

POPULATION-LEVEL PREVENTION OF SEVERE MENTAL DISORDERS

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Severe mental disorders (SMD) typically develop early, with 62.5% of people with a mental disorder first developing symptoms in adolescence or young adulthood (Solmi et al., 2022). Once established, they have extensive distressing effects on the individuals, their families and society (Estradé et al., 2023; Fusar-Poli et al., 2023, 2022; Fusar-Poli et al., 2024). Preventive approaches have been increasingly adopted as key strategies to improve cost-effective care for people with SMD and reduce their incidence (Fusar-Poli et al., 2021).

There are three key avenues for preventing SMD: (i) population-level or universal interventions, which aim to reduce the incidence of disorders in the general population; (ii) selective interventions, which aim to identify groups with risk factors that correspond to higher risk (e.g. individuals with parents who have an SMD diagnosis (Uher et al., 2023)); and (iii) indicated prevention, which aims to identify individuals with subtle sub-threshold symptoms that increase SMD risk (Fusar-Poli et al., 2020; Fusar-Poli et al., 2021; Martini et al., 2024). While indicated preventive interventions can substantially reduce the incidence of SMD (Dragioti et al., 2022; Oliver et al., 2022), developing preventive approaches that target the general population have the greatest promise to reduce the incidence of these disorders as they are not reliant on identifying groups at increased risk (Salazar de Pablo et al., 2021, 2020).

This special issue aims to improve population-level prevention of SMD by synthesising the available evidence for i) risk and protective factors for severe mental disorders to improve detection and prognosis; ii) similarities and differences of risk and protective factors across SMD diagnoses and cultures; and iii) effectiveness of population-level preventive interventions.

Risk and protective factors, neurodevelopment and the social context

Oliver et al. (2024) critically examined how 25 established environmental risk factors alter neurobiology to cause psychosis onset. While these exposures are consistently associated with increased psychosis risk, clarifying the mechanistic pathways linking them to illness onset can aid preventive efforts. The paper highlights that chronic psychosocial stressors (e.g. trauma, discrimination) drive HPA axis hyperactivity and inflammation. In addition, substance use (e.g. cannabis) and early-life infections exacerbate dopaminergic and glutamatergic dysfunction. The authors argue that understanding these shared pathways is essential for advancing biomarker-based risk prediction and developing preventive interventions targeting upstream mechanisms. The review advocates for large-scale, multimodal longitudinal studies to test and refine these mechanistic models in clinical high-risk populations.

Zahid et al. (2024) proposed a framework to address the complex interplay of social, physical, and mental health conditions that co-occur with psychosis. This framework relies on the concept of syndemics, which enables the clustering and interaction of two or more disorders and/or socioeconomic, environmental, or political factors within a population. This allows for better understanding of how co-occurring health and social conditions interact to shape population mental health and guide more effective prevention. These frameworks may better explain psychosis onset and outcomes than traditional models that may focus on the impact of one factor (e.g. socioeconomic status) in psychosis patients in isolation. They showed that co-

occurring factors (e.g. substance use, comorbid mental disorders, social deprivation and ethnic minority status) interact synergistically, amplifying psychosis risk, worsening health outcomes. This can also lead to widening disparities in terms of access to healthcare and economic opportunities. These syndemic effects are particularly pronounced among ethnic minority and economically deprived groups, highlighting structural inequities (e.g. inadequate access to education and healthcare (Anglin et al., 2021)). Understanding psychosis as part of a synergistic web of health and social adversities can yield novel insights for prevention and treatment through larger scale political, social and economic policies. New paradigms and datasets designed to capture these interactions over time and across populations can better inform targeted interventions and policies that improve mental health outcomes in marginalized communities. Moving beyond isolated risk factor models is essential to address the cumulative and interactive burden of adversity underpinning psychosis, such as the Psychosis Polyrisk Score (PPS) (Oliver et al., 2020, 2019).

Refining transdiagnostic prevention of SMD can be improved by transdiagnostic biomarkers, which could help individual-level prognosis and risk stratification. Widespread structural and functional changes are seen in the brain across SMD diagnoses, meaning that metrics capturing these changes have high potential utility. BrainAGE is an imaging-based biomarker that estimates a brain's predicted age from structural or functional neuroimaging against one's chronological age. A gap exists in understanding whether BrainAGE reliably captures accelerated biological aging in psychiatric and neurological disorders. To address this gap, Seitz-Holland et al. (2024) evaluated if BrainAGE meaningfully differs across conditions and whether it aligns with symptoms or disease severity. While methodologies varied, elevated BrainAGE was consistently found in clinical populations: notably in mild cognitive impairment/dementia, schizophrenia-spectrum/psychotic and bipolar disorders, and depression/anxiety. However, correlations with clinical variables (e.g. symptom scores, illness duration) were inconsistent, and few studies offered longitudinal data. To enable the use of BrainAGE as a reliable clinical and research measure, key limitations need to be addressed in future studies: lack of diverse training data, limited multimodal integration, insufficient external validation and scarcity of longitudinal data. If these limitations are addressed, there is potential for BrainAGE to be used as a biomarker for SMD and facilitate preventive efforts.

Griffiths (2024) integrated these findings in a commentary, recognizing that SMD cluster with issues like substance use, chronic disease, poverty and discrimination, there is a clear argument for moving beyond single-disease models to address synergistic interactions in specific social contexts. It is crucial to understand which conditions cluster together, how they biologically and socially interact and where they do not to effectively identify complex, intertwined drivers of SMD and points for population-level intervention.

Risk across cultures and psychopathological spectra

Rami et al. (2024) examined risk and protective factors for SMD in Asia, addressing the gap in region-specific data. While many studies on mental health are conducted in Western countries, their findings may not be applicable to Asian populations due to cultural and contextual differences. Risk factors that are common to Asia and Western studies include childhood adversity, substance use, and urbanicity.

However, several factors are more specific to Asia, such as familial expectations, academic pressure, and stigma surrounding mental illness, which significantly impact mental health outcomes. Protective factors identified include strong family support, religious involvement, and community cohesion, which are particularly salient in many Asian cultures. It is imperative to consider these cultural and societal contexts when developing mental health interventions and policies, particularly at an international level. Further region-specific research and culturally tailored approaches that incorporate traditional values and community structures can more effectively address the mental health needs of Asian populations.

Uher et al. (2024) synthesised prospective studies to identify factors that increase risk of depression, bipolar disorder and psychotic disorders. Certain early-life behaviours and experiences serve as transdiagnostic predictors for these disorders, specifically psychotic experiences, depressive symptoms, anxiety, disruptive behaviours, affective lability and sleep disturbances. Additionally, attention-deficit/hyperactivity disorder and hypomanic symptoms were uniquely predictive of bipolar disorder onset. The study also highlights significant gaps in the evidence base, such as the lack of examination of obsessive-compulsive disorder and eating disorders with psychosis, as well as limited investigation of rumination as a risk factor for bipolar disorder and psychosis. This requires further research to better understand the developmental trajectories leading to these mental health conditions. The authors advocate for enhanced screening and preventive measures during childhood and adolescence to mitigate the risk of developing these disorders. These findings underscore the importance of early identification and intervention strategies targeting these factors to prevent the onset of depression, bipolar disorder and psychosis at a population level.

Oliver (2024) outlined a vision for the future of preventive psychiatry, arguing that it must embrace precision and transdiagnostic principles. Traditional disorder-specific prevention strategies are less able to account for individual risk trajectories or overlapping risk factors across disorders. Prediction models that integrate biological, cognitive, environmental and psychosocial data to identify transdiagnostic risk profiles may be more impactful in preventing SMD holistically, though these are complex to develop and implement.

Cervenka and Sundström (2025) echoed this in their commentary by highlighting the complexity of SMD, evidenced by heterogeneity in clinical presentation and, in turn, treatment effects. The current one-size-fits-all approaches ignore individual differences in risk, biology and context. Optimal trial designs (including adaptive, stratified or cluster-randomized trials) can be supported by integrating transdiagnostic prediction models to identify who benefits most from specific interventions. By measuring moderators like biomarkers, symptom profiles, and social determinants, prevention strategies and treatment selection can be personalised to improve effective preventive care.

Population-level interventions to prevent severe mental disorders

Rahmati et al. (2024) synthesised evidence from 34 meta-analyses to assess the impact of physical activity on the prevention of mental health complications, including depression, anxiety and psychosis. Low and moderate physical activity was linked to

a lower risk of depression and anxiety. The lack of effect of high-intensity physical activity highlight the need for precise exercise guidelines, particularly when high-intensity physical activity can trigger the onset of manic episodes. Public health strategies to promote physical activity as a preventive measure against mental health complications, advocating for the integration of physical activity into daily routines and community health initiatives. This is particularly important considering that people with SMD experience increased risk of comorbid physical conditions and poorer physical health outcomes (Dragioti et al., 2023). Physical activity should be considered a cornerstone in the prevention of mental health disorders, with implications for policy development and clinical practice.

Brodeur et al. (2024) evaluated the effectiveness of population-level preventive interventions in reducing the incidence (i.e. first onset) of affective and psychotic disorders. Previous meta-analyses had typically focused on symptom severity, rather than incident diagnoses, limiting clinical relevance. The study included 18 randomized controlled trials with 66,625 participants, focusing on depression prevention. Notably, no studies were available investigating universal prevention for bipolar or psychotic disorders. Population-level preventive interventions demonstrated a significant preventive effect on reducing the incidence of depression, though these findings did not survive when restricting to studies directly reporting incidence, suggesting limited and inconsistent evidence. While population-level interventions may have some effect on reducing the incidence of depression, there is insufficient evidence to support their effectiveness for bipolar or psychotic disorders. Research into population-level and targeted (selective and/or indicated) prevention strategies should be pursued in tandem to effectively reduce the incidence of these conditions.

These papers are integrated in a commentary by Lund (2024), who suggested that hybrid prevention models (combining universal and targeted approaches) are crucial for effective prevention. These models can be complemented by improving population-level data collection (e.g. registry data) and cross-sector collaboration to address social determinants of mental health.

Together, in this special issue, we have outlined the mechanisms of how severe mental disorders develop at a biological and societal level, compared how these risk factors differ across different settings and disorders, and finally assessed the effectiveness of population-level interventions. These findings have elucidated that while our understanding of the underlying risk factors is growing, more research is needed to integrate and address these risk factors systematically to provide effective preventive psychiatry at a population-level. This can also allow us to identify subgroups at higher risk that could benefit from more intensive intervention. Furthermore, while there is substantial promise in population-level preventive interventions, these must be complemented by targeted (i.e. selective and indicated) prevention approaches for effective prevention and to ensure provision of care to vulnerable young people with distressing experiences.

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Conflicts of Interest

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