Schizophrenia Bulletin Advance Access published January 4, 2014

Schizophrenia Bulletin
doi:10.1093/schbul/sbt202

EDITORIAL

Prevention of Schizophrenia—Will a Broader Prevention Agenda Support This Aim?

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Arguably the greatest victories in modern medicine have come in the arena of prevention. The most spectacular successes have been in vaccination, but even in the non-communicable diseases, such as cardiovascular disease and cancer, this has been true. In cardiovascular disease, the greatest contribution to survival rates has been through smoking cessation programs and blood pressure and lipid monitoring and control, rather than through better treatment of myocardial infarction. Equally, in cancer, survival from metastatic disease remains poor; the advances have been in preventive strategies, early detection and intervention at the earliest stages when prognosis is better. In the mental health arena, we have an increased understanding of the operative risk factors in many psychiatric disorders, including schizophrenia. However, a larger and more diverse array of risk factors operates in psychiatric illnesses, and the individual contribution of these risk factors to disorders is smaller. The question then becomes, is the prevention of schizophrenia a realistic goal?

There is a growing interest in the possibilities for preventing mental disorders, partly driven by the strengthening evidence base for preventive interventions (eg, Beardslee et al[1]) but also by the emerging evidence identifying population level targets and new modes of delivery for preventing mental disorders.[2] In schizophrenia, we already have quality data, and existing programs, in the arena of tertiary prevention, from pharmacotherapy to prevent relapse, to psychosocial and family-based strategies,[3] and strategies to prevent the worst consequences of the disorder such as suicide.[4] In the arena of indicated prevention, the exemplar is the use of omega 3 fatty acids to prevent transition from a high-risk state to frank psychosis.[5] However, the greatest gaps in the evidence base, and possibly the greatest opportunities, exist in the area of primary prevention, where the focus is on reducing the incidence of schizophrenia.

So, what are the risk factors for schizophrenia and are they amenable to modification? Conceptually, many of the risk factors for schizophrenia overlap with risk factors for other psychiatric disorders, such as depression and bipolar disorder, as well as commonly comorbid medical disorders such as cardiovascular disease. While some of the risk factors are plastic and thus amenable to intervention, many, such as the genome, are arguably not. Stress is a nonspecific risk factor for a diverse range of psychopathologies, as is substance abuse. While severe macronutrient deficiencies during critical developmental periods have been implicated in the pathogenesis of both depressive[6] and psychotic illnesses,[7] and specific micronutrient insufficiencies appear to also be key factors in developmental outcomes related to the risk for schizophrenia,[8] emerging evidence from both preclinical and epidemiological studies suggest that factors relating to overnutrition may also play a role in the pathophysiology of mental disorders. Overnutrition also increases the risk for gestational diabetes, which is likewise of relevance to schizophrenia.[9] Similarly, new evidence suggests that maternal tobacco smoking is an independent risk factor for behavioral problems in offspring[10] and related to the risk for schizophrenia,[11] potentially mediated by altering epigenetic pathways and neurodevelopmental trajectories.[12] Maternal vitamin D deficiency appears to be a risk factors for schizophrenia and may be a key target for primary prevention,[13] while cytokine-associated inflammatory events during pregnancy, with their attendant oxidative and nutritional sequelae, are well established as key contributors to neurodevelopmental outcomes, including schizophrenia.[14] Other key risk factors for schizophrenia include advanced paternal age and cannabis smoking. A population-wide drive to reduce cannabis consumption may have an impact on the prevalence of schizophrenia, overlapping with existing programs in that domain.

Many of these seemingly diverse risk factors are transduced via common neuroprogressive pathways, including inflammation, oxidative stress, apoptosis, altered

neurogenesis, and mitochondrial energy dysregulation, and these pathways cross pollinate risk for comorbid disorders such as depression.[15] While factors including psychosocial stressors, poor diet, sedentary behavior, obesity, smoking, sleep, and vitamin D deficiency are all proinflammatory and increase oxidative stress, healthy diets, physical activity, and vitamin D supplementation reduce inflammation and oxidative stress,[16] as well as offering wider health benefits.

As such, a low-risk strategy for attempting schizophrenia prevention may consist of delivering health education and nutritional and lifestyle interventions to women during the antenatal period. This may also have utility in preventing a broader range of mental disorders and cognitive outcomes,[17–19] as well as having benefits for a wide range of other health outcomes in children, given the well-established importance of early life exposures to the risk for later heart disease, stroke, diabetes, and hypertension.[20] Such universal health strategies could be implemented in both antenatal and early childhood settings (ie, after the birth of the first child and anticipating the next), thus targeting both the preconception and antenatal periods. If successful, such interventions may help to improve many of the underlying pathophysiological pathways that feed into early life risk factors, including the risk for infections during pregnancy, and are clearly complemented by improvements in the control of infectious diseases in pregnancy and better obstetric and neonatal care.

On the other hand, while such educational approaches are relatively easy to execute and acceptable to women, the diffuse nature of such programs makes evaluation of the impact on the incidence of specific conditions problematic, particularly over the long time periods required to determine effects. Moreover, such interventions may fail to be effective at changing behaviors in the context of wider structural problems that feed into poor health, including socioeconomic disadvantage, urbanization, and government policies that fail to address the actions of the unhealthy commodity industries.[21] It is also the case that the utility of supplement use in pregnant women requires more rigorous evaluation utilizing randomized controlled trials with prospective evaluation of mental health outcomes in the offspring. Given the somewhat equivocal data concerning nutritional factors during pregnancy and outcomes in mothers and offspring,[8,22] understanding what dose of a nutrient supplement is required, to whom, when, and under what circumstances, is vital.

The relative lack of specificity of the relationships between exposures such as diet, stress, smoking, and physical activity and the large range of physical and mental health outcomes, the complex interactions and bi-directionality of such relationships and, importantly, the potential confounding role of social and other, possibly unrecognized, factors makes the assessment and confirmation of definitive causal associations problematic. However, recent commentaries have argued for the need to give equal weight to the development and evaluation of interventions to improve population health in epidemiology, rather than weighting our focus to the establishment of causality.[23] As such, there is an argument for expediting the development and evaluation of universal preventive approaches that are known to have broad health benefits in the absence of a perfect understanding of causality. Moreover, while the evidence base regarding the importance of health behaviors to mental health is certainly incomplete, future interventions designed to target the syndrome of schizophrenia by addressing health behaviors are likely to receive support from the public and clinical health sector. In this endeavor, bridges can easily be built alongside preventive strategies that are in existence for other disorders. Smoking cessation is arguably as relevant to mental health as it is for cancer and cardiovascular diseases.[24,25] Diet, smoking cessation, and physical activity programs can be partnered with existing efforts in the fields of noncommunicable disease prevention, and vitamin D programs developed in partnership with osteoporosis and rickets prevention strategies.[26] Public health messages that specifically focus on modifiable risk factors for mental disorders may be useful strategies, particularly if they successfully employ contemporary social media.

Activities that occur outside of the health silo may also feed into prevention efforts. A standout exemplar would be the Royal Commission into institutional responses to childhood sexual abuse in Australia. This started as a legal endeavor, but its efforts and the change in public attitudes and policies will deliver payoffs in reducing risk factors for a diversity of psychiatric problems.[27] It is also true that most of the successes in, eg, smoking cessation have been in the arena of public policy, rather than traditional health focused models. It is also critical to recognize that ecological factors, such as socioeconomic disadvantage, strongly feed into other more proximal risk factors, such as health behaviors and stress. Thus, necessary and effective policies to improve social inequalities are highly likely to feed into prevention efforts in mental health. Broader early life interventions that adequately support parents and families may avert the burden of illness attributable to suboptimal fetal and early childhood health and development.

To design an optimal preventive paradigm for mental disorders, prevention and mental health promotion needs to be integrated not only within the mental health space, but in coordinated partnership with other health promotion agencies and stakeholders that influence key risk factors. This creates significant potential difficulties but also opportunities. The opportunity is that for many of the efforts that will be required for attempting the prevention of schizophrenia, bridges can easily be built alongside preventive strategies that are in existence for other disorders. The difficulties relate to the fact that, while there are clear overlaps between risk factors for somatic and

mental illnesses, there are also likely to be instances of differential relationships. An exemplar would be the issue of vitamin D as a risk factor for psychosis and mood disorders. There are highly effective public health campaigns to reduce melanoma focusing on sunlight avoidance. A public health campaign to improve vitamin D levels risks conflicting messages and would need to be handled with great sensitivity. Nevertheless, in the context of the considerable burden of psychotic disorders, the inadequacy of current treatments and the massive social and economic costs, it would be most unwise not to embrace these preventive opportunities. A realistic appraisal of the scope and complexity of the challenge and the magnitude of the rewards is, however, needed and integrated programs rather than siloed approached mandated.

Funding

F.N.J. is supported by a fellowship from the National Health and Medical Research Council (628912).

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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