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Schizophrenia: A Concise Overview of Incidence, Prevalence, and Mortality

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Recent systematic reviews have encouraged the psychiatric research community to reevaluate the contours of schizophrenia epidemiology. This paper provides a concise overview of three related systematic reviews on the incidence, prevalence, and mortality associated with schizophrenia. The reviews shared key methodological features regarding search strategies, analysis of the distribution of the frequency estimates, and exploration of the influence of key variables (sex, migrant status, urbanicity, secular trend, economic status, and latitude). Contrary to previous interpretations, the incidence of schizophrenia shows prominent variation between sites. The median incidence of schizophrenia was 15.2/100,000 persons, and the central 80% of estimates varied over a fivefold range (7.7–43.0/100,000). The rate ratio for males:females was 1.4:1. Prevalence estimates also show prominent variation. The median lifetime morbid risk for schizophrenia was 7.2/1,000 persons. On the basis of the standardized mortality ratio, people with schizophrenia have a two- to threefold increased risk of dying (median standardized mortality ratio = 2.6 for all-cause mortality), and this differential gap in mortality has increased over recent decades. Compared with native-born individuals, migrants have an increased incidence and prevalence of schizophrenia. Exposures related to urbanicity, economic status, and latitude are also associated with various frequency measures. In conclusion, the epidemiology of schizophrenia is characterized by prominent variability and gradients that can help guide future research.

incidence; mortality; prevalence; review; schizophrenia

Abbreviation: SMR, standardized mortality ratio.

INTRODUCTION

Over the last decade, we have learned a great deal about the epidemiology of schizophrenia. New data have accumulated, and systematic reviews have enabled us to reevaluate older data. Some of the basic tenets of schizophrenia epidemiology have been questioned. For example, the dogmatic belief that the incidence of schizophrenia varies little between sites has been questioned (1, 2), as has the belief that schizophrenia affects men and women equally (3, 4). A lack of rigorously compiled data on the incidence of schizophrenia may have contributed to a degree of confusion within the research community. For example, Jablensky (5) concluded that, ''according to the great majority of studies, the prevalence and incidence rates of schizophrenia are similar across populations'' (6, p. 212). Other reviewers (7) have reached similar conclusions with respect to prevalence studies. In contrast, Torrey (8, 9), Eaton et al. (10–12), Warner and de Girolamo (13), and Goldner et al. (14) have all commented on the variability in schizophrenia incidence and/or prevalence estimates. For example, in an earlier review by Eaton (10), a 12-fold variation in point prevalence and a 10-fold variation in lifetime prevalence were noted. A recent systematic review by Goldner et al. observed a 13-fold variation in lifetime prevalence of schizophrenia. Leading commentators have also questioned the notion that the incidence of schizophrenia is essentially uniform across sites (1, 15).

Over the last decade, there has also been a growing appreciation that reviews should be based on data as complete

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and as free of bias as possible. The need for systematic reviews with respect to the incidence and prevalence of schizophrenia was recognized by Jablensky: ''Ideally, a meta-analysis involving a standardized recalculation of the rates from many previous studies should generate a distribution allowing one to estimate with some probability the extent to which populations differ'' (6, p. 219). Before we can attempt to build realistic models of the dynamics of schizophrenia in the population, the various epidemiologic estimates need to be collated systematically.

Systematic reviews need to cover four key epidemiologic indicators in order to promote understanding of the dynamics of a disorder in a population: incidence, prevalence, remission/recovery, and mortality. Incidence and prevalence express disease frequencies in different ways. Incidence counts the number of new cases per given population per year. In models linking incidence and prevalence, incidence rates are *inflow* variables (16). Prevalence measures the proportion of surviving individuals who manifest a disorder at a specified time (e.g., point prevalence) or during a specified period (e.g., annual prevalence, lifetime prevalence). Prevalence estimates are proportions and in a modeling exercise are called *stock* variables. Estimates related to mortality and remission/recovery (*outflow* variables) are also needed to fully specify disease models. Theoretical models can be constructed that integrate the ''hydraulics'' of inflow, stock, and outflow variables (17, 18).

Do we have sufficient data to build integrated and cohesive models of the epidemiology of schizophrenia in populations? Certainly, with respect to the stock and inflow variables, there is a wealth of data on the incidence and prevalence of schizophrenia (4, 19). As discussed below, these measures have been collected from many different sites, over many decades. In contrast, we know somewhat less about the outflow variables remission and mortality. Concerning remission, it is interesting to contrast recent advances in the identification of the *onset* of psychotic disorders (20, 21) versus our abilities to accurately understand the *offset* of schizophrenia (19). Categorical outcome measures (e.g., recovered vs. persistent illness) are not readily operationalized for chronic disorders such as schizophrenia. Dimensional symptom outcomes (e.g., positive or negative symptoms) and more ''downstream'' measures of disability (e.g., employment, social functioning) tend to fluctuate over time and show divergent trajectories. Compared with measuring incidence and prevalence, assessing clinical outcomes in schizophrenia is much more of a challenge (22, 23).

Compared with those for remission, high-quality, population-based estimates of mortality are more readily available. Standardized mortality ratios (SMRs) are calculated by dividing the ''observed'' mortality in a given population (e.g., the number of deaths in a group of individuals with schizophrenia) 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 than individuals in the general population. SMRs can be calculated for overall mortality (''all-cause'') or for more specific, widely used categories (e.g., cancer, cardiovascular, endocrine, suicide). In recent years, several scholarly reviews have noted higher mortality for individuals with schizophrenia compared with the general population (24–27). Two meta-analyses reported an all-cause SMR for schizophrenia of approximately 1.5 (25, 27). Schizophrenia is associated with elevated suicide rates (28) and an increased risk of premature death related to a wide range of comorbid somatic conditions (25).

This paper provides a concise review of the incidence, prevalence, and mortality associated with schizophrenia based on three systematic reviews that shared a common methodology (4, 19, 29). In addition, systematic compilation of estimates allows for testing of specific hypotheses related to gradients in the estimates. For example, evidence suggests that the incidence of schizophrenia is related to sex (3), migrant status (30), and urbanicity (31–33). Systematic reviews of season of birth (34, 35) suggest that the magnitude of the effect of season of birth is greater at higher latitudes. This effect, in turn, may influence incidence and prevalence at higher latitudes (36). Economic status (e.g., developed nation vs. developing nation) may also influence variables such as clinical outcome (37) and mortality (38). Commentators have often speculated about the stability of schizophrenia incidence and prevalence over time (8, 9). With respect to mortality, there is evidence that SMRs for schizophrenia may be worsening over time (39). Because the reviews included studies published over several decades, we also took the opportunity to explore the estimates for changes over time (i.e., secular change).

In summary, this review explores the distributions of the primary frequency estimates and summarizes the results of various analyses related to the influence of sex, migrant status, urbanicity, economic status, latitude, and secular trends on incidence, prevalence, and mortality. The reader will also be directed to publications and a website that provide additional information on these and related analyses.

METHODS

Guidelines outlined by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (40) were followed to identify and collate mortality studies. A broad search string in MEDLINE, PsychINFO, Web of Science, and Google Scholar was used to identify all research studies that investigated incidence, prevalence, or mortality associated with schizophrenia: ((schizo* OR psych*) AND ((incidence OR prevalence) OR (mortality OR outcome OR follow-up))). Potentially relevant papers (in all languages) were accessed in order to review the full text. Citations from significant papers and review papers were scrutinized to locate additional relevant articles, book chapters, and conference papers. The Web of Science Cited Reference Search system was also used to locate relevant articles. Finally, letters or e-mail messages were sent to the senior authors of papers that met the inclusion criteria. These authors were provided with an interim list of included papers and were asked to nominate missing studies.

We included studies that reported primary data on the incidence or prevalence of schizophrenia or reported on the mortality associated with schizophrenia. These studies were

first published between January 1965 and 1) December 2002 for the incidence and prevalence estimates or 2) January 2006 for the mortality estimates.

Once a study was included, data were extracted and entered into a three-level database that included study-level variables (e.g., authors, year of publication, site), middle-level variables (e.g., age group, recruitment duration, case finding method, diagnostic criteria), and estimate-level variables (e.g., types of estimates for persons, males, or females). Two or more of the authors checked all data used in the analysis. Disagreements that arose were resolved by consensus. If required, we contacted the original authors to clarify issues.

Systematic reviews need to avoid ''double counting'' the index variable by the same or different studies. Thus, to identify discrete frequency estimates, we applied sequential filters. For example, after identifying studies in which both time and place overlapped, we selected one representative estimate for inclusion in the relevant cumulative distributions based on the ''most informative'' rule. Doing so stipulated that, given overlapping estimates, preference would be given to the estimate based on the largest sample (e.g., preferring a wider over a narrower age range).

The distributions of relevant estimates were presented in cumulative plots, with every estimate contributing to the distribution. The distribution of the data was shown in rank order for estimate (lowest to highest ranks), with the cumulative percentage of estimates shown on the vertical axis. The plots show horizontal reference lines indicating the 50 percent (median) and the 25 and 75 percent quantiles (within which lies the interquartile range). To aid visual interpretation, some plots were truncated, excluding very high estimates. Key features of the full distributions (e.g., median; mean; geometric mean; standard deviation; quantiles at 10, 25, 50, 75, and 90 percent) were also presented in tables.

For the purposes of the current paper, we focused on standard, general-population-based incidence rates (referred to as ''core'' studies). Cohort-based cumulative incidence estimates, and incidence rates based on migrant and other special groups, are also available in the main incidence review paper (4). For prevalence, we divided the estimates into 1) point prevalence (at least 1 month), 2) period prevalence (1– 12 months), 3) lifetime prevalence, 4) lifetime morbid risk, 5) ''not otherwise specified'' (i.e., insufficient information was provided to allocate prevalence type), and 6) inpatient-census-derived data (not a true measure of prevalence but related to service utilization patterns). Lifetime morbid risk (also known as morbid risk or expectancy) differs from lifetime prevalence in that it attempts to include the entire lifetime of a birth cohort, both past and future, and includes those deceased at the time of the survey (41). In the presentation of mortality, we focus on all-cause SMR but mention selected other categories of SMRs related to specific causes (e.g., suicide).

Concerning economic status, we divided studies according to the per capita gross national product of the study site (based on 2004 data) (42). We used the following standard World Bank definition of country status (43): 1) least developed countries: mean income of less than US $2,995; 2) emerging economy countries: mean income of US $2,995–$9,266); and 3) developed countries: mean incomes of more than US $9,266.

TABLE 1. Results of the search strategy and selected features of the included studies in the systematic reviews of schizophrenia incidence, prevalence, and mortality

	Incidence	Prevalence	Mortality
Discrete no. of publications identified by the search strategy			
Electronic sources	834	1,112	1,726
Bibliographies	249	142	26
Writing to authors	41	98	16
No. of included studies (no. of included studies only published in languages other than English)	158 (10)	188 (17)	37 (4)
No. of countries represented in the included studies	32	46	25
Estimated total no. of cases contributing to the estimates	176,056	154,140	22,296

Concerning latitude, we allocated exact latitude values for cities and geocentroid values for larger regions by using standard geographic coordinates (44). On the basis of absolute latitude, we divided latitudes into three equal bands, namely, ''low'' (equator to 30°), ''medium'' (30°–60°), and ''high'' (above 60°). Concerning secular trend, we divided the studies into three approximately equal epochs according to first year of intake for incidence studies or midpoint year of intake for the prevalence and mortality reviews.

To assess the impact of sex, migrant status, urban status, secular trend, economic status, and latitude, we performed statistical analyses that compared the distributions when sorted by the variable of interest. These analyses take into account the need to control for within-study variation and the use of a log transformation (and geometric means) to analyze distributions that are often skewed positively. To minimize the number of comparisons, these analyses were restricted to 1) persons (apart from the specific analyses related to sex differences), 2) a ''combined prevalence'' category (which includes point, period, lifetime, and ''not otherwise specified'' prevalence types), and 3) ''all-cause'' SMR. Analyses were performed by using SAS version 9.2 software (SAS Institute, Inc., Cary, North Carolina).

The data sets used in the three main reviews are available on our Schizophrenia Epidemiology Resource website, as are key details of all the included studies (presented in tables sorted by country, year of publication, and first author) (45). Because of space limitations, the references for the primary data underlying the three systematic reviews and details of the statistical analyses are not shown in this review but are available elsewhere (4, 19, 29, 36, 46).

RESULTS

Table 1 summarizes selected details of the results of the search strategy. While most of the potentially relevant

TABLE 2. Quantiles and moments describing the distribution of estimates from the systematic reviews of schizophrenia incidence, prevalence, and mortality, by sex

Estimate type	No. of estimates	Quantile					Mean (standard deviation)	Geometric mean
		10%	25%	Median	75%	90%		
Incidence (per 100,000)								
Persons	170	7.7	10.2	15.2	22.0	43.0	23.7 (30.3)	15.9
Males	100	6.6	11.4	15.0	24.8	34.1	21.8 (27.4)	16.2
Females	100	3.0	6.3	10.0	21.8	30.2	21.3 (45.1)	11.3
Prevalence (per 1,000)								
Prevalence: point								
Persons	23	1.9	2.9	4.6	6.4	10.0	6.0 (5.9)	4.5
Males	11	1.7	2.6	4.3	9.0	11.0	8.1 (10.4)	5.0
Females	12	0.3	1.5	3.0	8.6	12.5	5.8 (6.7)	3.5
Prevalence: period								
Persons	42	1.3	2.0	3.3	6.0	8.2	5.7 (8.1)	3.5
Males	16	1.0	2.4	3.8	6.3	20.0	6.2 (7.3)	4.5
Females	16	2.0	2.8	3.6	6.8	11.0	5.4 (3.9)	4.4
Prevalence: lifetime								
Persons	29	1.8	3.0	4.0	6.6	11.6	5.5 (4.5)	4.3
Males	17	1.3	2.6	3.7	5.0	12.8	4.9 (4.5)	3.7
Females	17	0.7	1.6	3.8	7.0	11.4	4.8 (3.8)	3.4
Lifetime morbid risk								
Persons	27	3.1	4.7	7.2	17.2	27.1	11.9 (10.8)	8.6
Males	38	1.5	3.2	4.1	7.1	14.8	6.2 (5.9)	4.5
Females	38	0.9	3.0	4.6	6.1	12.4	5.6 (4.9)	4.4
Standardized mortality ratios: all cause								
Persons	38	1.2	1.9	2.6	3.6	5.8	3.0 (1.8)	2.7
Males	25	1.7	2.1	2.8	3.5	4.7	3.2 (1.7)	2.9
Females	22	1.5	2.2	2.5	3.0	5.4	3.7 (4.6)	2.8

studies were identified via electronic searches, the use of bibliographies and letters to authors were also fruitful strategies. After careful scrutiny, we included 158, 188, and 37 studies for the reviews of incidence, prevalence, and mortality, respectively (note that one study may provide more than one discrete estimate). Of the 383 studies included, 31 (8 percent) were only published in languages other than English. For the incidence review, data were identified from 32 countries, and the rates were based on an estimated 176,056 incident cases. For the prevalence review, data were identified from 46 countries, and the prevalence estimates were based on an estimated 154,140 cases. Finally, for the mortality review, data were identified from 25 countries, and the SMRs were based on an estimated 22,296 cases.

Incidence

The systematic review revealed 158 studies that generated 1,458 rates, and it identified 100 core (i.e., general population-based) studies. Twenty-four studies provided incidence rates for migrant groups, and 23 studies presented incidence estimates based on cohort studies. Fourteen studies reported incidence of schizophrenia in other population subgroups (e.g., twins, the deaf).

For the core incidence estimates, the median estimate (10, 90 percent quantiles) was 15.2 (7.7, 43.0) per 100,000 (table 2). The distribution was right skewed, with many high estimates in the upper tail. The distribution of incidence rates differed significantly between males and females, and the median (10, 90 percent quantiles) rate ratio for male:female estimates was 1.4 (0.9, 2.4). Curiously, the median rate based on persons was higher than the median rates for males and for females when assessed separately. This lack of internal consistency between estimates (also noted in certain prevalence distributions) is difficult to explain but may reflect the nature and quality of the different studies that contribute estimates to sex-specific distributions versus distributions for persons.

The distribution of incidence rates differed significantly between migrants and native-born individuals, and the migrant-to-native-born rate ratio median (10, 90 percent quantiles) was 4.6 (1.0, 12.8). The distribution of incidence

TABLE 3. Influence of sex, migrant status, urban status, secular trend, economic status, and latitude on the distribution of estimates from the systematic reviews of schizophrenia incidence, prevalence, and mortality

	Sex	Migrant status	Urban status	Secular trend	Economic status	Latitude
Incidence: core	Males > females	Migrant > native born	Urban > mixed urban and rural	Falling over time	No significant difference	High latitude > lower latitude (males only)
Prevalence: combined estimates	Males = females	Migrant > native born	No significant difference	Stable	Developed > least developed	High latitude > lower latitude
Standardized mortality ratio: all cause	Males = females	Not available	Not available	Rising over time	No significant difference	Not available

rates differed between those from exclusively urban settings when compared with mixed urban-rural settings (urban vs. mixed rural-urban median estimates: 19 vs. 13.3 per 100,000, respectively). The distribution of the estimates differed by intake epoch, with the earlier studies (1947–1976) having a higher median estimate (17.9 per 100,000) compared with later epochs (1977–1983, 1984–1995; 13.3, 13.5 per 100,000, respectively).

The distribution of estimates did not differ according to economic status (46). Studies based in higher latitudes were associated with higher median estimates for males, but not for females (36).

Prevalence

The systematic review identified 188 studies that provided 1,721 prevalence estimates. There were 132 general-population-based studies, 15 migrant studies (three of which overlap with discrete core studies), and 41 studies that reported the prevalence of schizophrenia in other special groups. Of the 132 general-population-based studies, we identified 21 for point prevalence, 34 for period prevalence, and 24 for lifetime prevalence. Thirty-two studies provided no information on the type of prevalence they reported. Nine studies reported lifetime morbid risk. Finally, 44 studies reported inpatient-census-derived data (which were excluded from further analyses).

The median values per 1,000 persons (10, 90 percent quantiles) for the distributions for point, period, lifetime, and lifetime morbid risk were 4.6 (1.9, 10.0), 3.3 (1.3, 8.2), 4.0 (1.6, 12.1), and 7.2 (3.1, 27.1), respectively (table 2). On the basis of combined prevalence estimates, we found no significant difference 1) between males and females; 2) between urban, rural, and mixed sites; or 3) across epochs. The prevalence of schizophrenia in migrants was higher compared with native-born individuals: the migrant-to-native-born ratio median (10, 90 percent quantiles) was 1.8 (0.9, 6.4). The distribution of prevalence estimates differed significantly when sorted by economic status, with developed countries having higher estimates than less-developed economies (median estimates: 3.3 vs. 2.6 per 1,000, respectively). Finally, the distribution of prevalence estimates differed significantly when sorted by latitude. Estimates from higher latitudes were associated with higher estimates compared with middle and low latitudes (geometric means: 7.5, 3.2, and 3.3 per 1,000 for high, medium, and low latitude bands, respectively).

Mortality

The systematic review revealed 37 studies that provided data on 561 SMRs for different causes of death. The median (10, 90 percent quantiles) 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 of the major causes-of-death categories were found to be elevated in schizophrenia. Full details of specific-cause SMR are provided elsewhere (29). The SMRs for all-cause mortality 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. The SMRs did not differ by economic status. There were insufficient data to explore the influence of migrant status, urban status, and latitude on SMR.

The influence of the various risk factors for incidence, prevalence, and mortality is summarized in table 3.

DISCUSSION

Systematic reviews have identified a wealth of information about the incidence, prevalence, and mortality associated with schizophrenia. The incidence of the disorder shows prominent variation between sites, with the central 80 percent of incidence distribution varying over a fivefold range. The distribution of incidence rates is right skewed, with high estimates located in the upper tail of the distribution.

Concerning prevalence, the median lifetime prevalence estimates for persons were 4.0 per 1,000 and for lifetime morbid risk were 7.2 per 1,000. These estimates are congruent with an earlier narrative review of 70 studies by Torrey (9), which reported an overall prevalence estimate of 4.6 per 1,000. Our median lifetime morbid risk estimate was 7.2 per 1,000, consistent with two previous narrative reviews (47, 48). The oft-quoted statistic that ''schizophrenia affects about one in a hundred'' is usually thought to be based on lifetime morbid risk data. Although the arithmetic mean value of 11.9 per 1,000 is more consistent with the ''one in a hundred'' dogma, the median is a more appropriate measure of central tendency for this skewed distribution. If we want to provide the general public with a measure of the likelihood that individuals will develop schizophrenia during their lifetime, then a more accurate statement would be that ''about seven individuals per 1,000 will be affected.''

Compared with the general population, people with schizophrenia have a two- to threefold increased risk of

dying. Although suicide contributes to the increased mortality associated with schizophrenia, individuals with schizophrenia have increased mortality risks due to a wide range of comorbid somatic conditions. Worryingly, over recent decades, the differential mortality gap associated with schizophrenia has been increasing. If mortality rates in the general population decrease over time at a faster rate than those for people with schizophrenia, then SMRs for schizophrenia will increase over time. Because our review found evidence to suggest that the case fatality rate in schizophrenia had remained stable in recent decades (29), the data suggest that the differential mortality gap has widened over time because the patient group did not share in the improved health of the general community. It is feasible that introduction of second-generation antipsychotic medications may further contribute to increased mortality in the decades to come. Compared with typical antipsychotics, several of the second-generation antipsychotics are more likely to cause weight gain and metabolic syndrome (49). Metabolic syndrome is associated with a twofold increase in all-cause mortality (50). Thus, in the absence of assertive management and treatment of these side effects, it is feasible that second-generation antipsychotics could contribute to even higher SMRs in the next few decades (51, 52).

Concerning sex differences in the incidence of schizophrenia, we found that the median male:female rate ratio was 1.4, which is consistent with another systematic review of sex difference in the incidence of schizophrenia by Aleman et al. (3). This study (which used meta-analysis) found that the pooled male:female rate ratio was 1.4 (95 percent confidence interval: 1.3, 1.6). Furthermore, the Aleman et al. study adjusted the analyses in an attempt to account for known biases (e.g., age range, quality of the study); however, the sex difference persisted. The data contributing to these two analyses have been collected over several decades from many different nations and have been based on many different design features. To ''wash out'' the male excess, several dozen studies that find equivalent incidences among males and females would need to be added to the distribution. In the face of such evidence, we now need to change what we teach: for every three men who develop schizophrenia, two women are affected.

The sex difference identified in the incidence rates is not reflected in prevalence estimates. Because narrative reviews conclude that the course of the illness tends to be more severe in men than in women (53), and because our review did not identify a sex difference in SMR, it seems reasonable to assume that the prevalence of schizophrenia would be higher in males compared with females. However, this was not the case. Curiously, a recent, high-quality prevalence study from Finland also confirmed the lack of sex difference in lifetime prevalence of schizophrenia (54). Such paradoxes can be potent catalysts for future research.

There were robust associations between migrant status and both an increased incidence and an increased prevalence of schizophrenia. Studies that examine the incidence and prevalence of disorders in migrant groups are prone to a range of methodological issues, including factors related to differential pathways to care, diagnostic inaccuracies (language and cultural practices may hinder accurate diagnosis), potential confounding due to socioeconomic factors, and problems in determining the numerator and denominator needed to calculate estimates. Even though the studies analyzed in these systematic reviews shared common biases, they were drawn from many different sites, included many different migrant groups, and differed regarding a range of methodological features. The association between migrant status and schizophrenia is one of the most startling gradients in schizophrenia epidemiology to emerge in recent decades (30). These findings have stimulated a range of hypotheses related to the mechanisms of action underlying this effect, including candidates from social biology such as social defeat (55), nutritional factors (56), and infection (57). Recent evidence from a US birth cohort reported an increased incidence of schizophrenia in African Americans (58). This study suggests that factors related to race/ethnicity may be more important with respect to the increased risk of schizophrenia than the immediate effects of migration per se.

The incidence of schizophrenia was higher in urban settings compared with mixed urban/rural settings; however, this gradient was not reflected in the distribution of prevalence estimates. The factors underlying this apparent gradient remain unclear (59, 60), but factors related to environmental pollutants (61) and stress related to overcrowding (62) have been proposed. Population demographics indicate increasing urbanization in both the developed and developing world (63). Although speculative, it would be a concern if the incidence of schizophrenia rises in parallel with exposure to an increasingly urban environment.

Concerning economic status, evidence suggests that both the incidence and the prevalence of schizophrenia are higher in developed nations compared with developing nations. While thought provoking, these analyses should be treated cautiously because 1) there is a relative lack of data from low- versus higher-income nations, and 2) using a single economic variable is a crude way to assess a complex and multidimensional concept.

In keeping with a previous analysis (64), the prevalence of schizophrenia was also found to be increased at higher latitudes. However, higher latitude was associated with an increased incidence of schizophrenia among males only (36). Latitude is a proxy variable related to a broad range of factors including genetic background, biometeorologic variables (e.g., temperature, ultraviolet radiation, and precipitation), and socioeconomic issues. Mindful of the limitations of ecologic studies, it of interest to note that low prenatal vitamin D levels have been proposed as a risk factor for schizophrenia (56). Hypovitaminosis D is more prevalent during winter and at higher latitudes, so populations living at high latitudes would be expected to have both a greater season of birth effects (as previously shown by Davies et al. (65)) and a higher incidence of schizophrenia.

Examination of secular changes suggested a reduction in the incidence of schizophrenia over time, while prevalence estimates have remained stable. However, there were insufficient studies based on the same catchment area that could be linked over time. Longitudinal studies would be required to address the issue of secular change directly. Curiously, studies based in London, United Kingdom, have indicated a doubling in the incidence of schizophrenia between 1965

and 1997 in this catchment area, which the authors attribute to an influx of migrants (66). Conversely, studies from Finland have suggested that the cumulative incidence of schizophrenia has declined in birth cohorts born between 1945 and 1965 (67).

In light of the variability in incidence rates between sites and the broad range of gradients identified in these reviews (e.g., migrant status, urbanicity, latitude), it seems reasonable to assume that a range of yet-to-be-identified risk factors could vary over time and space. These risk factors, in turn, could lead to fluctuations in the incidence of schizophrenia over time and space. No one needs to be reminded about the marked clinical and neurobiologic heterogeneity of schizophrenia (68). The research community is now comfortable with the notion that there are many different susceptibility genes, each of small effect, that display variability between populations (69). Given the marked variability in both the phenotype and genotype of schizophrenia, one might also predict similar heterogeneity in environmental factors.

Caveats

A wide range of methodological factors can influence the estimates summarized in this review. The influence of many of these factors (e.g., diagnostic criteria, case selection methods, study quality) was examined specifically in our previously published systematic reviews (4, 19, 29). We found that higher-quality studies were more likely to identify higher prevalence estimates (19), but, in general, the estimate distributions did not differ significantly when sorted by overall quality or by various methodological features. This finding suggests, but does not prove, that these design factors were not sufficient to account for an appreciable amount of the variance. In other words, although factors such as diagnostic criteria and age range clearly influence incidence rates and sex rate ratio (70), other sources of variation persist.

With respect to the comparison of incidence rates between sites and over time, the use of age and/or sex standardization needs to be taken into account. In the original systematic review of the incidence of schizophrenia (4), we explored this issue as a planned sensitivity analysis. However, we found that when the rates were divided into age standardized versus raw, these distributions did not differ significantly. The use of standardization, along with many other issues related to study design and analysis, can contribute to heterogeneity of the estimates.

Caution is also required when assessing secular trends in SMRs. These estimates are known to vary widely between sites because of 1) true differences in estimates related to age population distributions, differences is disease frequencies, and availability of services; and 2) variations introduced by methodology (e.g., phase of illness and source of patient cohorts, duration of follow-up, attrition). However, we note that a study based on comparable records in Sweden also found that SMRs have risen over recent decades (39).

Consensus is lacking about how best to summarize observational studies. In spite of the widespread use of meta-analyses to synthesize intervention studies, there has been relatively little discussion on the strengths and weakness of these techniques for summarizing frequency measures such as incidence and prevalence estimates (71, 72). We explored this issue in more detail elsewhere (73). Based on the subset of incidence and prevalence studies that provide sufficient information to calculate standard error (which is required to weight estimates in meta-analysis), the pooled values (derived from traditional meta-analysis) versus the median estimates (derived from the full distribution of estimates) were comparable. This was also the case for the analysis of mortality, where the median and pooled estimates were similar (2.6 and 2.5, respectively; all-cause SMR for persons). If pooled estimates are of interest, researchers need to be aware that studies based on large samples will leverage greater weight on the pooled value, which may not be appropriate for comparing frequency estimates. Furthermore, there is a case against collapsing data into one pooled estimate because cumulative distribution plots are superior to traditional meta-analytic approaches with respect to the assessment of variation.

Evidence from systematic reviews can be wrong. Observational epidemiology is never totally determinate (74), and, while doubts persist about potential sources of bias, we need to maintain a state of uncertainty about the interpretation of the data. It should also be noted that several important studies related to incidence (75), prevalence (54), and mortality (76) have appeared since our reviews were published. It is a healthy sign for our field that new data related to the epidemiology continue to accumulate.

Future directions

Understanding the incidence and prevalence of a disorder is the bedrock of risk factor epidemiology (77). Such frequency estimates are also critical for evaluating disease-burden measures such as the disability-adjusted life year, a metric increasingly relied on for prioritizing health care and service planning (78, 79). However, despite the abundance of data on the incidence and prevalence of schizophrenia, relatively few studies provide both frequency measures for the same population and epoch. We are currently identifying incidence and prevalence estimates based on matched catchment areas and epochs. With the assistance of modeling software such as DisMod (80), we will attempt to build models incorporating published incidence, prevalence, and mortality estimates. The utility of models that attempt to integrate frequency estimates has recently been explored by Hickman et al. (81), who used a modeling approach based on published incidence and prevalence data to explore the impact of increased use of cannabis on schizophrenia frequency measures. Based on the hypothesis that cannabis use can increase the risk of developing schizophrenia, their models quantified the theoretical increase in the incidence and prevalence of schizophrenia that may follow a populationwide increase in the use of cannabis. These ''thought experiments'' can help guide policy development and inform future research directions (82).

Future incidence studies may want to look for sites that enable them to ''amplify the signal'' for putative risk factors. For example, if urbanicity is a risk factor for schizophrenia, then it should be readily detected in incidence studies in very

large cities. Recently, an incidence study from Sao Paulo, Brazil (the world's second largest city, 10.3 million), reported a relatively low incidence of schizophrenia (83). A recent within-nation, multisite incidence study (the Aetiology and Ethnicity in Schizophrenia and Other Psychoses; AESOP) (75) identified significant variation in incidence rates between three cities in the United Kingdom (London, Nottingham, and Bristol). This study was also able to explore the influence of migrant status within each of the sites. Even when migrant/ethnic status was accounted for, the incidence of psychosis was significantly higher in London compared with the other two sites. There are no reasons to expect that schizophrenia frequency estimates will obediently map onto geopolitical boundaries. Thus, the contours of schizophrenia epidemiology within nations may be more informative than previously appreciated (82).

In conclusion, the use of consistent and thorough systematic review methodology enabled us to ''populate'' the epidemiologic landscape of schizophrenia. The contours of this landscape can no longer be considered flat and featureless (84). Instead, the epidemiology of schizophrenia (6) is characterized by considerable variability and tantalizing gradients. Schizophrenia epidemiology is much more interesting than previously suspected. There are rich and informative gradients that can guide future research.

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