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# The Prevention of Schizophrenia—What Can We Learn From Eco-Epidemiology?

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**The search for the causes of schizophrenia has predominantly originated from 2 research paradigms; genetics and epidemiology. While each approach has made important contributions to etiological understanding, neither has fully resolved the exact milieu of risk factors for schizophrenia, and there is growing recognition that several pathways to the onset of such disorders may exist. Eco-epidemiology offers an integrative framework to study schizophrenia etiology, incorporating multiple, interactive levels of causation, including genetic, epigenetic, individual, familial, community, and societal domains over the life course. In this article, we review the current evidence base, through the lens of eco-epidemiology, to determine whether it warrants the design and implementation of putative prevention strategies for schizophrenia. We argue that while there are potentially large public health gains available, we do not currently have sufficient empirical data to design effective prevention strategies. It will be important for the research community to more fully elucidate the likely multifactorial, multilevel, polygenetic, and eco-epidemiological basis of schizophrenia before we can design useful prevention strategies. We conclude by speculating on the forms effective strategies might take.**

*Key words:* schizophrenia/prevention/epidemiology/genetics/public health/eco-epidemiology/preventive medicine

## Introduction

One century on from Bleuler's first application of the term "schizophrenia" to a set of severe disorders with psychotic symptoms, we stand at a crossroads in schizophrenia research. For much of the intervening period, 2 distinct research paths have guided the search for the causes of schizophrenia grounded in the principles of nature (genetics) or nurture (the environment), respectively. On the one hand, genetic research has demonstrated that schizophrenia and its spectrum has a polygenetic basis, with many candidate genes of small effect contributing to individual risk.[1–4] Such important discoveries have been tempered with the acknowledgment that the genetic basis of these disorders is more complex than previously envisaged, with gene-environment interactions and epigenetic processes likely to be important in understanding heterogeneity.[5,6] On the other hand, the epidemiology of schizophrenia has largely drawn on traditional approaches to identify risk factors for psychosis. Only more recently have researchers begun to address how individual (genetic) risk might be influenced by broader, socioenvironmental factors, ranging from socioeconomic deprivation to neighborhood social cohesion, and the way that these factors measured at the individual level might interact with those conceived as operating between individuals, such as social networks, in terms of modifying risk for schizophrenia. Thus far, we know that urban birth and living,[7] being a migrant or their offspring,[8] being a member of a minority group[9] or exposure to a range of negative events across the life course, are associated with higher rates of disorder.[10] The effect sizes (rate ratios) for these "risk factors" are of an order of magnitude higher than nearly all corresponding genetic effects (Few exceptions exist, but a deletion on chromosome 22, which results in velocardiofacial [VCS] syndrome [or 22q11 deletion syndrome], has been established with a large increased risk of schizophrenia. An estimated 30% of people with VCS go onto experience psychosis.[11]), but concepts of both causality and specificity continue to provide methodological challenges in the epidemiology of schizophrenia.

While each approach has made important contributions to etiological understanding, neither has fully resolved the exact milieu of risk factors for schizophrenia and its spectrum disorders. Importantly, which research avenue we choose to take from this crossroads will likely shape the next 100 years of schizophrenia research.

There is growing recognition that several pathways to the onset of schizophrenia spectrum disorders will exist, putatively determined by a complex interplay of multiple factors across the life course. Here, the concept of "eco-epidemiology" offers a theoretical framework within which we might integrate factors between several layers of causation, including genetic, epigenetic, individual, familial, community, and societal influences.[12,13] The approach emphasizes understanding the interconnectedness and interdependence of these levels, their developmentally sensitive nature over the life course, and the wider sociotemporal contexts that shape disease risk. Eco-epidemiology therefore offers a framework within which to empirically test more realistically complex causal models, unrestricted by the constraints of purely biological or epidemiological explanations of disease.[14] It is the whole biological system that is considered, not merely 1 or 2 aspects of it. Necessarily, the theory has largely preceded empirical attempts to elucidate such complexity in regard to schizophrenia, but this disorder is an excellent candidate for its full application in terms of causation and prevention.

Such integrative research in an explicitly eco-epidemiological framework has begun, though is yet to be fully applied. Studies are investigating putative interactions between genes and the environment in psychosis as well as between seemingly disparate environmental factors.[6] Recognizing that neither genetic susceptibility nor exposure to environmental factors are sufficient, alone, to lead to the onset of psychosis, such studies look to test whether both may be necessary, through various types of interaction,[15] to cause disease. There is currently hope that the absence of a complete genetic or epidemiological explanation for the considerable heterogeneity in schizophrenia risk may be found in such interactions.

One early example of this type of interaction was reported by Caspi *et al*[16] between the now disputed candidate gene for schizophrenia,[17] catechol-*O*-methyltransferase (COMT), and exposure to cannabis intoxication during adolescence. Although based on a post hoc, subgroup analysis of people in the Dunedin birth cohort, the authors nonetheless observed that the risk of schizophreniform disorder at 26 years of age was dependent on a functional polymorphism at codon 158 of the COMT gene and whether or not you had smoked cannabis during adolescence. COMT is involved in the regulation of dopamine, the chief neurotransmitter involved in reward processing and positive psychotic symptoms. At codon 158, you can have 2 copies of the methionine (met) allele, one copy of the met allele and one copy of the valine (val) allele, or 2 copies of the val allele. The authors[16] found that cannabis smoking increased the risk of later schizophreniform disorder, but this was conditional upon an increasing presence of the val allele, known to raise COMT enzymatic activity. Furthermore, this effect was restricted to adolescent (vs adult) cannabis use, suggesting that timing of exposure to environmental factors is also likely to be critical in determining psychosis risk. Attempts to replicate this finding have, however, been mixed,[18–20] and the evidence for a main effect of COMT in schizophrenia remains equivocal.[21] Nevertheless, these 2 issues are not sufficient to refute their observation alone, given possible heterogeneity in genetic samples,[22] the importance in understanding timing of exposure, as well as exposure itself and given that the absence of main effects does not preclude the possibility of interactive effects.

Dedicated gene-environment interaction studies are now underway, seeking to overcome some of these caveats. One such example is the European Union Gene-Environment Interaction study of schizophrenia and other psychotic disorders,[6] an international, multicenter case-sibling-control study which will collect detailed genetic, social, and clinical data to permit testing of putative gene-environment interactions, identification of which would have major implications for both etiology and public mental health. Delineation of the suite of genetic, epigenetic, and environmental factors relevant to psychosis etiology would move us closer to the holy grail of schizophrenia research, interventions which attempt to prevent the onset of psychosis. Until now, we, as a research community, have paid only lip service to the idea of prevention, our failure to fully resolve the etiological basis of schizophrenia and its spectrum preventing us from implementing cost-effective, efficacious intervention strategies. But by continuing to investigate the multifactorial, multilevel etiology of schizophrenia over the life course, via illustrative frameworks such as eco-epidemiology, schizophrenia prevention can move from the epidemiological horizon to the public health foreground. And because (socio)environmental factors, rather than susceptibility genes, present better targets for modification (though we acknowledge that epigenetic processes may alter gene expression and, themselves, be altered), it is primarily through our ability to advance epidemiological knowledge of schizophrenia and related psychotic disorders that any preventive medicine successes or failures will be measured.

In this article, we briefly review the current evidence base regarding major epidemiological findings in psychosis and attempt to consider the potential public health gains removal of such factors would have in terms of the prevention of schizophrenia before reviewing how near we are, as a research community, to proposing and implementing any prevention strategies based on eco-epidemiology. We conclude with some blue-sky thinking about what form such prevention strategies might take.

## What Has Eco-Epidemiology Taught Us?

Epidemiologists have long recognized that considerable variation in the incidence of schizophrenia not only

exists[23–25] but is also critical to our understanding of etiology.[12,23] That schizophrenia spectrum disorders have a classical, highly replicable age and sex distribution,[26,27] with the highest incidence rates occurring in early adult life and declining thereafter, more strongly for men than women, is in little doubt. What is more surprising to researchers unfamiliar with the epidemiology of schizophrenia are the important discoveries that variation exists along a number of other fascinating domains, including migration and minority status,[8] place of birth and upbringing,[28] life events and social disadvantage,[29] pre- and perinatal stressors[30] (ie famine or viruses), and, potentially, hypovitaminosis D.[31]

One of the most highly replicable epidemiological findings in psychiatric epidemiology is the consistent evidence that rates of psychotic disorders (not limited to schizophrenia) are raised in immigrants and their offspring born and brought up in the host country.[8] These findings were first observed in migrant groups to the United States[32–34] but have since been replicated in several European settings, including the United Kingdom,[35,36] the Netherlands,[37,38] Sweden,[39,40] Denmark,[41] and Israel.[42] The exact magnitude of this increased risk varies according to the group under study, with rate ratios ranging from around 1.5 to 10. Interestingly, while all immigrant populations and their offspring have some elevation in risk, it appears that the more visible the minority group the larger the corresponding effect size.[8] Several hypotheses have been proposed, some of which have been refuted (selection,[43] misdiagnosis,[35] higher rates in the country of origin,[44–46] and confounding by socioeconomic status[47]), while others remain more viable, eg, discrimination.[48] Importantly, although the epidemiological literature supports migration or ethnic minority status as a marker of increased risk, other less well-established underlying processes (such as discrimination) presumably provide the ''active'' component of this exposure marker. We will see later that this has important implications for designing effective prevention strategies.

A similar pattern emerges for another broad marker of increased risk identified from traditional epidemiological studies, namely, urbanicity. Several studies have consistently observed higher rates of schizophrenia in progressively more urban environments across a variety of settings.[28] Researchers have explored a number of either social (social isolation, fragmentation, or class) or biological (infection, malnutrition, or hypovitaminosis D) explanations for this effect. These observations are paralleled by a series of studies, beginning with Faris and Dunham,[25] conducted ''within'' urban environments at the level of the community or neighborhood, which have also demonstrated variation in the incidence of schizophrenia, often associated with levels of social disorganization or fragmentation.[28,49] The possibility of reverse causality explaining these findings has been considered[50,51] because we know that the onset of schizophrenia is also often associated with a marked decline in social standing, the ability to remain in employment, and secure quality accommodation, and as a consequence, this results in drift both socially and geographically, often into poorer, more urban environments. To minimize this issue, epidemiologists have examined the relationship between place of birth and upbringing and later schizophrenia risk because these markers are less vulnerable to the effects of social drift because they are measured prior to the onset of the prodromal phase of psychotic disorder. Such studies show a strong dose-response effect between the urbanicity of place of birth/upbringing and later schizophrenia risk.[7,52,53]

Pedersen and Mortensen have extended these studies of urbanicity from a conventional risk factor paradigm to an eco-epidemiological approach by testing whether place of upbringing has its effect on schizophrenia risk at the individual or familial level.[54] In a population-based, Danish birth cohort of over 700 000 individuals, they found that in addition to a direct individual effect of place of birth on schizophrenia risk, schizophrenia risk was elevated among individuals brought up in rural environments but whose older sibling was born in a more urban environment. This finding allows the possibility that some of the exposures associated with urban upbringing occur at the familial level and persist after movement to more rural environments (ie after removal of the exposure). Here, we are presented with an analogous situation to the migration findings that ''urbanicity'' can only be a marker for an underlying suite of environmental exposures that have more direct effects on important neurobiological mechanisms in schizophrenia.

We suggest that migration and urbanicity may be underpinned by an overlapping suite of risk factors (though each might also have distinct features), which have their effect on schizophrenia risk through a latent construct which we broadly term as ''socioenvironmental disadvantage.'' Here, we define disadvantage broadly to mean any socioenvironmentally mediated factor that adversely impacts on an individual's objective or subjective social, economic, or health position. As such, this term incorporates a range of exposures over the life course, including negative life events such as abuse, bullying and discrimination, familial discord, substance misuse, social isolation and fragmentation, and factors allied to socioeconomic status, such as education, employment, and income. It should be noted that this term encompasses environmental insults beyond the social sphere, such as (prenatal) malnutrition, influenza or hypovitaminosis D, and (proband) substance misuse, which may have their biological effects on psychosis risk more directly.

One socially oriented example of how migration and urbanicity may be underpinned by a common disadvantage paradigm in regard to schizophrenia risk comes from the emerging literature on the ''ethnic density hypothesis.'' This hypothesis sets out to test whether the risk

of schizophrenia for an individual of a given ethnicity is conditional upon the proportion of other people in that individual's neighborhood from the same ethnic background. Several studies have now demonstrated a role for ethnic density in schizophrenia,[9,55,56] such that an individual's risk increases as the proportion of people of similar ethnic backgrounds living in their neighborhood falls.[9,55,56] Tantalizingly, this suggests a role in psychoses etiology for broader ecological factors operating at the community or societal rather than individual level, such as social isolation or its corollary, cohesion. This hypothesis begins to employ a methodology more closely aligned with eco-epidemiology, although a relevant limitation here is that, thus far, studies of ethnic density have been restricted to ethnic density close to the time of onset. Given we know that potential exposures allied to urbanicity may have their effects earlier in the life course, resolving the critical timing of exposure of ethnic density provides a future challenge in the application of eco-epidemiology to schizophrenia.

Notwithstanding, researchers have continued to tease apart the ethnic density findings in other ways. Our own group has explored this effect further by considering the specific residential patterning of ethnic groups within each neighborhood, termed "ethnic fragmentation."[57] In addition to an independent ethnic density effect, we observed that the incidence of schizophrenia decreased in neighborhoods where each ethnic group lived in a more cohesive residential pattern. These findings putatively support the hypothesis that minority groups may be buffered from exposure to social stressors in neighborhoods where they are able to access social support from people who share similar cultural values and backgrounds. Based on this proposition, Veling *et al*[48] tested whether there was a direct association between ethnic discrimination and schizophrenia risk, finding a dose-response increase in the incidence of schizophrenia as the level of discrimination experienced by ethnic minority groups rose. Thus, eco-epidemiology has begun to reveal the constellation of risk factors that might underpin raised rates of schizophrenia in immigrant groups and their offspring. These factors may operate at many levels (individual, familial, community, or societal), making the links with urbanicity immediately apparent. At the community level, there is growing evidence that neighborhoods that are more socially fragmented, or have lower levels of social capital, have higher incidence rates of schizophrenia[58,59], a finding not apparently confounded by socioeconomic deprivation.[57]

Progress to identify putative societal-level factors using an eco-epidemiological perspective has been mirrored by efforts to identify more specific individual-level environmental factors over the life course, which may later increase schizophrenia risk. For example, there is evidence that negative life events in childhood, such as prolonged separation from parents[29] or childhood trauma,[60] are associated with greater risk of schizophrenia and psychosis. Intriguingly, evidence is emerging that these environmental stimuli might have their mechanistic effects through altered stress response.[61] There is also strong evidence that nonsocial prenatal exposures may confer increased risk of later psychosis, putatively implicating more than one potential pathway to psychosis. In an elegant series of studies, Susser, Brown and colleagues have demonstrated compelling evidence that people exposed to a range of prenatal stressors at critical points of gestation, including influenza,[62] toxoplasmosis,[63] and malnutrition,[30] are between 2 and 7 times more likely to develop schizophrenia later in life than people unexposed to these factors. Fascinatingly, epigenetic processes may provide a potential pathway through which environmental exposures, from very early in life, alter gene expression[64] and perhaps later psychosis susceptibility.[65] McGrath *et al*[66] have also proposed that prenatal vitamin D deficiency may adversely affect fetal brain development via its influence on altered neural growth, and there is some evidence from a Finnish birth cohort that men who were not given vitamin D supplementation early in life had a significantly higher risk of later schizophrenia than their counterparts who received supplementation.[31] While further research needs to bear out this hypothesis, there is good evidence that winter birth, urban living, and darker skin are risk factors for hypovitaminosis D,[67] and importantly, we know that these factors are associated with increased rates of psychosis.

Although eco-epidemiology has yet to be fully applied to psychosis, we can see how early attempts to integrate components of this framework have begun to elucidate an exciting suite of genetic, epigenetic, and socioenvironmental factors that may underpin psychosis. In turn, this has led to growing calls to consider and implement prevention strategies that may reduce the incidence and prevalence of schizophrenia.[68] In 2008, the British government published a foresight report on mental capital and well-being,[69] which included a working article to explore possible prevention strategies in relation to the increased risk of psychosis in immigrant and ethnic minority groups.[70,71] Before leaping headlong into devoting resources to such strategies, however, it is important to consider any potential gains in relation to possible pitfalls based on current knowledge.

## From Eco-Epidemiology to Public Mental Health: Are Prevention Strategies Achievable?

One way to understand the "theoretical" public health benefits of strategies to prevent the onset of schizophrenia is to calculate "measures of impact" from published research. One such measure is the population attributable risk fraction (PAF), which estimates the proportion of all cases of a disorder which could be prevented if you could completely remove the risk factor under study. A number

of assumptions are made in its estimation (for more details, see Rockhill *et al*[72]), but essentially the effect size (ie rate ratio, odds ratio, etc) for disorder associated with a given risk factor is weighted according to the prevalence of the risk factor in the population at risk. Although these assumptions are rarely satisfied,[73] PAF may still be illustrative of the potential preventive gains available if we could identify and remove the etiological determinants underpinning schizophrenia and related disorders.

Attempts have been made to estimate PAFs for migration and urbanicity in relation to schizophrenia spectrum disorders. For example, Harrison and colleagues[74] suggested that if the factors associated with increased risk of psychoses in black Caribbean migrants and their offspring could be removed, 19% of the total incidence of psychoses in the United Kingdom could be prevented. This figure was almost identical to that observed in a more recent study we conducted using data from 2 subsequent first-episode studies in United Kingdom.[27,75] We estimated that if all the risk factors associated with an increased risk of psychotic illness in black and minority ethnic populations could be successfully identified and removed from the whole population, we could prevent up to 21.6% of all cases of psychosis.[70] Put another way (technically, the ''attributable risk fraction''), within specific ethnic minority populations in the United Kingdom, such as the black Caribbean and black African populations, we could ''theoretically'' prevent a staggering 81.0% and 74.4% of incident cases from affecting them, respectively.[76]

Similarly, large measures of impact are apparent in relation to factors in the urban environment, if causal. For nonaffective psychosis, the PAF associated with urban birth in Denmark was estimated to be as much as 34.6%,[7] in the Netherlands this figure was placed at 31%,[77] and in our English study this estimate was 27%.[70] These theoretical public health gains are undoubtedly substantial. If they could be realized, they would potentially improve the lives of millions of people, both for those who would develop psychosis and those upon whom the burden of care would have fallen. These public health gains would also present large economic incentives, both in terms of the direct costs saved to mental health services and indirect costs which would be avoided by keeping people in the labor market. That said, we have already alluded to the fact that the concept of the PAF relies on assumptions that, strictly speaking, are not fulfilled in these studies, and furthermore, we have to ask whether such PAF figures are ''tangible.''

We suggest that, presently, they are not. We attempt to show why this is so by considering prevention in terms of the 2 main types of strategies that can be used in public health to prevent disorder, a population-based prevention approach, where the intervention is delivered to everyone in the population at risk (such as the chlorination of water supplies), or a high-risk–based approach, which targets individuals identified as being at high risk for the disorder (eg, influenza vaccination in winter for the elderly).

Presently, we believe that population-based prevention strategies are unlikely to be successful (defined either by cost effectiveness or efficacy) because of issues surrounding the specificity of risk factors for schizophrenia, which is a function of both the disorder's absolute rarity (roughly 20 new cases per 100 000 person years[27]) and the ubiquity of urbanicity or ''migration'' as markers of increased risk. Thus, most people exposed to these markers will not go onto experience psychosis. Therefore, using the tools of eco-epidemiology, it will be important to continue to identify the suite of underlying socioenvironmental risk factors that operate further along the causal pathway to increase the risk of schizophrenia. It is reasonable to assume that because we elucidate more specific risk factors for psychosis, the corresponding public health impact of their removal will be smaller, given that a smaller proportion of the population at risk will be exposed to any single factor (cf urban living or migration). Translating this to putative public health strategies, these caveats favor high-risk rather than population-based strategies, given the absolute rarity of schizophrenia; a population-based strategy would still mean that the vast majority of people given the intervention would not have gone onto develop the disorder anyway.

Turning our attention to high-risk prevention strategies, however, and we see that as informed by the current evidence base, these strategies are also potentially problematic. High-risk strategies are dependent on both an ability to identify specific risk factors for the disorder, critical timing of exposure (over the life course), and an ability to identify individuals at high risk of disorder.[78] However, high-risk prevention strategies will not achieve their true potential until we can more fully understand the etiology of schizophrenia. Such understanding will allow us to develop highly tailored high-risk interventions targeting people with specific genetic vulnerability, where additional exposure to an environmental factor would be deleterious in terms of schizophrenia risk. For example, we could imagine a situation analogous to the COMT example described earlier,[16] where cheap, reliable genotyping might allow a prevention strategy to reduce cannabis smoking in teenagers carrying at least one copy of the val allele. We acknowledge that the effectiveness of such a strategy will also depend on a number of other factors, including genotyping costs, the allelic frequency in the population at risk, the ability to implement the strategy, and the rarity of disorder. That said, we also acknowledge the fact that more benefit may accrue from a population-wide drive to reduce cannabis consumption, seeing any reduction in schizophrenia as just one of many positive results.

## From the Crossroads to the Skies: Putative Prevention Strategies in Schizophrenia

We have suggested that schizophrenia research stands at an important crossroads, with the potential for great discoveries in gene-environment interactions, epigenetics, and neurobiology coming closer to the fore, as researchers from traditionally different disciplines acknowledge the likely multifactorial, multilevel, and ecogenetic basis of schizophrenia over the life course. Elucidating some of these pathways will allow us to more precisely understand schizophrenia's complex etiology, thus allowing public mental health to develop appropriate, effective, and preventive medicine. We feel that schizophrenia research can currently make its greatest contribution to the development of future prevention strategies by continuing to establish the evidence base in this way, employing paradigms such as those advocated by eco-epidemiology.[14] Fortunately, such changes are beginning to happen,[6,79] providing reason for optimism that effective prevention strategies are moving closer to the epidemiological horizon.

Having acknowledged limitations to currently introduce viable prevention strategies, it is worth considering what form future strategies might take. We frame our thinking around 3 levels of intervention; indicated, selective, and universal prevention strategies.[80] Indicated strategies are predicated on the ability to reliably identify high-risk individuals and provide appropriate strategies to prevent their transition to disorder. In many ways, such strategies may be most appropriate for schizophrenia, given the absolute rarity of the disorder, provided we can delineate specific socioenvironmental risk factors for psychosis and the (genetic) groups particularly vulnerable to psychosis. Some indicated strategies already exist, though may yet to be fully realized. Here, we acknowledge the important work done by early intervention in psychosis services (EIS).[78] The provision of these services was established, in part, to prevent transition from "at risk mental states" (ARMS) to psychosis and intervene earlier in the progression of disorder for those with first-episode psychosis to improve later course and outcome. The efficacy of such services remains equivocal[81] and therefore highly contested,[82,83] though recent reports provide more optimism.[84] We reiterate that with better identification of the underlying basis of psychosis, EIS will be better positioned to first identify ARMS; second, provide genuine highly indicated prevention to individuals (cannabis cessation and more social support); and to reduce transition rates to psychosis. Importantly, the infrastructure for such efforts is already well established in many countries.

Selective prevention strategies involve the identification of subpopulations (cf specific individuals), broadly at raised risk of schizophrenia, where the intervention may be applied to the entire group in order to prevent disorder. Our own research on raised rates of schizophrenia in immigrant groups and their offspring in the United Kingdom provides a relevant example.[70] We suggest that in terms of the largest theoretical public health gains in the prevention of psychosis in the United Kingdom, strategies, which aimed to prevent disorder in black Caribbean groups, would have the single greatest impact, preventing up to 80% of potential cases of psychosis within black Caribbean communities, a huge effect, and reducing about 1 in 20 of the overall population rate.[70] Focus on non-British white migrants and people from the Indian subcontinent would be the next logical step if there needed to be distinct approaches. Necessarily, any such strategies still rely on the identification of the social factors underpinning raised rates in these groups. In this regard, we know that the black Caribbean community experiences more markers of social exclusion, including higher levels of unemployment,[85] people living alone,[85] discrimination,[48] and cumulative social disadvantage[86], factors known to be associated with an increased incidence of psychoses.[55] Fostering improved social networks and support through improving community cohesion may therefore be part of a parallel strategy to reduce the incidence of psychoses in such populations, but care needs to be taken here. For example, in the United Kingdom, various attempts to reduce social exclusion and enhance neighborhoods and communities have been made via the creation of governmental departments such as the former Social Exclusion Unit (now Neighborhoods and Local government) or via programs such as Sure Start, which aim to promote education, health, social, and family support for young people in the most deprived communities. However, their effectiveness varies by place, domain, and subgroup,[87] highlighting the complexity of introducing broad-based intervention strategies. Furthermore, whether such strategies generate social cohesion, which has the same properties (and potential protective effects) as social cohesion which arises organically, requires empirical study. We emphasize that, while there would be great benefits from tailored interventions, any efforts to meet the needs of such communities would have to be exquisitely sensitive to avoid stigmatization.

Finally, we turn our attention to universal, population-based prevention strategies, which we have already noted are unlikely to be successful based on current empirical knowledge (see above). This is not to say that such strategies will be redundant in the future, particularly given better identification of socioenvironmental risk factors and opportunities for synergy in their prevention across several domains. The literature on pre- and perinatal birth complications provides an opportunity to explore this issue. There is increasing evidence for the role of pre- and perinatal growth and health in terms of determining the level of risk and protection for a number of long-term health outcomes and chronic disease, not only schizophrenia. This "common cause" hypothesis

relies on the programming of a number of physical parameters, potentially priming effects on the later stress response as one pathway to psychoses.[88] Indeed, the biological mediation of the stress response may be relevant to a number of health outcomes, not limited to mental disorder, with exact outcomes determined by customized genetic vulnerability and epigenetic effects.

Thus, any efforts to improve the health of the growing fetus and mother are likely to have wide-ranging beneficial effects. We consider that, for mental illness, the context of "growth" also includes psychological health and the early development of social cognition but discuss more physical aspects, here. In terms of schizophrenia risk, maternal infection such as influenza (where vaccination is available and safe), maternal malnutrition, anemia, smoking, and other factors that affect fetal growth are all potential avenues of primary prevention for many illnesses. Low birth weight and developmental delays have been associated with a range of poor outcomes over the life course,[89] not limited to psychoses,[90,91] but including hypertension,[92] diabetes mellitus,[93] poorer educational performance,[94] poorer employment prospects, and increases in common mental disorders.[95,96] None of these is specific to schizophrenia, though some may play an independent role in increasing risk. However, optimizing fetal and early childhood health may be important in averting the cascade of many adverse outcomes that may be more likely in those not having an optimal start in the earliest and crucial phases of growth; increased schizophrenia risk may be but one of these.

We suggest an analogous argument can be put forward for markers of social disadvantage at the individual, family, and societal levels, which appear to be associated with raised rates of schizophrenia. Reducing the occurrence of stressful life events during childhood, adolescence, and even into adulthood may present a tangible target for intervention in the general population, and targeted interventions to improve family and community support would have positive effects in reducing later onset of psychotic disorders. Furthermore, such strategies will have crossover benefits in other health and social care domains, where the roles of social factors have also been established, including potential reductions in crime,[97,98] civic disorder, and other adverse social outcomes[99] and improvements in education, employment, and a range of health outcomes, including physical activity,[100] childhood obesity,[101] teenage pregnancy,[102] all cause mortality, cardiovascular mortality, and mortality in accidents and suicide.[103,104] We suggest that any universal prevention strategies might be most cost effective and efficacious when their focus is on preventing specific exposures (ie social disadvantage) rather than any specific disorder (ie schizophrenia).[105] However, we must also make attempts to appraise the potential unintended consequences any prevention strategy may simultaneously create. For example, a societal-level strategy to improve community cohesion may, if not implemented carefully, only benefit certain groups, leading to a potential widening of social inequalities and adverse social, economic, and health outcomes. Furthermore, some strategies may have opposing effects for different outcomes. An illustrative example here is the supplementation of folic acid during the periconception period of pregnancy to prevent neural tube defects in the developing fetus.[106] There is some evidence that supplementation beyond the recommended gestational period may be associated with later allergies and asthmatic conditions in the offspring.[107] This example highlights the need to carry out a full, careful, and thorough cost-benefit analysis of any eventual prevention strategies that are developed for schizophrenia spectrum disorders. Necessarily, this will involve sensitive, multidisciplinary, and domain-cutting collaborations, which emphasize local variations in need. Prior to that, it will be vital to continue to establish a reliable, replicable evidence base for schizophrenia and other disorders.

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