

COMMENTARY

The Surprisingly Rich Contours of Schizophrenia Epidemiology

RESearchers like to be surprised by the data. When new data challenge old beliefs, the field becomes primed for discovery. The aim of this commentary is to let the broader psychiatric community know about recent discoveries in schizophrenia epidemiology, and to speculate on how best to leverage these discoveries to advance knowledge.

For those who do not follow the literature closely, recent research in the epidemiology of schizophrenia may come as a surprise. The once cardinal notions that schizophrenia affects men and women equally and is found in all societies with comparable (or equal) incidence are no longer supported by the data. Schizophrenia is not the egalitarian disorder that we once thought it was.¹

See also page 19

In this issue of the ARCHIVES, Perälä and colleagues² report on what is arguably the most thorough study ever undertaken on the prevalence of psychotic disorders. Overall, the lifetime prevalence of psychotic disorders in Finnish adults was 3.48%. This is a startling proportion. The lifetime prevalence of nonaffective psychoses was 2.29%. For schizophrenia, the lifetime prevalence was 1%, which, while at the higher end of the range,³ is comparable to other studies from Finland. Regardless of how we partition the psychotic disorders, the survey by Perälä and colleagues² reminds us just how common psychotic disorders are in the general population. While they may be less prevalent than depression or substance abuse, we should probably not mislead people by labeling psychoses as low-prevalence disorders.

Apart from enumerating cases, what else has epidemiology taught

us about schizophrenia? The short message is this: the epidemiology of schizophrenia is no longer a flat and featureless horizon.⁴ In its place we find that the epidemiological horizon of schizophrenia⁵ is much more interesting than previously suspected. There are rich and informative gradients that can guide future research. For example, a recent systematic review of the incidence of schizophrenia (drawing on 1458 incidence rates from 33 countries) found prominent variation in the incidence of schizophrenia between sites (>5-fold), and a skewed distribution of rates, with many high rates in the upper tail of the distribution.⁶ These data challenge the equal incidence notion promulgated after the publication of the World Health Organization Ten Nation Study.⁷

Despite what we read in textbooks and diagnostic manuals, the incidence of schizophrenia is different in men and women. Two systematic reviews have provided convergent evidence that the male-female rate ratio is 1.4:1.^{6,8} The male excess persists even when factors such as age range and diagnostic criteria are taken into account. While this finding may surprise some, it will not come as a surprise to clinicians. It will be interesting to see how long it takes for this important epidemiological feature to percolate into the textbooks and diagnostic manuals. In the meantime, we need to now teach that for every 3 men who develop schizophrenia, there are 2 women developing the disease.

There are several other startling findings to emerge from the epidemiology of schizophrenia. Some, but not all, migrant groups have astonishingly high rates of schizophrenia.^{6,9} This epidemic cannot be explained away by confounds related to selective migration or methodological biases. Similarly, the evi-

dence is robust that those born and/or raised in cities have an increased risk of developing schizophrenia compared with those born and/or raised in rural regions.¹⁰⁻¹² Recently in the ARCHIVES, Kirkbride and colleagues¹³ presented a 3-site study of the incidence of schizophrenia in England. Even when accounting for migrant/ethnic status, the incidence of psychosis was significantly higher in London compared with the other sites (Nottingham and Bristol). What is it about migrant status or city life that increases the risk of developing schizophrenia? What are the candidate exposures and what are the mechanisms of action? Somewhat embarrassingly for our field, the quality of the data linking urbanicity to schizophrenia is now much stronger than the quality of the hypotheses that have been proposed to explain the association. In part, the evidence linking schizophrenia risk with migrant status and urbanicity has contributed to the current renaissance of social psychiatry research in the field.^{14,15}

The list of curious findings in schizophrenia epidemiology goes on. Some long-standing clues have become more precise, thanks to new data and/or the application of systematic review and meta-analysis. For example, there is an increased risk of schizophrenia associated with older paternal age,^{16,17} prenatal famine,^{18,19} winter/spring birth,²⁰ higher latitude,²¹ prenatal infection,²²⁻²⁵ and pregnancy and birth complications.²⁶

Why should we be surprised to find that schizophrenia epidemiology is so interesting and complex? No one needs to be reminded about the marked clinical and neurobiological heterogeneity of the disorder.²⁷ With respect to genetics, the research community is now comfortable with the notion that there

are many different susceptibility genes, each of small effect, which display variability between populations.²⁸ These genetic factors (which influence susceptibility and/or clinical features²⁹) are embedded in complex causal pathways that involve a dynamic matrix of genetic and environmental factors over development.³⁰ In light of the marked variability in both the phenotype and genotype, one might predict similar heterogeneity in environmental factors. One might also expect that these environmental factors would vary between sites and across time; they do for most human diseases. Epidemiology should be able to capture at least some of these gradients.

What type of epidemiological research needs to be done now? First and foremost, the schizophrenia research community needs to generate a sense of urgency about unraveling the environmental risk factors contributing to the gradients. Take, for example, the fact that urban birth is associated with a substantial (30%) population-attributable risk.¹¹ Population demographics indicate increasing urbanization in both the developed and developing world.³¹ While speculative, it is feasible that the population-attributable fraction of schizophrenia associated with urban birth will rise in the decades to come. By any standards, these are startling projections that should galvanize the research community. It is interesting to speculate about what the response would be if the health outcome was cardiovascular disease rather than mental illness. One would predict that government funding agencies would invest heavily in projects aimed at understanding the mechanisms of action linking the variables of interest. (Think of the epidemic of cardiovascular disease in the mid-20th century and the Framingham Heart study.) The fact that this has not yet happened for schizophrenia is a cause for concern. If the research community responds to these new epidemiological signals in a lethargic and ataxic fashion, why should funding agencies get excited? We urgently need more research on understanding the mechanisms of action underpinning the epidemiological gradients of schizophrenia.

Second, we need to broaden our categories of observation beyond narrow diagnostic criteria to explore symptoms associated with psychosis that can be found in otherwise well individuals.³² Several large community-based samples have identified surprisingly high proportions of the general community who report hallucinations and delusional-like experiences.^{33,34} This type of research can complement traditional schizophrenia studies.

Third, we need to add value to future epidemiological studies. Counting heads purely for the purposes of enumeration may not be the best investment for the research dollar.³⁵ While incidence and prevalence studies can help service development and identify unmet needs, the return for the research dollar can be enriched by including other informative variables (eg, blood for genotyping, neuroimaging, and neurocognitive measures). While it may not be feasible to collect such data from all subjects in large descriptive epidemiological studies, smaller case-control studies can be nested into the overall design. Needless to say, if genetic factors influence or mediate candidate environmental exposures, then studies should seek to measure these (see recent reviews on mendelian randomization³⁶). Another way to add value is to select the samples to amplify the putative environmental exposure. For example, if urbanicity is a risk factor for schizophrenia, then this should be more readily detected in incidence studies conducted in very large cities. The 3-center study from England mentioned previously is an intelligent example of this strategy, as it was able to capture within-country gradients in both urbanicity and migrant status.¹³

Finally, and most importantly, epidemiology needs to build stronger links with molecular, cellular, and behavioral neuroscience. This is especially important when it comes to progressing candidate risk factors derived from ecological studies. Epidemiology is a blunt instrument when it comes to exploring these questions; neuroscience is needed to evaluate the biological plausibility of candidate exposures. However, modern neurosci-

ence is an intensely fertile and energetic discipline; thus it is unlikely that signals that emerge from schizophrenia epidemiology would excite this discipline without some type of affirmative action. The schizophrenia research community needs to generate candidate exposures and test (and reject) these candidates quickly and efficiently. For example, if we think that particular types of social stress contribute to the association between migrant status and risk of schizophrenia,³⁷ we need to engage the neuroscience community to refine our models from a neurobiological perspective. Which particular brain systems are most vulnerable to which particular types of stressors? What type of animal models could be designed to assess candidate exposures? Neuroscience can help us refine our questions, which can then influence the design and choice of exposure measures in future analytical (eg, case-control) epidemiological studies. However, we cannot expect the new ideas currently being generated by schizophrenia epidemiology to influence neuroscience merely by passive osmosis. We need to build shared research platforms that encourage greater cross-fertilization between schizophrenia epidemiology and neuroscience.

Such dialogues can be rewarding for all parties. By way of demonstration, based on various clues from epidemiology (eg, season of birth), our group proposed that developmental vitamin D deficiency was a candidate risk-modifying factor for schizophrenia.³⁸ Initially, there was an absence of information on the biological plausibility of this candidate. However, animal experiments have since confirmed that transient low prenatal vitamin D levels cause a range of neuroscience outcomes in the adult animal that are informative for schizophrenia research (eg, enlarged ventricles and disrupted dopaminergic/glutamatergic pathways).³⁹⁻⁴³ Clues from schizophrenia epidemiology have uncovered previously unsuspected pathways involving vitamin D and brain development.

Environmental risk factors clearly contribute to the prominent variations in the incidence of schizophre-

nia across time and place. The nature of the exposures remains to be clarified. Renewed interest in the environment and schizophrenia should not be misread as somehow lessening the importance of genetic contributions.⁴⁴ Schizophrenia researchers, like those interested in the etiology of chronic diseases in general, have nature-vs-nurture fatigue. The research community is united in a sincere desire to unravel the hidden layers of complexity underpinning schizophrenia. We cannot afford to waste the clues being generated by epidemiology. Acknowledging the variations in the epidemiology of schizophrenia is liberating; gradients in the incidence of schizophrenia allow the researcher to gain traction on these contours.⁴⁵ There is a sense of expectancy in schizophrenia epidemiology presently. We can only hope that this field will continue to surprise us. If we are lucky, these surprises will challenge our preconceptions. As Niels Bohr noted, "No paradox, no progress."

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