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Variations in the Incidence of Schizophrenia: Data Versus Dogma

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The schizophrenia research community has shared a belief that the incidence of schizophrenia shows little variation. This belief is related to the dogma that schizophrenia affects all individuals equally, regardless of sex, race, or nationality. However, there is now robust evidence that the incidence of schizophrenia is characterized by substantial variability. There is prominent variation in the incidence of schizophrenia between sites. The incidence of schizophrenia is significantly higher in males than in females (male:female ratio = 1.4). Migrants and those living in urban areas have a higher incidence of schizophrenia. The incidence of schizophrenia has fluctuations across time. In addition, the prevalence of schizophrenia is also characterized by prominent variation. The realization that schizophrenia is characterized by rich and informative gradients will serve as a catalyst for future research.

Key words: epidemiology/prevalence/variability

Introduction

A defining feature of the scientific method is the vigorous, transactional process between data and belief systems. As data accumulate, we revise our research models and set up hypotheses that, ideally, allow us to reject or refine our models. When evidence allows us to reject a research model, science can make progress. However, on occasions certain beliefs become dogma (i.e., a strongly held belief that is proclaimed without data). This article argues that schizophrenia research has been disproportionately influenced by the dogmatic belief that there is little variation in the incidence of schizophrenia.

In 1986 the World Health Organization published the preliminary report of a landmark multicenter study of schizophrenia.[1] This study employed uniform methodology in order to generate schizophrenia incidence rates from 8 sites (in 7 nations). The incidence of ICD-9 schizophrenia ranged from 16 to 42 per 100,000. When a subset of these patients was extracted according to narrow criteria, the incidence ranged from 7 to 14 per 100,000. Both definitions found at least a twofold difference between the highest and lowest sites, and this difference for the broad (but not narrow) definition was statistically significant. However, in spite of their own data, the authors of this study conclude, "The results provide strong support for the notion that schizophrenic illnesses occur with comparable frequency in different populations."[1(p909)] While the full report of this study is more circumspect in its interpretation of the issue of between-site variation,[2] the preliminary report has been frequently cited by researchers and has contributed to a broader belief that schizophrenia has a "flat" epidemiological profile across space and time. Such beliefs may have contributed to an undervaluing of the relative contribution of environmental (and gene × environmental) factors to the etiology of schizophrenia. For example, Crow has stated: "The evidence points to the singular conclusion that, contrary to almost any other common condition, the incidence of schizophrenia is independent of the environment and a characteristic of human populations."[3(p119)]

It has been argued elsewhere that this "equal incidence" belief may have tapped into a deeper, unspoken myth about schizophrenia being an "egalitarian disorder."[4] This myth, in its strongest form, suggests that schizophrenia occurs with equal incidence in all nations (rich and poor), in all races and creeds, and in men and women equally. While the notion that schizophrenia respects human rights is vaguely ennobling, it is also frankly bizarre. A generation of researchers has been inoculated with these false beliefs, which has led to an ideological resistance to data that challenge the underlying myths.[5] However, there are now robust data showing that schizophrenia is characterized by prominent variations across time and place. This article will use data from several recent systematic reviews in order to describe these variations.

The Incidence of Schizophrenia Has Prominent Variations Between Sites

A recent systematic review of the incidence of schizophrenia included data from 158 studies drawn from

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32 countries.[6] The distribution of rates had a median value of 15.2 per 100,000 and was positively skewed (i.e., the distribution contained more high rates than low rates). Based on conservative estimates (i.e., the central 80% of the cumulative distribution), rates for the incidence of schizophrenia fell within a range of 7.7 to 43.0 per 100,000, which is over a fivefold difference. Epidemiologists in fields such as diabetes have labeled similar incidence distributions as "prominent worldwide variation."[7(p883)]

The Incidence of Schizophrenia Has Prominent Variation by Sex

Two independent systematic reviews, using different summary methods, have concluded that the incidence of schizophrenia is significantly higher in men than in women.[6, 8] Both studies found the overall male:female risk ratio to be 1.4 and that this difference could not be accounted for by methodological factors related to age range or diagnostic criteria.

The Incidence of Schizophrenia Has Prominent Variation by Urbanicity

Several high-quality studies have indicated that those *born* in cities have approximately a twofold increased risk of developing schizophrenia, compared to those born in rural regions.[9–12] As a large proportion of individuals in the developed world are born in cities, the population-attributable fraction for this exposure is substantial (about 30%).[11–12] A systematic review recently reported that those *living* in cities also had significantly higher incidence rates of schizophrenia compared to those living in mixed urban–rural sites.[6]

The Incidence of Schizophrenia Has Prominent Variation by Migrant Status

A coherent and consistent body of research has emerged in recent years demonstrating that migrants have an increased risk of schizophrenia.[13–16] Two recent systematic reviews have confirmed that migrants have a significantly increased risk of developing schizophrenia (approximately a three- to fivefold risk ratio).[17–18]

Schizophrenia Has Variations According to Month of Birth

Individuals born in winter and spring have a small but significantly increased risk of developing schizophrenia.[19] This finding, one of the most consistently replicated findings in schizophrenia epidemiology, was confirmed in a systematic review of studies based on the Northern Hemisphere sites.[20] This same meta-analysis found that the size of the winter/spring excess was positively associated with latitude.[20] A well-designed study from Denmark estimated that while the odds ratio for schizophrenia associated with winter/spring birth was very small (relative risk = 1.11), because birth in winter/spring is such a common exposure, the population-attributable fraction associated with season of birth was sizable (10.5%).

The Incidence of Schizophrenia Has Changed Over Time

Narrative reviews based on historical texts have speculated that the incidence of schizophrenia has fluctuated over the centuries.[21] In fact, recent empirical studies provide support for this notion. Studies in southeast London between 1965 and 1997 show that the incidence of schizophrenia at this site doubled during the intervening decades.[22] In contrast, a systematic review of the incidence of schizophrenia establishes that more recent studies have found significantly lower incidence rates compared to earlier studies.[6] Such fluctuation would be expected in light of the dynamic shifts in population structure (e.g., the aging population) and exposure to various risk factors (e.g., migration, urbanicity, substance use). Fluctuations in the incidence of schizophrenia across time would also be congruent with the evidence that so-called schizophrenia birth rates (i.e., the proportion of individuals born in a certain month or year who later go on to develop schizophrenia) shows secular change[23] and intradecadal fluctuations.[24]

The Prevalence of Schizophrenia Varies Widely

While not the main focus of this article, it should be noted that the *prevalence* of schizophrenia also has prominent variations between sites.[25] Regardless of the type of prevalence estimate (i.e., point, period, lifetime, lifetime morbid risk), these distributions have prominent variation (i.e., five- to sixfold differences based on conservative criteria). This same systematic review found that the prevalence of schizophrenia in migrants was higher compared to that in native-born individuals and that developed countries had significantly higher prevalence estimates compared to developing nations.

Conclusions

Contrary to widespread beliefs, the incidence of schizophrenia has prominent variation over several criteria. The epidemiology of schizophrenia is fertile ground for the generation of new hypotheses. Gradients across time and place are the "stuff" of epidemiology—they allow us to gain "traction on the epidemiological landscape."[26]

This article argues that dogma has blinkered us to the prominent and informative variations in the incidence of schizophrenia. One of the key figures in the modern synthesis of evolutionary biology, Ernst Mayr, has commented on the resistance to change within a field of science: "One can go so far as to claim that the resistance of a scientist to a new theory almost invariably is based on ideological reasons rather than on logical

reasons or objections to the evidence on which the theory is based."[27(p835)] It has been argued that some resistance to change is a necessary part of the scientific process—it is a source of strength and stability.[28] However, when the accumulated evidence no longer fits with the dominant research model, it is time to look for fresh models. We must be "slaves to the data."

As with Ernst Mayr and evolutionary biology, it is now time for our field to usher in a *modern synthesis* of the causes of schizophrenia—which acknowledges that the incidence of schizophrenia has prominent variations across time and place. Such a modern synthesis should avoid rehashing wearisome debates about the relative importance of genes versus the environment—schizophrenia researchers have "nature-versus-nurture fatigue." Instead, variations in the incidence of schizophrenia should be seen as valuable opportunities to generate and test novel candidate exposures. These exposures operate against a backdrop of susceptibility genes. Identifying these susceptibility genes will provide us with further clues about how the environment can help optimize brain development.

Understanding the factors that cause variations in the incidence of schizophrenia will be a challenge. However, if the next generation of researchers appreciates these gradients, innovative research models will emerge, and these should be powerful catalysts for discovery.

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