Invited Commentary: Gaining Traction on the Epidemiologic Landscape of Schizophrenia

John J. McGrath

From the Queensland Centre for Schizophrenia Research, University of Queensland, Wacol, Australia.

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Background

In his scholarly review of the field, Jablensky (1) outlined how the wealth of epidemiologic data about schizophrenia has enriched the "epidemiological horizon" of schizophrenia. This metaphor reminds us of how essential it is to chart the epidemiologic gradients across time and space in order to guide research. In this commentary, I argue that the task for the researcher is not only to continue to refine this map but also to gain "traction" on this landscape to generate, and test, candidate risk factors for schizophrenia.

Schizophrenia is a group of imperfectly understood brain disorders characterized by alterations in higher functions related to perception, cognition, communication, planning, and motivation. The syndrome is defined reliably (if not validly) by applying diagnostic criteria related to the presence of hallucinations, delusions, thought disorder, and negative symptoms such as blunted affect and reduced speech (2). Symptoms of the disorder (which has a lifetime morbid risk of about 1 percent) usually emerge in early adulthood, and, although many affected persons make a good recovery, many have intermittent or persistent symptoms for decades. The good news is that advances in biological and psychosocial treatments are improving outcomes for people with schizophrenia and their families. Unfortunately, despite these better treatment options, schizophrenia is still a leading contributor to the global burden of disease (3). Service improvements and the reduction of stigma can cushion the impact of disability; however, even if unlimited funding was available to treat schizophrenia, most of the burden would remain unavoidable. This sober realization keeps the research community focused on finding the causes of schizophrenia.

After Herculean efforts, the search for susceptibility genes for schizophrenia appears to be finally paying dividends. Several susceptibility genes have recently been identified, and some of these findings have been replicated (4). Although results are still preliminary, these genes suggest that pathways related to glutamatergic neurotransmission and synaptic formation may be implicated in schizophrenia (5). Complementing the genetic research, there has been a steady accumulation of risk indicators and putative risk-modifying factors derived from the epigenetic/nongenetic domain. Many of these risk factors operate during the prenatal and perinatal period (6). The neurodevelopmental hypothesis of schizophrenia, which rests on a diverse and reasonably robust evidence base (refer to Weinberger and Marenco (7)), proposes that genetic and/or environmental factors disrupt prenatal brain development. The behavioral sequelae of this disruption are thought to be clinically dormant until after puberty, when maturational events lead to emergence of the symptoms of the disorder.

More recent revisions of the neurodevelopmental hypothesis have suggested that events proximal to onset of the illness may also be necessary to "precipitate" psychosis. In other words, more than one "hit" may be required to "cause" schizophrenia (8). For example, good evidence now exists showing that migrant status is associated with an increased risk of schizophrenia (9, 10), suggesting that factors operating between the time of migration and illness onset are important. While not discounting the importance of these factors, the evidence for the neurodevelopmental hypothesis of schizophrenia is probably stronger and more coherent than would be the case for other adult-onset chronic disorders more widely associated with the "fetal-origins-of-disease" hypothesis (11).

Early life exposures and schizophrenia risk

Two early life exposures associated with schizophrenia, season of birth and urbanicity (place) of birth, are very crude risk indicators (proxy markers of yet-to-be-elucidated risk-modifying factors). Curiously, those persons born in winter and spring have an increased risk of schizophrenia. While the finding is stubbornly consistent in Northern Hemisphere studies, the effect size for this exposure is relatively small (e.g., relative risk = 1.11 in a large Danish study (12)).

Correspondence to Professor John J. McGrath, Queensland Centre for Schizophrenia Research, The Park Centre for Mental Health, Wacol QLD 4076, Australia (e-mail john_mcgrath@qcsr.uq.edu.au).
Candidate risk factors include perinatal infections (13, 14) and low levels of prenatal vitamin D (15). More recently, place of birth has emerged as an informative risk indicator. Two population-based studies, one from Holland (16) and one from Denmark (12), found that a person’s relative risk of developing schizophrenia when he or she is born in the city versus the country is about 2.4. However, because “exposure” to urban birth was prevalent in the two studies, the estimated population attributable fraction for this variable was substantial (about 30 percent). The risk-modifying factors responsible for this gradient remain to be elucidated.

Interesting new candidates have emerged from the domain of prenatal infection (17). The epidemiologic evidence for these candidates has moved from crude ecologic studies (18, 19) to analytic case-control studies based on banked sera. Evidence has been found linking schizophrenia to serologically confirmed prenatal exposure to herpes simplex (20) and rubella (21). Prenatal nutrition is also a domain of interest; studies based on the “Dutch Hunger Winter” have suggested that exposure to famine prenatally is associated with an increased risk of schizophrenia (22).

The association of pregnancy and birth complications with risk of schizophrenia has been a focus of intermittent research for over seven decades (refer to the review by Cannon et al. (23)). On the basis of a meta-analytic synthesis of eight prospective population-based studies, Cannon et al. reported that three groups of obstetric complications were associated with an increased risk of schizophrenia: 1) complications of pregnancy (e.g., antepartum hemorrhage, maternal diabetes, rhesus blood group incompatibility, and preeclampsia); 2) abnormal fetal growth and development (e.g., low birth weight and congenital malformations); and 3) delivery complications (e.g., uterine atony, asphyxia, and emergency cesarean section). On the basis of issues such as 1) a lack of power to detect the relatively small effects associated with these exposures (pooled estimates were generally less than 2) and 2) problems with the reliable definition and measurement of obstetric complications, Cannon et al. suggested that this type of research may be coming to the end of its heuristic potential. They highlighted the need for collaborations with other disciplines (developmental biology, neuropathology, genetics) and the application of different research methods (e.g., birth cohort with stored prenatal sera, use of animal experiments to explore new candidates).

A paper by Gunnell et al. (24) in this issue of the Journal suggests that new clues can emerge from the study of birth variables. This study examined the association between birth weight, adult height, and schizophrenia in a large, representative sample of Swedish men. As in other studies, these authors reported a significant (but imprecise) association between low birth weight (<2.5 kg) and increased risk of schizophrenia. However, the study also reported an association between heavier birth weight (>4 kg) and increased risk of schizophrenia. This finding is consistent with that from another study based on the north Finland birth cohort (25). The other strength of the study by Gunnell et al. (24) is that they linked neonatal anthropometric measures with adult height. By assuming that the combination of low birth weight and taller adult height could serve as a proxy marker of intrauterine growth retardation, the authors postulated that this group should have had an increased risk of schizophrenia. However, infants in the lowest and middle tertiles of birth weight, whose subsequent growth moved them into the highest tertile of adult height, had a reduced risk of schizophrenia. This finding argues against mechanisms related to intrauterine growth retardation being implicated in this subgroup.

The study by Gunnell et al. (24) provides several other novel features to add to the landscape of schizophrenia epidemiology. For example, the association between adverse adult outcome and both low and high birth weight (a reverse J-shaped association) allows us to cross-link to other disorders. Coronary heart disease also shares this pattern (26). The association between heavier birth weight also enables us to cross-link with maternal diabetes, a risk factor already associated with increased risk of schizophrenia (23). Furthermore, the authors of the Swedish study have also examined the curious links between adult height and altered risk of cancer (27) and insulin resistance and cardiovascular disease (28). This type of cross-fertilization between research disciplines is more likely to facilitate candidate generation. However, the critical issue for the schizophrenia research community is that, although adding features to the epidemiologic landscape is an important and worthy pursuit, we need to do more than just add fine details to the map. We must try to gain traction on the epidemiologic landscape to generate, and test, novel candidate risk factors.

Generating novel candidates requires both imagination and courage, because the history of schizophrenia research shows us that most new candidates will eventually be rejected. However, the study by Gunnell et al. (24) leaves us with some tantalizing leads related to the environmental factors that influence birth weight and adult height. For example, studies from Ireland (29), New Zealand (30), and Denmark (31) showed within-year variations in birth anthropometry, with winter/spring birth being associated with heavier and larger babies (regardless of hemisphere of birth). A study of Austrian males (32) also found that those born in winter and spring were taller as adults compared with those born in other seasons. Curiously, the study by Gunnell et al. (24) found a significant excess of winter/spring births among those who subsequently developed schizophrenia. It is tempting to speculate that exposures that fluctuate with the seasons influence not only birth anthropometry and adult height but also schizophrenia. These links may allow us to “triangulate” in on informative candidate exposures. At present, prenatal exposures to infection (33) and maternal hypovitaminosis D (15) seem reasonable candidates, but we will need to be creative to generate additional parsimonious candidates that “map” onto this terrain.

Because the developing human brain is not open to ready observation, many research groups are now translating risk factors derived from epidemiology into animal experiments. Although no animal model can replicate the phenotype of schizophrenia, these studies can provide important clues related to unraveling the mechanism of action for candidate exposures. In particular, animal experiments can help us decide whether a candidate exposure has biological plausibility (i.e., does it impact on brain development, and are
there morphologic or behavioral features that are related to schizophrenia?). For example, animal models in schizophrenia research have included early lesioning of selected brain areas (34, 35), prenatal exposure to specific viruses such as influenza (36, 37) and Borna virus (38), prenatal hypoxic/ischemic insults (39), and prenatal hypovitaminosis D (40). The potential to extend this type of research with the use of genetic “knock-out” mice (looking for gene-environment interactions) and gene expression profiling offers powerful new tools to elucidate the association between early life exposures and schizophrenia. Discoveries that emerge from this type of research can provide iterative feedback in order to suggest new candidates.

Finally, if we can gain traction on the epidemiologic landscape, and novel candidates are generated, how are we to prioritize these candidates for the next phases of research? When the researcher is presented with a smorgasbord of candidate risk-modifying variables, and each of these variables is equally lacking in consistency, coherence, and biological plausibility, what strategies can we adopt to rank order these factors? First, in a field of equally weak candidate exposures, the exposures with the potential for amelioration via public health interventions should be given priority. The potential return on the research investment is greatest for these candidates in primary prevention (e.g., vaccination to prevent prenatal rubella, folate supplementation to reduce the incidence of spina bifida). Second, in a field of equally weak candidate exposures, the candidate associated with the widest spectrum of adverse outcomes should be given priority (41).

Schizophrenia epidemiology has made substantial advances in recent decades; however, we face some important challenges if we are to make progress. We need to adopt a more assertive and creative stance in generating novel candidate exposures. Furthermore, these candidates need to be examined promptly and efficiently in a more analytic framework (e.g., animal experiments to explore mechanisms of action, use of banked sera from birth cohorts). We can expect that many of the novel candidates will ultimately be rejected—a familiar scenario in schizophrenia research. However, these failures can serve to correct the epidemiologic landscape of schizophrenia and help us detect true risk-modifying factors. In light of the large unavoidable disability associated with schizophrenia, we need to have a sense of urgency about this task.

REFERENCES