New directions in the epidemiology of schizophrenia

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ABSTRACT

- New primary data and systematic reviews have prompted the review of some long-held views about the epidemiology of schizophrenia.
- The incidence and prevalence of schizophrenia show prominent variation between locations.
- Males are more likely to develop schizophrenia than females (1.4 : 1).
- Migrant status, urban birth or residence, and advanced paternal age are associated with an increased risk of developing schizophrenia.
- Prenatal infection and nutrition are associated with an increased risk of schizophrenia.
- Individuals with schizophrenia have a 2–3-fold increased mortality risk compared with the general population. This differential mortality gap may have worsened in recent decades.
- Epidemiology is good for generating candidate exposures but poor at proving them. Cross-disciplinary projects between epidemiology and neuroscience may help us understand the pathways leading to schizophrenia.

MJA 2009; 190: S7–S9

Over the past few decades, we have learned a great deal about the epidemiology of schizophrenia. The quality of research in the field has improved with access to larger and better characterised patient and general population samples. In addition to the influx of new data, systematic reviews have allowed re-evaluation of data in an unbiased fashion. Although there is still much work to be done in clarifying the boundaries of this poorly understood group of disorders, recent research based on traditional diagnostic classifications has challenged some long-held basic tenets about schizophrenia epidemiology.

Incidence, prevalence and mortality

Incidence counts the number of new cases per given population per year (thus, it is a rate), and is called a flow variable in models linking incidence and prevalence. Prevalence measures the proportion of surviving individuals who manifest a disorder at a specified time (ie, point prevalence), or during a specified period (eg, annual prevalence, lifetime prevalence). Prevalence estimates are proportions, and are called stock variables in modelling exercises. Mortality and remission or recovery (outflow variables) also need to be included in models. Theoretical models can be constructed to represent the dynamics of flow, stock and outflow variables.

For many decades, it was believed that the incidence of schizophrenia varied little between locations.[1] However, a recent systematic review has shown that the reverse is true, reporting that the median incidence of schizophrenia (for persons) was 15.2 per 100 000, and the central 80% of estimates varied over a fivefold range (7.7–43.0 per 100 000).[2]

A recently published systematic review of the prevalence of schizophrenia also identified prominent variation between sites.[3] The median lifetime prevalence estimate for persons was 4.0 per 1000, while the median estimate for lifetime morbid risk (LMR) was 7.2 per 1000. The oft-quoted statistic that "schizophrenia affects about one in a hundred" is usually thought to be based on LMR data. The systematic review found that the mean value of the distribution of LMR estimates was 11.9 per 1000 (the mean value was higher than the median because the distribution was skewed with several high estimates). Thus, the mean LMR is consistent with the "one in a hundred" dogma.

Concerning sex differences, a 2004 review found that the median male : female rate ratio was 1.4 : 1,[2] which is remarkably consistent with another systematic review of sex difference in the incidence of schizophrenia.[4] The earlier review, which used meta-analysis to pool the rate ratios, found that the risk ratio for men to develop schizophrenia relative to women was 1.42 (95% CI, 1.30–1.56).[4] This review adjusted the analyses in an attempt to account for known biases (eg, age range, quality of the study), however, the sex difference persisted. The data analysed in these two reviews were collected over several decades from many different countries, and have been based on many different design features. In light of these findings, we need to update what we teach and what we write in textbooks. Schizophrenia does *not* affect men and women equally — for every three men who develop schizophrenia, there are two women affected.

Mortality

The standardised mortality ratio (SMR), an index of relative mortality, is calculated by dividing the observed mortality in a given population (eg, the number of deaths in a group of individuals with schizophrenia over a certain period of observation) by the expected mortality in that same group (as predicted by the age- and sex-matched general population). Thus, an SMR of 2 would indicate that individuals with schizophrenia are twice as likely to die over that period of observation than the general population. SMRs can be calculated for overall mortality ("all-cause"), or for more specific, widely used categories (eg, cancer, cardiovascular, endocrine, suicide).

Two meta-analyses reported an all-cause SMR for schizophrenia of about 1.5.[5,6] Schizophrenia is associated with elevated suicide rates[7] and an increased risk of premature death associated with a wide range of comorbid somatic conditions.[5] A recent systematic review identified 37 studies that provided 561 SMRs for different causes of deaths.[8] The median (10th–90th percentile) SMR for persons for all-cause mortality was 2.6 (1.2–5.8). No sex difference was detected. Suicide was associated with the highest SMR (12.9); however, most major categories of causes of death were found to be elevated in schizophrenia. Worryingly, the SMRs for all-cause mortality have significantly increased over recent decades ($P = 0.03$) —

the median SMRs for the 1970s, 1980s and 1990s were 1.8, 3.0 and 3.2, respectively. If mortality rates in the general population decrease over time at a faster rate than those for people with schizophrenia, SMRs for schizophrenia will increase over time.

Risk factors for schizophrenia

Nutrition

Prenatal nutritional deprivation is a biologically plausible risk factor for schizophrenia. The Dutch *hongerwinter* (hunger winter) was a well documented famine during World War II. Individuals who were in utero during this famine showed an increased risk of schizophrenia and schizophrenia spectrum personality disorders.[9] The risk-increasing effect of maternal starvation on schizophrenia in the offspring was also seen in those exposed prenatally to a catastrophic famine in China during the Cultural Revolution.[10] With respect to the association between risk of schizophrenia and specific maternal micronutrients, homocysteine (a marker of folate metabolism) levels were significantly elevated in third trimester serum samples taken from mothers of individuals with schizophrenia.[11] There is some preliminary evidence to suggest that low levels of vitamin D during early life may be associated with schizophrenia.[12,13]

Infection

Although much of the early epidemiological research linking prenatal exposure to infection and risk of schizophrenia was based on ecological studies, access to biobanks has allowed stronger tests of this hypothesis. To date, there is evidence to suggest that the risk of schizophrenia is elevated in those with prenatal exposure to influenza,[14] rubella,[15] and *Toxoplasma gondii*.[16,17] There is mixed evidence for herpes simplex virus type 2.[18,19]

Pregnancy and birth complications

There is good evidence that pregnancy and birth complications are associated with an increased risk of schizophrenia. Several meta-analyses of these data are now available.[20,21] Overall, there is robust evidence that pregnancy and birth complications have a significant but modest effect in increasing the risk of later schizophrenia (odds ratio of about 2). Based on prospective population-based studies, the following specific exposures were associated with increased risk: antepartum haemorrhage, diabetes, rhesus incompatibility, pre-eclampsia, low birthweight, congenital malformations, reduced head circumference, uterine atony, asphyxia, and emergency caesarean section.[21]

Advanced paternal age

In recent years, several high-quality studies have confirmed an association between advanced paternal age and increased risk of schizophrenia.[22-24] The association between paternal age and schizophrenia has been repeatedly shown to be present in those with no family history of the disorder, but not in those with a positive family history. This finding raises the possibility that accumulation of de-novo mutations in paternal sperm with ageing contributes to the risk of schizophrenia. The strengthened evidence linking advanced paternal age and schizophrenia has influenced a range of aetiological theories of schizophrenia. For example, the persistence of schizophrenia in the population in spite of reduced fertility could be explained by the transgenerational accumulation of paternally-derived mutations. Paternal exposure to micronutritional deficiencies such as folate could further amplify copy-error mutations in the male germ cell lines. Finally, it is also feasible that epigenetic processes (eg, chromatin folding, methylation of CpG bases) could be compromised in the sperm of older fathers, and that these mechanisms may contribute to the increased risk of schizophrenia in the offspring of older fathers.

Urban residence, migrant status and socially mediated exposures

There is now robust evidence linking place of birth and risk of schizophrenia. Population-based studies from Holland[25] and Denmark[26] found a relative risk of developing schizophrenia of about 2.4 when born in metropolitan areas, compared with being born in rural areas. Place of birth could be a proxy marker for a risk-modifying variable operating at or before birth. However, because most people who are born in metropolitan areas are also brought up there, it is difficult to disentangle pre- and perinatal effects from those operating later in childhood.

There is robust evidence showing that some migrant groups have a markedly increased risk of schizophrenia.[2,27] These studies showed that first- and second-generation migrants have an increased risk of developing schizophrenia, and that the effect is most pronounced in migrants from areas where most of the population is black.[27]

It has long been accepted that childhood trauma is associated with a broad range of adverse mental health outcomes. However, whether childhood trauma is associated with schizophrenia has been controversial.[28,29] Based on a review of 20 studies that explored the prevalence of childhood abuse in those with a psychotic disorder, about half of the participants (male and female) reported either childhood sexual or physical abuse.[29] Population-based studies from the United Kingdom and Australia have found that those exposed to trauma are more likely to have a psychotic disorder or report isolated symptoms of psychosis (eg, delusions, hallucinations).[30,31]

Generally, the search for biological explanations for migrant status and urban residence has proved negative, leading to increased research in social biology. For example, there is growing interest in measuring various forms of early childhood and adult adversity, neighbourhood characteristics (eg, social capital, ethnic density). Although some environmental risks can be assessed at the individual level (eg, exposure to an infectious agent), other factors are best examined at the level of the family, neighbourhood or society. Multilevel studies can capture both ecological-level variables (eg, a neighbourhood marker of social capital or poverty) and individual-level variables (eg, experience-sampling methodology to assess changes in individual stress levels).

Cannabis

Data from several longitudinal studies have identified an association between cannabis use and subsequent risk of either isolated psychotic symptoms or schizophrenia. Several systematic reviews (which have been reviewed in detail elsewhere[32]) found that the greater the exposure to cannabis, the greater the risk of developing schizophrenia.

Future directions

Epidemiological research has proven itself a good source for generating candidate exposures, but history has also shown that risk-factor epidemiology can sometimes enter cycles of uninformative replications ("circular epidemiology"). Although analytical epidemiology is still a critical research tool, various types of "translational epidemiology" can provide complementary research strategies. Linking exposures with genetic polymorphisms in genes that impact on relevant pathways is one such option.[33] Building stronger links between schizophrenia epidemiology and neuroscience is also a valuable research strategy. This is especially important for exploring the biological plausibility of candidate risk factors derived from ecological studies.[34] Cross-disciplinary projects between epidemiology and neuroscience may help us understand the pathways leading to schizophrenia.

The epidemiology of schizophrenia has become more interesting in recent years.[34] Some new candidate exposures have been added to the list. Although some of these candidates will turn out to be false leads, we can expect that this list will continue to grow in the years to come. In light of the marked variability in both the phenotype and the genotype of schizophrenia, it seems reasonable that we should expect similar heterogeneity with respect to environmental risk factors.[34] Like genetic risk factors, environmental risk factors will probably be of small effect, and will probably vary considerably between populations. Regardless of this heterogeneity, the clues that have been generated by epidemiology are too valuable to neglect.

Competing interests

John McGrath has received support from Eli Lilly to attend conferences on schizophrenia.

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References

1 McGrath JJ. Myths and plain truths about schizophrenia epidemiology — the NAPE lecture 2004. *Acta Psychiatr Scand* 2005; 111: 4-11.
2 McGrath J, Saha S, Welham J, et al. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med* 2004; 2: 13.
3 Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med* 2005; 2: e141.
4 Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Arch Gen Psychiatry* 2003; 60: 565-571.
5 Brown S. Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry* 1997; 171: 502-508.
6 Harris EC, Barraclough B. Excess mortality of mental disorder. *Br J Psychiatry* 1998; 173: 11-53.
7 Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia — a reexamination. *Arch Gen Psychiatry* 2005; 62: 247-253.
8 Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007; 64: 1123-1131.
9 Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch hunger winter of 1944–1945. *Arch Gen Psychiatry* 1992; 49: 983-988.
10 St Clair D, Xu M, Wang P, et al. Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959–1961. *JAMA* 2005; 294: 557-562.
11 Brown AS, Bottiglieri T, Schaefer CA, et al. Elevated prenatal homocysteine levels as a risk factor for schizophrenia. *Arch Gen Psychiatry* 2007; 64: 31-39.
12 McGrath J, Saari K, Hakko H, et al. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth-cohort study. *Schizophr Res* 2004; 67: 237-245.
13 McGrath J, Eyles D, Mowry B, et al. Low maternal vitamin D as a risk factor for schizophrenia: a pilot study using banked sera. *Schizophr Res* 2003; 63: 73-78.
14 Brown AS, Begg MD, Gravenstein S, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry* 2004; 61: 774-780.
15 Brown AS, Cohen P, Greenwald S, Susser E. Nonaffective psychosis after prenatal exposure to rubella. *Am J Psychiatry* 2000; 157: 438-443.
16 Brown AS, Schaefer CA, Quesenberry CP Jr, et al. Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *Am J Psychiatry* 2005; 162: 767-773.
17 Mortensen PB, Norgaard-Pedersen B, Waltoft BL, et al. Early infections of *Toxoplasma gondii* and the later development of schizophrenia. *Schizophr Bull* 2007; 33: 741-744.
18 Buka SL, Tsuang MT, Torrey EF, et al. Maternal infections and subsequent psychosis among offspring. *Arch Gen Psychiatry* 2001; 58: 1032-1037.
19 Brown AS, Schaefer CA, Quesenberry CP Jr, et al. No evidence of relation between maternal exposure to herpes simplex virus type 2 and risk of schizophrenia? *Am J Psychiatry* 2006; 163: 2178-2180.
20 Geddes JR, Verdoux H, Takei N, et al. Schizophrenia and complications of pregnancy and labor: an individual patient data meta-analysis. *Schizophr Bull* 1999; 25: 413-423.
21 Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiatry* 2002; 159: 1080-1092.
22 Malaspina D, Harlap S, Fennig S, et al. Advancing paternal age and the risk of schizophrenia. *Arch Gen Psychiatry* 2001; 58: 361-367.
23 El-Saadi O, Pedersen CB, McNeil TF, et al. Paternal and maternal age as risk factors for psychosis: findings from Denmark, Sweden and Australia. *Schizophr Res* 2004; 67: 227-236.
24 Sipos A, Rasmussen F, Harrison G, et al. Paternal age and schizophrenia: a population based cohort study. *BMJ* 2004; 329: 1070.
25 Marcelis M, Navarro-Mateu F, Murray R, et al. Urbanization and psychosis: a study of 1942-1978 birth cohorts in the Netherlands. *Psychol Med* 1998; 28: 871-879.
26 Mortensen PB, Pedersen CB, Westergaard T, et al. Effects of family history and place and season of birth on the risk of schizophrenia. *N Engl J Med* 1999; 340: 603-608.
27 Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. *Am J Psychiatry* 2005; 162: 12-24.
28 Read J, van Os J, Morrison AP, Ross CA. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatr Scand* 2005; 112: 330-350.
29 Morgan C, Fisher H. Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma — a critical review. *Schizophr Bull* 2007; 33: 3-10.
30 Bebbington PE, Bhugra D, Brugha T, et al. Psychosis, victimisation and childhood disadvantage: evidence from the second British National Survey of Psychiatric Morbidity. *Br J Psychiatry* 2004; 185: 220-226.
31 Scott J, Chant D, Andrews G, et al. Association between trauma exposure and delusional experiences in a large community-based sample. *Br J Psychiatry* 2007; 190: 339-343.
32 Murray RM, Morrison PD, Henquet C, Di Forti M. Cannabis, the mind and society: the hash realities. *Nat Rev Neurosci* 2007; 8: 885-895.
33 Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol* 2004; 33: 30-42.
34 McGrath JJ. The surprisingly rich contours of schizophrenia epidemiology. *Arch Gen Psychiatry* 2007; 64: 14-16.

(Received 9 Jun 2008, accepted 25 Aug 2008) ❑