artificial intelligence, big data, and robotics."[69] Such a definition builds common ground in an area that has grown exponentially over the last 5 years. As early as 2018, The *Lancet* Commission on global mental health and sustainable development[70] identified the transformative potential of digital technologies across several areas of mental health. They can play a pivotal role in improving mental health literacy, reducing stigma, fostering well-being, facilitating screening and diagnosis, supporting treatment and care, enhancing training and supervision (thus expanding mental health care capacities), and strengthening health care systems (by incorporating artificial intelligence).

In the wake of the COVID-19 pandemic, digital health has shifted from a mere aspiration to a tangible reality. It is now used to address numerous health problems on both individual and population levels. On an individual level, digital health interventions, such as tele-mental health, smartphone apps, chatbots, and virtual reality are being used and/or evaluated for a broad spectrum of mental health disorders including anxiety, depression, substance abuse, and schizophrenia.[71] Hundreds of apps currently provide psychoeducation, improve therapeutic adherence, and allow patients to identify and manage their symptoms.[72] In addition, the use of avatars is widespread in various psychotherapeutic or psychological approaches, including cognitive-behavioral therapy, behavioral activation, mindfulness, as well as techniques for managing anxiety and improving sleep.[73] Moreover, digital phenotyping allows the ecological measurement of behavior, using data collected by mobile devices.[74] Active data collection (ecological momentary assessment) is being used to determine patients' physical and mental state in a number of apps. At an early level of technological readiness, passive data collection relies on cell phone instruments, such as actigraphs, accelerometers, and global positioning systems to extract clinically relevant information. These tools can detect stress through cell phone usage patterns, identify risk exposure for binge drinking through geolocation, and identify opioid poisoning according to breathing patterns captured through the microphone. In vulnerable groups, such as older people and lesbian, gay, bisexual, transgender, queer, questioning, intersex, ally youth, interventions that increase mental health literacy can lead to even greater gains.

Implementing and scaling up these interventions, however, remains challenging. Despite important advances in efficacy evaluation for digital health interventions, innovative research designs are needed to assess long-term outcomes due to their rapid obsolescence rate and loss of user engagement, retention, and adherence. Few mental health apps have been tested in randomized clinical trials, although some have met regulatory steps for clinical use (Technology Readiness Level 9). In November 2018, reSET-O, which uses cognitive-behavioral techniques to treat opioid addiction, was the first app approved by the U.S. Food and Drug Administration for use in mental health treatment.[75] A year later, the same company obtained approval for Somryst, which was developed for chronic insomnia.[76] EndeavorRX, a video game designed to treat attention deficit hyperactivity disorder, received approval in 2020.[77] Finally, NightWare, a digital watch designed to help post-traumatic stress disorder patients, monitors user physiology during sleep to identify the occurrence of nightmares or disturbing dreams and wakes them through vibrations.[78]

Artificial intelligence, which will be increasingly needed to integrate and analyze app-collected data and digitally phenotype medical records, neuroimaging, and biomarkers, holds promise for precise diagnosis and personalized treatment.[79] Algorithms can assist in patient diagnosis, treatment, and monitoring.

On a population level, digital public health is becoming increasingly visible as means of achieving public health goals, such as health promotion, disease prevention, health care system improvement, and universal health coverage.[80] Digital public health is based on technological advances that allow huge amounts of data to be collected, processed, and analyzed, which are then used to guide actions/interventions.[81] This was brought to bear on a large scale during the COVID-19 pandemic, when large amounts of data (from epidemiological surveillance systems, as well as global positioning systems and Bluetooth apps) were processed in real time and guided virus control strategies. Moreover, electronic medical records simplify data management. A 2015 study of the English health care system showed that almost 30% of a general physician's consultation time is spent on bureaucratic tasks rather than patient care.[82] Five out of nine of the proposals in this document are related to app, automation, and teleservice technologies and simplified data collection. Such advances may seem far from public mental health services, given that the World Mental

Health Report identified information, governance, service, and resource gaps as major barriers to be overcome. However, previous experience in other areas has paved the way for the transformation of mental health services, given that stakeholders, researchers, and the society have already witnessed these tools' potential.

The rapid pace of innovation in digital health presents a significant opportunity to revolutionize mental health care. However, a number of novel challenges accompany these advances, which require thorough examination. Chief among them are concerns about privacy, confidentiality, and data security and curation. Mental health data is highly sensitive and must be handled in a way that avoids stigma and discrimination.[83] The collection and storage of mental health data can risk patient privacy. Robust measures are needed to protect against unauthorized access and misuse. Moreover, the ethical and social aspects of Industry 4.0 must be considered in mental health. Technologies must be used ethically and responsibly so that they do not contribute to greater social inequality or further stigmatize people with mental disorders.

The ''digital health paradox'' must also be considered, i.e., those who could reap the greatest benefits from digital health often face the greatest barriers to access, primarily due to issues such as digital exclusion.[84] Innovative technologies can be expensive and inaccessible to many people, especially in developing countries. Hence, addressing digital exclusion is of paramount importance, since it can perpetuate and exacerbate structural inequalities related to sex, race, and socioeconomic status.[85]

To fully leverage digital health's potential to enhance mental well-being, robust policies and regulations are imperative. The World Health Organization and the Pan American Health Organization have emphasized the need for policies based on principles of transparency, accessibility, scalability, replicability, interoperability, privacy, security, confidentiality, user-centeredness, and non-discrimination.[86,87]

In conclusion, although digital health and digital public health may revolutionize mental health care, it is our job to ensure that the transformation is inclusive, ethically grounded, and sustainable in the long term. Digital innovations can only advance mental health care on a global scale if concerted effort is made to address their associated challenges.

Interventional psychiatry

Interventional psychiatry involves methodological and therapeutic innovations that can be of great value to mental health care in the future. Transcranial electrical stimulation can be applied remotely and can be self-administered, making it suitable for home use.[88] Transcranial magnetic stimulation was approved for clinical use in 2010. Its mechanism of action is to modulate brain circuits through electromagnetic pulses from a coil positioned over the target region. This technique has been approved for depression, obsessive-compulsive disorder, and tobacco addiction. Inducing convulsive crises through electromagnetic pulses (a technique called magnetic seizure therapy) can be an effective alternative to electroconvulsive therapy, producing fewer side effects.[89] Vagus nerve stimulation consists of implanting a pacemaker that discharges electrical pulses into the vagus nerve, resulting in long-term antidepressant effects. Finally, ketamine is an injectable pharmacological intervention performed in a hospital environment using an infusion pump.[90] Highly effective, its clinical use has expanded rapidly in just a few years. Since it often presents transient effects, it is best indicated for patients with acute conditions and suicidal ideation.

Centro Nacional de Ciência e Inovação em Saúde Mental

The Centro Nacional de Ciência e Inovação em Saúde Mental (Center for Research and Innovation in Mental Health, CISM), a partnership of researchers from three top-ranked universities in Brazil and two city governments, is supported with public and private funding. Its mission is to advance knowledge about mental health conditions and to improve well-being in the state of São Paulo and surrounding regions through innovative interventions. The center involves three modules. Module I, Precision Neuroscience, is expanding brain and behavioral investigations based on the Brazilian Transgenerational High Risk Cohort for Mental Conditions, a robust database to train researchers and students in academic institutions. Module II, Assessment and Incubation of Digital Interventions in Mental Health, is empirically testing novel technological innovations for the assessment, prevention, and treatment of mental disorders that can be incorporated in the public and private health sectors. Module III, Transferring Science and Technology to Society, is assisting with implementation of evidence-based interventions in two cities, as well as subsequent dissemination in Brazil and other low-and middle-income countries.

The Precision Neuroscience Module is currently in the fourth wave of data collection from a large community-based cohort of 2,511 probands who are now reaching young adulthood.[91] This wave, in which more than 1,500 participants have already been interviewed, includes detailed mental health phenotyping, whole genome sequencing, a carefully designed structural and functional magnetic resonance imaging protocol, and other clinical and neurobiological assessments. The probands and their parents will be interviewed, making this a trans-generation study. Several important insights have arisen from the extensive database, and numerous research questions are being explored through this information (e.g., more than 100 papers have been already published using this database).

The Digital Mental Health Module is expanding interaction with the innovation and technology sector, raising awareness among stakeholders of the need for empirical evidence to support or refute the claims of products such as mobile health apps for anxiety, depression, or other mental health problems.[74] Hence, this module serves as a nationally relevant laboratory for pragmatic studies on technological solutions. It is currently hosting clinical

studies for numerous digital solutions, including a contingency management app for alcohol use disorder that connects smartphones with portable breathalyzers for continuous abstinence measurement, a virtual reality exergame that encourages high intensity exercise as a complementary treatment for attention-deficit/hyperactivity disorder, an algorithm that reads micro-expressions of facial photographs as a measure of depression symptoms, and an app for treating maternal depression through basic cognitive-behavioral techniques.

The Science Implementation Module is closely connected to the public health systems of two medium-sized cities in Brazil, developing projects at the intersection of research and health care to narrow the gap between evidence-based interventions and their implementation (bench to bedside).[92] One of these projects is a large trial of digital cognitive-behavioral therapy interventions (with or without supervision by clinical psychologists) for common mental health problems like depression, anxiety, and insomnia in primary care units. Its protocols are based on proven references from other countries but are tailored to local social and cultural contexts. A nurse visitation program for socially vulnerable pregnant teenagers is being implemented, which aims to foster attachment and family support so that the child thrives emotionally and socially during its first 1,000 days of life.[93] Due to the burden of mental disorders among young people, a program has been developed to help educators identify the most common mental health issues among students and refer them for help. Similar attention is being given to university students: a large longitudinal survey of mental disorders among college students is now underway to understand and map them and support planning for future interventions.

In summary, the CISM can help transform mental health research in Brazil, resulting in translational science that is more consistent, purposeful, and socially-oriented. To this end, it will continue investing in studies of high added value, solidifying partnerships in the public and private sectors to develop new ideas with innovative potential, and providing systematic interventions with real-world impact, improving the lives of people in our communities who need care.

Modeling innovative mental health systems

The development of mental health systems that are innovative, guided by scientific evidence, and respectful of human rights is a pressing issue in the global health agenda.[94,95] As we approach the forthcoming S20 health meeting, it is imperative to establish principles that will transform mental health policies and systems among member countries. This document discusses urgent priorities for crafting mental health systems that are equipped to face the challenges of the future.

First, innovative health systems require integration of technology and community-oriented mental health care.[70] The approach is twofold: 1) leveraging centralized digital services to enable direct care, such as telepsychotherapy; and 2) employing distributed community interventions that are brief, standardized, and effective.[96-100] This approach ensures that technologically extended mental health care remains sensitive to cultural and contextual nuances. A paradigm shift is needed away from top-down solutions and towards the involvement of individuals who have experienced mental health issues in shaping care delivery, thus promoting autonomy and safeguarding human rights.[100]

Second, continuity of care is vital and must be supported by robust electronic health records that enable measurement-based care.[101-105] Such systems must continuously evaluate interventions, resulting in data-based real-time improvements in care delivery.[106,107] These records are essential for managing complex cases through stratified care pathways, which range from psychoeducation to intensive case management, ensuring tailored care for each patient.[108,109]

Third, stratified care that recognizes the diversity of patient needs is another key principle.[110,111] This requires care pathways suited to individual requirements, ensuring that each patient receives the appropriate level of intervention – from psychoeducation for some to complex case management for others.[112] Initially, this will involve shifting from a disease-centered model towards a staging approach focused on health promotion and disease prevention, especially community-based initiatives in schools and workplaces.[100] This stratified system entails progressive therapeutic interventions in accordance with a dimensional view of mental health issues, paying special attention to marginalized communities and case management.[86] Interventions designed for marginalized communities could be supervised by community leaders to foster trust and increase the relevance of care.[113,114] To prevent system overload and ensure efficient resource use, specialized multidisciplinary case management teams must be formed for individuals with complex needs to address the multifaceted nature of mental health issues.[115,116]

Fourth, the importance of continuous care quality measurement cannot be overstated.[100,117,118] Care must be assessed through instruments that gauge the structure, process, and outcomes of care, thus encouraging improvement.[70,119] These instruments must align with human rights principles, ensuring that services are both effective and equitable, respectful of individual rights, and responsive to community needs. Prioritizing people with lived experience will be critical in performance monitoring, embracing outcomes that matter to patients, as suggested by models such as valued-based health care.[120,121]

Finally, drastic shift is needed in investment priorities towards implementation science, which is crucial for evaluating the efficiency of mental health systems.[122] This scientific approach will identify factors that enable or hinder effective mental health service delivery, consequently improving care in S20 nations.[123]

Final considerations and recommendations

This second part of the S20 mental health report, which was formulated by a group of Brazilian experts, has focused on the implications of climate change, the role of environmental factors in NDD, integrating SMI and

precision psychiatry, the intersection of physical and mental health conditions, recent progress in biomarker research, the utilization of digital health solutions, the implementation of interventional psychiatry approaches, and the design of future innovative mental health systems that prioritize both innovation and human rights principles.

The climate crisis has deeply affected global mental health through chronic stressors that erode social cohesion and exacerbate vulnerabilities among already marginalized groups. However, because most studies have been conducted in high-income countries, research is lacking on the most affected populations in low-and middle-income countries. There is a notable lack of research on resilience-building strategies and adapting health care systems to meet the needs of these populations, particularly among young people. Further research is urgently needed to comprehensively assess the true extent of climate change's impact on mental health and to quantify its burden on mental health outcomes.

Although autism has traditionally been attributed a high heritability rate (80-90%), which implies relatively little influence from environmental factors, recent research suggests that environmental factors may play a greater role in autism spectrum disorder, accounting for 40-50% of the risk.[124] During critical developmental stages, such as pregnancy and early childhood, studies have indicated that pesticide exposure could be linked with an increased risk of NDD, including learning disabilities. Evidence is also emerging of a potential association between pesticide exposure and autism spectrum disorder. However, these studies are ongoing, and further research is needed to comprehensively understand the potential cause-and-effect relationship between pesticide exposure and autism spectrum disorder.[125]

One key challenge for psychiatry is how to achieve better outcomes for severe mental disorders. Current limitations to treatment success may stem from the very definitions of these disorders themselves. Diagnoses should ideally reflect underlying brain function, paving the way for more precise treatment (precision psychiatry). However, current databases are heavily skewed towards high-income countries, neglecting the rich tapestry of human genetic diversity. The future lies in developing truly personalized treatment that considers individual factors like genetic predisposition and a deeper understanding of brain circuit activity. Limited access to treatment creates additional hurdles, impeding early identification, a critical factor for a positive prognosis. It also hinders efforts to combat stigma, promote social support, and establish effective rehabilitation programs – all essential components for addressing individual social needs and the broader determinants of mental health.

Comorbidity, the simultaneous occurrence of multiple medical conditions, is a multifaceted phenomenon characterized by interactions that can exacerbate disease prognosis. The relationship between mental and physical health is bidirectional, i.e., compromised physical health can impact mental health, and vice versa. Various factors, including lifestyle choices, socioeconomic status, and education level, contribute to the complexity of this relationship. Neglecting treatment can trigger a positive feedback loop, worsening both mental and physical disorders.

Recognizing comorbidity as a significant public health concern, concerted efforts are being made to identify and address it. Screening tools play a crucial role in evaluating the extent of comorbidity, and tailored treatment plans encompassing medication, therapy, lifestyle modification, and support networks are imperative. Psychotherapy, an interdisciplinary approach involving collaboration between mental health and medical professionals, is vital for accurate diagnosis and effective treatment planning. Comprehensive strategies tailored to individual needs are essential to enhance the well-being and quality of life of individuals grappling with comorbidity. Should psychiatric patients receive treatment in general hospitals due to the high prevalence of comorbidity between physical and mental disorders? Reassessing treatment settings for psychiatric patients in general hospitals, where their mental and physical needs are addressed by a multidisciplinary team, should be prioritized in mental health policy. However, there are practical challenges to overcome, including staff training, the suitability of general hospitals, implementation costs, stigma reduction, and bed availability. Coordinating a comprehensive approach that integrates mental and physical health care would greatly benefit psychiatric patients and represent a proactive step towards greater longevity.

Biomarkers are biological indicators that reflect the underlying state or process of a disease. They should be easily detectable through blood tests, brain scans, or other methods, and must be specific to a particular disorder. Psychiatry has traditionally relied on descriptive sets of behaviors to diagnose mental health conditions. While biomarker alterations have been found in various psychiatric conditions (e.g., brain derived neurotrophic factor, interleukin-6, tumor necrosis factor-alpha, and C-reactive protein), they lack the specificity needed for definitive diagnosis. In essence, a perfect psychiatric biomarker would be specific to a single disorder and would be easily detectable through non-invasive means. Unfortunately, none of the currently identified peripheral biomarkers have achieved this level of specificity. Thus, it is likely that a combination of approaches will be necessary for accurate diagnosis in the future.

There are significant barriers to the widespread use of digital psychiatry. Those who stand to benefit the most from digital health interventions often encounter the greatest obstacles to access. Nevertheless, these interventions can play a critical role in improved screening and diagnosis, reduced stigma, increased psychotherapeutic support, and better integration of artificial intelligence into data collection and risk behavior surveillance. Although many new apps and tools are in development, their long-term effectiveness must be verified through additional research. It is important to view digital tools as supplements, rather than substitutes, for traditional in-person care, and they should be seamlessly integrated into existing health care systems.

Although Industry 4.0 has great potential to revolutionize mental health care, many challenges must be overcome, the first of which is accessibility. Innovations in

mental health care open a range of possibilities to transform care and support for patients, offering more accessible, personalized, and efficient tools. Technologies such as mobile apps, artificial intelligence, and virtual reality can significantly improve patient quality of life, reduce the stigma associated with mental illness, and optimize health care system resources. However, these innovations must be accompanied by rigorous clinical validation processes and regulatory adaptations to ensure their effectiveness and safety. The road ahead is challenging, but the potential rewards for patients, health care professionals, and society are immeasurable, signaling a new era in mental health treatment.

Interventional psychiatry, a growing sector in mental health care, employs techniques beyond medication to address severe or treatment-resistant conditions. It operates in tandem with, rather than as a substitute for, traditional therapies, offering a more holistic treatment approach. Complementing conventional talk therapy and pharmacotherapy, it involves interventions such as electroconvulsive therapy, transcranial magnetic stimulation, and ketamine infusion to modulate brain activity. These interventions are typically sought when conventional methods fail to alleviate conditions like major depression, obsessive-compulsive disorder, or bipolar disorder. The objective of these procedures is to activate or regulate specific brain regions implicated in mood and emotional regulation.

The CISM is a testament to advances in Brazilian psychiatry. Selecting two mid-sized cities in the state of São Paulo as epidemiological laboratories, it seeks to pilot mental health policy interventions that can be scaled up in Brazil and abroad. The CISM holds promise for revolutionizing Brazilian mental health research, aiming for greater consistency, purposefulness, and social relevance in translational science. In pursuit of this goal, it is committed to investment in high-value studies, forging and strengthening partnerships across the public and private sectors to cultivate innovative ideas. It also strives to deliver systematic interventions with real-world effects, ultimately improving the lives of the most vulnerable members of our communities, in addition to transforming these interventions into effective public policies.

Innovative mental health systems require cooperation between sectors that traditionally do not communicate. Technology and human rights must be integrated to provide both centralized and distributed services, stratified care, and quality control through continuous measurement. Marginalized groups must be prioritized and investment must be made in implementation science. As the S20 countries prepare for the future, we need principles that can advance innovation, uphold human rights, and strive for the highest standards in mental health care.

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DPB: Methodology, Writing – original draft.
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References

1 Marcantonio R, Fuentes A. Environmental violence: a tool for planetary health research. Lancet Planet Heal. 2023;7:e859-67.
2 Von Koerber K, Bader N, Leitzmann C. Wholesome nutrition: an example for a sustainable diet. Proc Nutr Soc. 2017;76:34-41.
3 Emmelin A, Fantahun M, Berhane Y, Wall S, Byass P. Vulnerability to episodes of extreme weather: Butajira, Ethiopia, 1998-1999. Glob Health Action. 2009;2:1829.
4 Carter T, Jepsen JR. Exposures and health effects at sea: report on the NIVA course: maritime occupational medicine, exposures and health effects at Sea Elsinore, Denmark, May 2014. Int Marit Health. 2014;65:114-21.
5 Palinkas LA, Wong M. Global climate change and mental health. Curr Opin Psychol. 2020;32:12-6.
6 Ebi KL, Capon A, Berry P, et al. Hot weather and heat extremes: health risks. Lancet. 2021;398:698-708.
7 Charlson F, Ali S, Benmarhnia T, Pearl M, Massazza A, Augustinavicius J, et al. Climate Change and Mental Health: A Scoping Review. Int J Environ Res Public Health. 2021;18:4486.

8 De Figueiredo CS, Sandre PC, Portugal LCL, Mázala-de-Oliveira T, da Silva Chagas L, Raony Í, et al. COVID-19 pandemic impact on children and adolescents' mental health: biological, environmental, and social factors. Prog Neuro-Psychopharmacology Biol Psychiatry. 2021;106:110171.
9 Burke SEL, Sanson A V, Van Hoorn J. The psychological effects of climate change on children. Curr Psychiatry Rep. 2018;20:35.
10 What happens when climate change and the mental-health crisis collide? Nature. 2024;628:235.
11 Hickman C, Marks E, Pihkala P, Clayton S, Lewandowski RE, Mayall EE, et al. Climate anxiety in children and young people and their beliefs about government responses to climate change: a global survey. Lancet Planet Heal. 2021;5:e863-73.
12 Ojala M, Cunsolo A, Ogunbode CA, Middleton J. Anxiety, Worry, and Grief in a Time of Environmental and Climate Crisis: A Narrative Review. Annu Rev Environ Resour. 2021;46(1):35-58. doi: 10.1146/annurev-environ-012220-022716
13 Griffin BJ, Purcell N, Burkman K, Litz BT, Bryan CJ, Schmitz M, et al. Moral injury: an integrative review. J Trauma Stress. 2019;32:350-62.
14 Cordeiro VL, Pena RFO, Ceballos CAC, Shimoura RO RA. Application of information theory to neuroscience. Rev Bras Teach Phys. 2019;41(2):100-2.
15 Kempermann G. Environmental enrichment, new neurons and the neurobiology of individuality. Nat Rev Neurosci. 2019;20:235-45.
16 Toda T, Gage FH. Review: adult neurogenesis contributes to hippocampal plasticity. Cell Tissue Res. 2018;373:693-709.
17 Ayeni EA, Aldossary AM, Ayejoto DA, Gbadegesin LA, Alshehri AA, Alfassam HA, et al. Neurodegenerative diseases: implications of environmental and climatic influences on neurotransmitters and neuronal hormones activities. Int J Environ Res Public Health. 2022;19:12495.
18 Marzola P, Melzer T, Pavesi E, Gil-Mohapel J, Brocardo PS. Exploring the role of neuroplasticity in development, aging, and neurodegeneration. Brain Sci. 2023;13:1610.
19 Aggarwal V, Mehndiratta M, Wasay M, Garg D. Environmental toxins and brain: Life on earth is in danger. Ann Indian Acad Neurol. 2022;25:15.
20 Carlsson T, Molander F, Taylor MJ, Jonsson U, Bölte S. Early environmental risk factors for neurodevelopmental disorders – a systematic review of twin and sibling studies. Dev Psychopathol. 2021;33:1448-95.
21 Yang Y, Zhou S, Xing Y, Yang G, You M. Impact of pesticides exposure during neurodevelopmental period on autism spectrum disorders – A focus on gut microbiota. Ecotoxicol Environ Saf. 2023;260:115079.
22 Fujiwara T, Morisaki N, Honda Y, Sampei M, Tani Y. Chemicals, nutrition, and autism spectrum disorder: a mini-review. Front Neurosci. 2016;10:174.
23 Scorza FA, Beltramim L, Bombardi LM. Pesticide exposure and human health: toxic legacy. Clinics. 2023;78:100249.
24 Pathak VM, Verma VK, Rawat BS, Rawat BS, Kaur B, Babu N, et al. Current status of pesticide effects on environment, human health and it's eco-friendly management as bioremediation: a comprehensive review. Front Microbiol. 2022;13:962619.
25 Damiani S, Montalvão MTL, Mendes RA, Costa ACG, Passos CJS. Water and sediment pesticide contamination on indigenous lands surrounded by oil palm plantations in the Brazilian Amazon. Heliyon. 2023;9:e19920.
26 Rigotto RM, Vasconcelos DP, Rocha MM. Pesticide use in Brazil and problems for public health. Cad Saude Publica. 2014;30:1360-2.
27 Solmi M, Radua J, Olivola M, Croce E, Soardo L, Pablo GS, et al. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol Psychiatry. 2022;27:281-95.
28 Levinson D, Lakoma MD, Petukhova M, Schoenbaum M, Zaslavsky AM, Angermeyer M, et al. Associations of serious mental illness with earnings: results from the WHO World Mental Health surveys. Br J Psychiatry. 2010;197:114-21.
29 GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9:137-50.
30 Arias D, Saxena S, Verguet S. Quantifying the global burden of mental disorders and their economic value. EClinicalMedicine. 2022;54:101675.
31 Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. Bull World Health Organ. 2004;82:858-66.
32 Wang PS, Demler O, Kessler RC. Adequacy of treatment for serious mental illness in the united states. Am J Public Health. 2002;92:92-8.
33 Dagani J, Signorini G, Nielssen O, Bani M, Pastore A, Girolamo G, et al. Meta-analysis of the interval between the onset and management of bipolar disorder. Can J Psychiatry. 2017;62:247-58.
34 Howes OD, Whitehurst T, Shatalina E, et al. The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. World Psychiatry. 2021;20:75-95.
35 Crossley NA, Alliende LM, Czepielewski LS, Townsend L, Onwordi EC, Mak TLA, et al. The enduring gap in educational attainment in schizophrenia according to the past 50 years of published research: a systematic review and meta-analysis. Lancet Psychiatry. 2022;9:565-73.
36 Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of 'precision psychiatry'. BMC Med. 2017;15:80.
37 Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372:793-5.
38 Fleck DE, Ernest N, Adler CM, Cohen K, Eliassen JC, Norris M, et al. Prediction of lithium response in first-episode mania using the LITHium Intelligent Agent (LITHIA): pilot data and proof-of-concept. Bipolar Disord. 2017;19:259-72.
39 Koutsouleris N, Kahn RS, Chekroud AM, Leucht S, Falkai P, Wobrock T, et al. Multisite prediction of 4-week and 52-week treatment outcomes in patients with first-episode psychosis: a machine learning approach. Lancet Psychiatry. 2016;3:935-46.
40 Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. A marker for Stevens-Johnson syndrome. Nature. 2004;428:486.
41 Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimäki M. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. Brain Behav Immun. 2015;49:206-15.
42 Khan A, Leonard D, Defina L, Barlow CE, Willis B, Brown ES. Association between C reactive protein and depression in a population of healthy adults: the Cooper Center longitudinal study J Investig Med. 2020;68:1019-23.
43 Figueroa-Hall LK, Xu B, Kuplicki R, Ford BN, Burrows K, Teague TK, et al. Psychiatric symptoms are not associated with circulating CRP concentrations after controlling for medical, social, and demographic factors. Transl Psychiatry. 2022;12:279.
44 Köhne ACJ, van Os J. Precision psychiatry: promise for the future or rehash of a fossilised foundation? Psychol Med. 2021;51:1409-11.
45 Fonseca L, Sena BF, Crossley N, Lopez-Jaramillo C, Koenen K, Freimer NB, et al. Diversity matters: opportunities in the study of the genetics of psychotic disorders in low- and middle-income countries in Latin America. Brazilian J Psychiatry. 2021;43:631-7.
46 Fiorillo A, Girolamo G, Simunovic IF, Gureje O, Isaac M, Lloyd C, et al. The relationship between physical and mental health: an update from the WPA Working Group on Managing Comorbidity of Mental and Physical Health. World Psychiatry. 2023;22:169-70.
47 Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality. JAMA. 2011;306:1241.
48 Wu Q, Kling JM. Depression and the risk of myocardial infarction and coronary death. Medicine (Baltimore). 2016;95:e2815.
49 Meijer A, Conradi HJ, Bos EH, Anselmino M, Carney RM, Denollet J, et al. Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis. Br J Psychiatry. 2013;203:90-102.
50 Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations. Circulation. 2014;129:1350-69.
51 Shi S, Liu T, Liang J, Hu D, Yang B. Depression and risk of sudden cardiac death and arrhythmias: a meta-analysis. Psychosom Med. 2017;79:153-61.
52 Nouwen A, Adriaanse MC, van Dam K, Iversen MM, Viechtbauer W, Peyrot M, et al. Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. Diabet Med. 2019;36:1562-72.
53 Hofmann M, Köhler B, Leichsenring F, Kruse J. Depression as a risk factor for mortality in individuals with diabetes: a meta-analysis of prospective studies. PLoS One. 2013;8:e79809.

54 Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, et al. Overweight, obesity, and depression. Arch Gen Psychiatry. 2010;67:220-9.
55 Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. Psychol Med. 2010;40:1797-810.
56 Bosker FJ, Hartman CA, Nolte IM, Prins BP, Terpstra P, Posthuma D, et al. Poor replication of candidate genes for major depressive disorder using genome-wide association data. Mol Psychiatry. 2011;16:516-32.
57 Taporoski TP, Negrão AB, Horimoto ARVR, Duarte NE, Alvim RO, Oliveira CM, et al. Shared genetic factors of anxiety and depression symptoms in a Brazilian family-based cohort, the Baependi Heart Study. PLoS One. 2015;10:e0144255.
58 Smoller JW, Block SR, Young MM. Genetics of anxiety disorders: the complex road from DSM to DNA. Depress Anxiety. 2009;26: 965-75.
59 Hsin H, Fromer M, Peterson B, Walter C, Fleck M, Campbell A, et al. Transforming psychiatry into data-driven medicine with digital measurement tools. NPJ Digit Med. 2018;1:37.
60 Yuan N, Chen Y, Xia Y, Dai J, Liu C. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. Transl Psychiatry. 2019;9:233.
61 García-Gutiérrez MS, Navarrete F, Sala F, Gasparyan A, Austrich-Olivares A, Manzanares J. Biomarkers in psychiatry: concept, definition, types and relevance to the clinical reality. Front Psychiatry. 2020;11:432.
62 Angst J, Merikangas K. The depressive spectrum: diagnostic classification and course. J Affect Disord. 1997;45:31-40.
63 Fernandes BS, Molendijk ML, Köhler CA, Soares JC, Leite CM, Machado-Vieira R, et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med. 2015;13:289.
64 Fernandes BS, Steiner J, Berk M, Molendijk ML, Gonzalez-Pinto A, Turck CW, et al. Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications. Mol Psychiatry. 2015;20:1108-19.
65 Molendijk ML, Spinhoven P, Polak M, Bus BAA, Penninx BWJH, Elzinga BM. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N=9484). Mol Psychiatry. 2014; 19:791-800.
66 Wang M, Chen H, Yu T, Cui G, Jiao A, Liang H. Increased serum levels of brain-derived neurotrophic factor in autism spectrum disorder. Neuroreport. 2015;26:638-41.
67 Munkholm K, Vinberg M, Kessing L V. Peripheral blood brain-derived neurotrophic factor in bipolar disorder: a comprehensive systematic review and meta-analysis. Mol Psychiatry. 2016;21: 216-28.
68 Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015;2:1002-12.
69 World Health Organization (WHO). Global strategy on digital health 2020-2025. Geneva: WHO; 2021.
70 Patel V, Saxena S, Lund C, Thornicroft G, Baingana F, Bolton P, et al. The Lancet Commission on global mental health and sustainable development. Lancet. 2018;392:1553-98.
71 Zangani C, Ostinelli EG, Smith KA, Hong JSW, Macdonald O, Reen G, et al. Impact of the COVID-19 pandemic on the global delivery of mental health services and telemental health: systematic review. JMIR Ment Heal. 2022;9:e38600.
72 Bush NE, Armstrong CM, Hoyt TV. Smartphone apps for psychological health: a brief state of the science review. Psychol Serv. 2019;16:188-95.
73 Larsen ME, Huckvale K, Nicholas J, Torous J, Birrell L, Li E, et al. Using science to sell apps: evaluation of mental health app store quality claims. NPJ Digit Med. 2019;2:18.
74 Torous J, Bucci S, Bell IH, Kessing LV, Faurholt-Jepsen M, Whelan P, et al. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality. World Psychiatry. 2021;20:318-35.
75 Food and Drug Administration. FDA permits marketing of mobile medical application for substance use disorder [Internet]. 2017 Sep 14. [cited 2024 Jul 5]. https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-mobile-medical-application-substance-use-disorder#:~:text=Today%2C%20the%20U.S.%20Food%20and,cocaine%2C%20marijuana%20and%20stimulant%20SUDs
76 Morin CM. Profile of somryst prescription digital therapeutic for chronic insomnia: overview of safety and efficacy. Expert Rev Med Devices. 2020;17:1239-48.
77 Canady VA. FDA approves first video game Rx treatment for children with ADHD. Ment Heal Wkly. 2020;30:1-7.
78 NightWare [Internet]. [cited 2024 Jul 5]. https://nightware.com/
79 Ben-Zeev D, Brian R, Wang R, Wang W, Campbell AT, Aung MSH, et al. CrossCheck: integrating self-report, behavioral sensing, and smartphone use to identify digital indicators of psychotic relapse. Psychiatr Rehabil J. 2017;40:266-75.
80 Wong BLH, Maaß L, Vodden A, van Kessel R, Sorbello S, Buttigieg S, et al. The dawn of digital public health in Europe: Implications for public health policy and practice. Lancet Reg Heal Eur. 2022;14: 100316.
81 Wienert J, Jahnel T, Maaß L. What are digital public health interventions? First steps toward a definition and an intervention classification framework. J Med Internet Res. 2022;24:e31921.
82 Primary Care Foundation. Making time in general practice [Internet] Oct 2015. [cited 2024 Jul 5]. https://thehealthcreationalliance.org/wp-content/uploads/2018/11/Making-Time-in-General-Practice-FULL-REPORT-06-10-15.pdf
83 Smith KA, Blease C, Faurholt-Jepsen M, Firth J, van Daele T, Moreno C, et al. Digital mental health: challenges and next steps. BMJ Ment Heal. 2023;26:e300670.
84 Van Kessel R, Hrzic R, O'Nuallain E, Weir E, Wong BLH, Anderson M, et al. Digital health paradox: international policy perspectives to address increased health inequalities for people living with disabilities. J Med Internet Res. 2022;24:e33819.
85 Sieck CJ, Sheon A, Ancker JS, Castek J, Callahan B, Siefer A. Digital inclusion as a social determinant of health. NPJ Digit Med. 2021;4:52.
86 World Health Organization. World mental health report: transforming mental health for all Geneva: WHO; 2022.
87 World Health Organization (WHO). Ethics and governance of artificial intelligence for health. Geneva: World Health Organization; 2021.
88 Borrione L, Suen PJC, Razza LB, Santos LA, Sudbrack-Oliveira P, Brunoni AR. The flow brain stimulation headset for the treatment of depression: overview of its safety, efficacy and portable design. Expert Rev Med Devices. 2020;17:867-78.
89 Daskalakis ZJ, Dimitrova J, McClintock SM, Sun Y, Voineskos D, Rajji TK, et al. Magnetic seizure therapy (MST) for major depressive disorder. Neuropsychopharmacology. 2020;45:276-82.
90 Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. Mol Psychiatry. 2018;23:801-11.
91 Salum GA, Gadelha A, Pan PM, Moriyama TS, Graeff-Martins AS, Tamanaha AC, et al. High risk cohort study for psychiatric disorders in childhood: rationale, design, methods and preliminary results. Int J Methods Psychiatr Res. 2015;24:58-73.
92 Betancourt TS, Chambers DA. Optimizing an era of global mental health implementation science. JAMA Psychiatry. 2016;73:99.
93 Alarcão FSP, Shephard E, Fatori D, Amável R, Chiesa A, Fracolli L, et al. Promoting mother-infant relationships and underlying neural correlates: Results from a randomized controlled trial of a home-visiting program for adolescent mothers in Brazil. Dev Sci. 2021;24: e13113.
94 Frankish H, Boyce N, Horton R. Mental health for all: a global goal. Lancet. 2018;392:1493-4.
95 World Health Organization. Comprehensive mental health action plan 2013-2030 Geneva: WHO; 2021.
96 Brohan E, Chowdhary N, Dua T, Barbui C, Thornicroft G, Kestel D, et al. The WHO Mental Health Gap Action Programme for mental, neurological, and substance use conditions: the new and updated guideline recommendations. Lancet Psychiatry. 2024;11:155-8.
97 Fu Z, Burger H, Arjadi R, Bockting CLH. Effectiveness of digital psychological interventions for mental health problems in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Psychiatry. 2020;7:851-64.
98 Keynejad R, Spagnolo J, Thornicroft G. WHO mental health gap action programme (mhGAP) intervention guide: updated systematic

review on evidence and impact. Evid Based Ment Heal. 2021;24:124-30.
99 Naslund JA, Aschbrenner KA, Araya R, Marsch LA, Unützer J, Patel V, et al. Digital technology for treating and preventing mental disorders in low-income and middle-income countries: a narrative review of the literature. Lancet Psychiatry. 2017;4:486-500.
100 Patel V, Saxena S, Lund C, Kohrt B, Kieling C, Sunkel C, et al. Transforming mental health systems globally: principles and policy recommendations. Lancet. 2023;402:656-66.
101 Basch E, Barbera L, Kerrigan CL, Velikova G. Implementation of patient-reported outcomes in routine medical care. Am Soc Clin Oncol Educ B. 2018;38:122-34.
102 Hallgren KA, Bauer AM, Atkins DC. Digital technology and clinical decision making in depression treatment: current findings and future opportunities. Depress Anxiety. 2017;34:494-501.
103 Horn ME, Reinke EK, Mather RC, O'Donnell JD, George SZ. Electronic health record-integrated approach for collection of patient-reported outcome measures: a retrospective evaluation. BMC Health Serv Res. 2021;21:626.
104 Lewis CC, Boyd M, Puspitasari A, Navarro E, Howard J, Kassab H, et al. Implementing measurement-based care in behavioral health. JAMA Psychiatry. 2019;76:324-35.
105 Riahi S, Fischler I, Stuckey MI, Klassen PE, Chen J. The value of electronic medical record implementation in mental health care: a case study. JMIR Med Informatics. 2017;5:e1.
106 Black WE, Nagarkatti-Gude DR, Jetmalani A, Keepers G. Harnessing technology to implement measurement-based care. Acad Psychiatry. 2018;42:711-6.
107 Lyon AR, Wasse JK, Ludwig K, Zachry M, Bruns EJ, Unützer J, et al. The contextualized technology adaptation process (CTAP): optimizing health information technology to improve mental health systems. Adm Policy Ment Heal Ment Heal Serv Res. 2016;43: 394-409.
108 Hickie IB, Scott EM, Cross SP, Iorfino F, Davenport TA, Guastella AJ, et al. Right care, first time: a highly personalised and measurement-based care model to manage youth mental health. Med J Aust. 2019;211:S3-46.
109 Hong RH, Murphy JK, Michalak EE, Chakrabarty T, Wang Z, Parikh SV, et al. Implementing measurement-based care for depression: practical solutions for psychiatrists and primary care physicians. Neuropsychiatr Dis Treat. 2021;17:79-90.
110 Cornish PA, Berry G, Benton S, Barros-Gomes P, Johnson D, Ginsburg R, et al. Meeting the mental health needs of today's college student: reinventing services through Stepped Care 2.0. Psychol Serv. 2017;14:428-42.
111 Raviola G, Naslund JA, Smith SL, Patel V. Innovative models in mental health delivery systems: task sharing care with non-specialist providers to close the mental health treatment gap. Curr Psychiatry Rep. 2019;21:44.
112 Thornicroft G, Tansella M. The balanced care model for global mental health. Psychol Med. 2013;43:849-63.
113 Hoeft TJ, Fortney JC, Patel V, Unützer J. Task-sharing approaches to improve mental health care in rural and other low-resource settings: a systematic review. J Rural Heal. 2018;34:48-62.
114 Munodawafa M, Mall S, Lund C, Schneider M. Process evaluations of task sharing interventions for perinatal depression in low and middle income countries (LMIC): a systematic review and qualitative meta-synthesis. BMC Health Serv Res. 2018;18:205.
115 Lukersmith S, Millington M, Salvador-Carulla L. What is case management? A scoping and mapping review. Int J Integr Care. 2016;16:2.
116 Ponka D, Agbata E, Kendall C, Stergiopoulos V, Mendonca O, Magwood O, et al. The effectiveness of case management interventions for the homeless, vulnerably housed and persons with lived experience: A systematic review. PLoS One. 2020;15:e0230896.
117 Kilbourne AM, Beck K, Spaeth-Rublee B, Ramanuj P, O'Brien RW, Tomoyasu N, et al. Measuring and improving the quality of mental health care: a global perspective. World Psychiatry. 2018;17:30-8.
118 Saxena S, Kline S. Countdown Global Mental Health 2030: data to drive action and accountability. Lancet Psychiatry. 2021;8:941-2.
119 Saxena S, Kestel D, Sunkel C, London E, Horton R, Patel V, et al. Countdown Global Mental Health 2030. Lancet. 2019;393:858-9.
120 Chevance A, Ravaud P, Tomlinson A, Le Berre C, Teufer B, Touboul S, et al. Identifying outcomes for depression that matter to patients, informal caregivers, and health-care professionals: qualitative content analysis of a large international online survey. Lancet Psychiatry. 2020;7:692-702.
121 Zanotto BS, Etges APBS, Marcolino MAZ, Polanczyk CA. Value-based healthcare initiatives in practice: a systematic review J Healthc Manag. 2021;66:340-65.
122 Wainberg ML, Gouveia L, McKinnon K. Generating better implementation evidence to improve mental health care everywhere. Lancet Psychiatry. 2024;11:317-9.
123 McGinty EE, Alegria M, Beidas RS, Braithwaite J, Kola L, Leslie DL, et al. The Lancet Psychiatry Commission: transforming mental health implementation research. Lancet Psychiatry. 2024;11: 368-96.
124 Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Mol Autism. 2017;8:13.
125 He X, Tu Y, Song Y, Yang G, You M. The relationship between pesticide exposure during critical neurodevelopment and autism spectrum disorder: A narrative review. Environ Res. 2022;203: 111902.