A Systematic Review of Mortality in Schizophrenia

Is the Differential Mortality Gap Worsening Over Time?

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Context: Despite improvements in mental health services in recent decades, it is unclear whether the risk of mortality in schizophrenia has changed over time.

Objective: To explore the distribution of standardized mortality ratios (SMRs) for people with schizophrenia.

Data Sources: Broad search terms were used in MEDLINE, PsychINFO, Web of Science, and Google Scholar to identify all studies that investigated mortality in schizophrenia, published between January 1, 1980, and January 31, 2006. References were also identified from review articles, reference lists, and communication with authors.

Study Selection: Population-based studies that reported primary data on deaths in people with schizophrenia.

Data Extraction: Operationalized criteria were used to extract key study features and mortality data.

Data Synthesis: We examined the distribution of SMRs and pooled selected estimates using random-effects meta-analysis. We identified 37 articles drawn from 25 different nations. The median SMR for all persons for all-cause mortality was 2.58 (10%-90% quantile, 1.18-5.76), with a corresponding random-effects pooled SMR of 2.50 (95% confidence interval, 2.18-2.43). No sex difference was detected. Suicide was associated with the highest SMR (12.86); however, most of the major causes-of-death categories were found to be elevated in people with schizophrenia. The SMRs for all-cause mortality have increased during recent decades ($P=.03$).

Conclusions: With respect to mortality, a substantial gap exists between the health of people with schizophrenia and the general community. This differential mortality gap has worsened in recent decades. In light of the potential for second-generation antipsychotic medications to further adversely influence mortality rates in the decades to come, optimizing the general health of people with schizophrenia warrants urgent attention.

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IT IS NOW WIDELY ACKNOWL-edged that schizophrenia contributes substantially to the global burden of disease.[1,2] It is also well known that schizophrenia is associated with elevated suicide rates.[3] Less widely appreciated is the fact that people with schizophrenia are at increased risk for premature death associated with comorbid somatic conditions.[4] Apart from adverse effects related to medication, schizophrenia can trigger a cascade of socioeconomic and lifestyle factors that, in turn, can translate into adverse physical health outcomes. These comorbid physical conditions contribute to increased mortality risks among people with schizophrenia.

The association between severe mental illness and increased mortality rates has long been recognized.[5] With respect to the group of disorders now labeled schizophrenia, increased mortality rates have been the object of scrutiny since the early 20th century.[6-8] The quality of research on this topic has improved greatly in recent decades, with access to larger, better-characterized samples and the availability of high-quality mortality data for the general population. Access to these data allows the calculation of the standardized mortality ratio (SMR), which compares mortality in people with schizophrenia vs the general population. The SMRs are calculated by dividing the observed mortality rates in a given population (eg, the number of deaths in a group of individuals with schizophrenia) by the expected mortality rates in that same group as predicted by age- and sex-specific mortality rates for a standard population. Thus, an SMR of 2.0 would indicate that people

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with schizophrenia are twice as likely to die compared with the general population. The SMRs can be calculated for overall mortality (all-cause) or for more specific, widely used categories (eg, cancer, cardiovascular disease, endocrine disorders, or suicide).

In recent years, several scholarly reviews[4,9-11] have noted higher mortality in schizophrenia compared with the general population. A meta-analysis,[4] based on 18 studies published between 1969 and 1996, reported an all-cause SMR for people with schizophrenia of 1.51. Another meta-analysis,[11] based on 20 studies published between 1973 and 1995, reported a similar SMR for people with schizophrenia (1.57). Although these 2 systematic reviews agreed on the size of the pooled SMR associated with schizophrenia, there were discrepancies in the sex difference of overall mortality ratios. Brown[4] found a small but significant male excess in the overall mortality ratio, whereas other studies[12,13] reported either no sex difference[11] or higher mortality ratios in females compared with males.

In collating data from different sites, systematic reviewers need to appreciate the structure of the underlying data. In light of the differing population age structure and disease profile among sites,[1,14] we would expect substantial variation in mortality ratios among sites. For example, one would predict that SMRs for people with schizophrenia would differ between developed and developing nations, where the profiles of disease and the access to services vary markedly.

Because of the increased focus on mental health care seen in many countries during the last few decades, one might predict that SMRs associated with disorders such as schizophrenia should be decreasing over time.[15,16] However, several authors have suggested that SMRs in schizophrenia have been increasing during recent decades. For example, Osby et al[17] found a linear increasing trend of mortality during 5-year periods from 1976 to 1995 among people with schizophrenia. The meta-analysis by Brown[4] also reported significantly higher mortality in the 1980s compared with the 1970s. Deinstitutionalization may have influenced recent secular changes in mortality rates in schizophrenia. Although deinstitutionalization started in the 1950s, findings on its relationship to mortality have been inconsistent.[10,11,18]

The aims of this study were to undertake a systematic review of mortality in schizophrenia and to examine a limited number of planned sensitivity analyses. In keeping with our previous systematic review of the incidence[19] and prevalence[20] of schizophrenia and considering that variability is to be expected in systematic reviews of SMRs,[4,21] we sought to preserve the expected variation in the data rather than to focus only on pooled values derived from meta-analysis. Thus, for the main analyses, we present distributions of mortality estimates with measures of central tendency (eg, median or means) and quantiles (10% and 90% quantiles). On the basis of all-cause SMR, we predicted that the SMRs of males and females would not differ significantly. We also predicted that SMRs from the developed world would differ from those from the developing world (nondirectional hypothesis). We wished to explore the impact of study quality on SMRs. With the assumption that higher-

quality studies would be more likely to identify deaths in schizophrenia, we predicted that SMRs derived from such studies would be higher compared with those from lower-quality studies. On the basis of previous systematic reviews and commentaries, we predicted that SMRs would increase over time.

METHODS

DATA SOURCES

Most mortality studies are based on record linkage. People with schizophrenia are identified via psychiatric case registers and then subsequently linked to registers of cause of death. Some studies[13,22] report mortality ratios based on hospital inpatient cohorts. Other studies[23,24] have used community-based follow-up data for people with schizophrenia who are first identified through community surveys and then followed up for extended periods.

IDENTIFICATION OF STUDIES

Guidelines outlined by the Meta-analysis of Observational Studies in Epidemiology[25] were followed to identify and collate mortality studies. The broad search string of (*schizo* or psych**) and (*mortality or outcome or follow-up*) was used in MEDLINE, PsychINFO, Web of Science, and Google Scholar to identify all research studies that investigated mortality in schizophrenia. Potentially relevant articles (in all languages) were accessed to review the full text. Citations from significant articles and review articles 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-mails were sent to the senior authors of articles that met the inclusion criteria. These authors were provided with an interim list of included studies and asked to nominate missing studies.

INCLUSION AND EXCLUSION RULES

Studies were included if they met all the following criteria: (1) published and/or available between January 1, 1980, and January 31, 2006, (2) reported deaths in people with schizophrenia as diagnosed by any criteria, (3) studied a population 15 years and older, (4) reported primary data on all-cause mortality and/or cause-specific mortality, and (5) reported SMRs and/or data on observed and expected deaths sufficient to calculate SMRs. Studies were excluded if they (1) involved people with a diagnosis other than schizophrenia (ie, studies that reported on broader categories of psychosis were excluded), (2) reported duplicate data, (3) reported SMRs solely attributable to suicide (this was the focus of a recent systematic review and meta-analysis[3]), and (4) reported mortality in subgroups of the population (eg, homeless people,[26] twins,[27] and those involved in clinical trials).

DATA ABSTRACTION

Once a study was included, data were extracted and entered into a 3-level, normalized database that included study-level variables (eg, authors, year of publication, and site), middle-level variables (eg, age group, recruitment duration, case-finding method, and diagnostic criteria), and estimate-level variables (eg, general and specific-cause SMRs for all persons, males, or females). Two or more of the authors checked all data used in the analysis. When disagreements arose, these were re-

solved by consensus. If required, we contacted the original authors for clarification of issues. The full data set is available from the authors (www.qcmhr.uq.edu.au/epi).

To assess the impact of overall quality of the distribution of SMRs, we devised a quality score. On the basis of operationalized criteria, this score rewarded studies that (1) used superior research design features (eg, more thorough case ascertainment, published diagnostic criteria, methods to confirm diagnosis, and longer periods of follow-up) and (2) provided comprehensive reporting of the study results (eg, provision of numerator, denominator, SMRs, details of subject attrition, and description of the completeness of the data source). Full details of the quality score used in this review are available from the authors (www.qcmhr.uq.edu.au/epi).

In systematic reviews, it is important to avoid double counting of the index variable (deaths) by the same or different studies. Thus, a key feature of this review is the application of sequential filters to identify discrete mortality estimates. We applied a similar sorting algorithm to that used in our previous reviews of schizophrenia.[19,20] Briefly, the mortality estimates were sorted into different causes of death. Study-level and middle-level filters were applied to isolate data from multiple studies that overlapped in both time and place. The third filter was used to select 1 representative mortality estimate for inclusion in the cumulative distribution using the "most informative" rule. For example, if 1 study presented multiple overlapping ratios, the ratios based on the largest sample were preferred (ie, the widest age range was preferred over narrower age strata).

The highest-order (and most reliable) category of death, all-cause mortality, can be further subdivided according to rules such as those codified by the *International Classification of Diseases, Ninth Revision (ICD-9)*.[28] Almost all included studies in this review were coded with the *ICD-9*. Although death can result from the combination of many different health problems, in circumstances in which several codes may be suitable, emphasis is given to the underlying cause of death. More specific causes of death can be allocated to categories according to organ systems (eg, cardiovascular or gastrointestinal) or nature of disease (eg, cancers are coded together). Apart from codes for these specific domains, studies occasionally report SMRs for middle-level categories such as all-unnatural (*ICD-9* codes E800-E999) (which includes codes for suicide, accident, and homicide) and all-natural (*ICD-9* codes 001-799; the remainder from all-cause when all-unnatural cause is excluded).

The SMRs were extracted from the publications or calculated by dividing the sum of observed deaths by the sum of expected deaths (when sufficient data were available to calculate these). The distributions of SMRs were assessed in cumulative plots, with every SMR contributing to the distribution. The distribution of the data was assessed in rank order for SMRs (lowest to highest ranks) with the cumulative percentage of SMRs shown on the vertical axis. Key features of these distributions are presented (eg, median, mean, geometric mean, standard deviation, and quantiles at 10%, 25%, 50%, 75%, and 90%).

For all-cause death, we were often able to extract data on case fatality rate (CFR). The CFR is calculated by dividing the number of deaths in people with schizophrenia during a certain period by the number of people with that disorder at the beginning of the period. An annualized CFR was derived to allow comparisons among studies of different durations.[14]

In keeping with definitions from our previous systematic reviews of schizophrenia,[20,29] we divided studies according to the per capita gross national product of the study site (based on 2004 data)[30] and used a standard World Bank definition of country status[31]: (1) least developed countries, mean income of less than US $2995; (2) emerging economy countries, mean income between US $2995 and $9266; and (3) developed countries, mean income of greater than US $9266.

To assess secular trends, we used meta-regression to examine the relationship between the midpoint of the follow-up period and all-cause SMR for persons. Study quality scores were divided into tertiles, and the distribution of all-cause SMR for persons were compared according to these 3 levels.

We performed statistical analyses for the test of significance between distributions of different SMRs. These analyses take into account (1) the need to control for within-study variation (estimates drawn from the same study tend to be more alike than SMRs drawn from different studies) and (2) the use of a log transformation to analyze distributions that are often positively skewed. Analyses were performed with SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

We also undertook a secondary analysis based on conventional meta-analytic techniques. Because SMRs are known to vary widely among sites because of population and disease frequency differences, we adopted a random-effects model to estimate a pooled SMR for all-cause mortality for persons.[21] When necessary, 95% confidence intervals (CIs) were generated according to the formula detailed by Rothman and Greenland.[21] Heterogeneity among the studies was tested using the Cochran heterogeneity statistic.[32] Apart from the specific analyses related to sex differences, we restricted the analyses to persons to limit the number of planned comparisons. The funding source played no part in the design, analyses, writing, or submission of this study.

RESULTS

The electronic search identified 1726 articles, whereas manual reference checking identified an additional 26 references. We received responses from 16 authors, who provided an additional 11 references. Four articles from languages other than English were included after translation. Eleven studies[33-43] were excluded because they completely overlapped with other included studies. Further details of the results of the search strategy and key features of the included studies are available from the authors (www.qcmhr.uq.edu.au/epi).

The systematic review identified 37 studies[9,12,13,18,22-24,44-73] that provided data on 561 SMRs for different causes of deaths drawn from 25 different countries: Australia (n=2),[59,68] Brazil (n=1),[61] Bulgaria (n=1),[53] Canada (n=3),[50,51,65] China (n=1),[53] Columbia (n=1),[53] Czech Republic (n=1),[53] Denmark (n=2),[63,64] Finland (n=3),[18,22,23] France (n=2),[46,48] Germany (n=1),[57] Hong Kong (n=1),[53] India (n=2),[12,53] Indonesia (n=1),[58] Ireland (n=2)[53,62] Israel (n=1),[73] Italy (n=2),[60,67] Japan (n=3),[53,69,71] Norway (n=1),[52] Russia (n=1),[53] Sweden (n=2),[9,66] Taiwan (n=1),[49] the Netherlands (n=1),[13] the United Kingdom (n=5),[44,47,53,54,56] and the United States (n=6).[24,45,53,55,70,72] The SMRs were based on an estimated total of 22 296 discrete deaths. Thirty-seven studies[9,12,13,18,22-24,44-73] provided SMRs for all-cause mortality for either all persons, males, or females.

Figure 1 shows the distribution for all-cause SMRs for all persons, males, and females. The median all-cause SMR for all persons (based on 38 SMRs) was 2.58, with 10% and 90% quantiles ranging from 1.18 to 5.76 (**Table 1**). In other words, people with schizophrenia had 2.5 times the risk of dying compared with the general population, and the central 80% of all SMRs varied over a 4-fold range. The median annualized all-cause CFR for all persons was
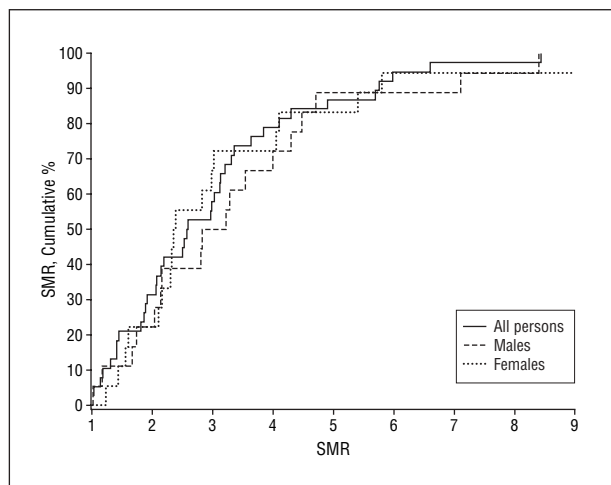
Figure 1. Cumulative plots of standardized mortality ratios (SMRs) for all-cause mortality associated with schizophrenia by sex.

95.4 per 10 000 population, with 10% and 90% quantiles ranging from 57.2 to 301.7 (5-fold range).

The median all-cause SMR for males (3.02) was slightly higher than females (2.37); however, these 2 distributions were not statistically significantly different ($F_{1,18}=0.0003$; $P=.99$). For all persons, the median SMR for natural causes of death was 2.41, and the 10% and 90% quantiles ranged from 0.99 to 4.10 (Table 1). Elevated median SMRs were found in all of the specific causes of death apart from cerebrovascular diseases.

Seven studies[18,47,49,51,56,65,66] published data for the summary category of unnatural causes of death for all persons, males, or females. Table 1 gives the distributions of SMRs for unnatural causes of death. People with schizophrenia had 12 times the risk of dying of suicide compared with the general population (median SMR, 12.86).

Twenty-two studies* were identified that contributed 28 SMRs for developed countries, 3 studies[53,58,61] contributed 6 SMRs for emerging economy countries, and 1 study[53] contributed 4 SMRs for least developed countries. When divided according to this criterion, the all-cause SMR distributions were not significantly different ($F_{2,34}=0.30$; $P=.74$); the median all-cause SMRs for least developed, emerging economy, and developed countries were 2.02, 2.19, and 2.79, respectively (**Table 2**).

When the all-cause SMRs for all persons were divided into study quality score tertiles, no significant differences were found between SMR distributions ($F_{2,24}=0.61$; $P=.55$). On the basis of follow-up periods, we identified 8 studies[24,45,51,54,55,63,71,72] with SMRs from the 1970s, 10 studies[47,53,57-60,65-67,73] with SMRs from the 1980s, and 7 studies[22,46,48,53,61,62,68] with SMRs from the 1990s. Concerning secular change, meta-regression confirmed a significant positive association between the follow-up period midpoint year and all-cause SMR (slope coefficient, 0.06; 95% CI, 0.01-0.11; $z=2.21$; $P=.03$). The median SMRs for the 1970s, 1980s, and 1990s were 1.84, 2.98, and 3.20, respectively. Concerning CFRs, the median rates per 10 000 population (all-cause mortality) were 162.2,

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*References 22, 24, 45-48, 51, 53-55, 57, 59, 60, 62, 63, 65-68, 71-73.

95.4, and 108.3 for the 1970s, 1980s, and 1990s, respectively. The CFRs for the 3 decades were not statistically significantly different ($F_{2,23}=0.38$; $P=.38$).

The 38 studies that report all-cause SMRs for all persons are shown in a traditional forest plot with a pooled estimate based on a random-effects model in **Figure 2**. Using traditional meta-analytic techniques, we found that the pooled random-effects all-cause SMR (based on 37 SMRs with finite standard errors) for all persons was 2.50 (95% CI, 2.18-2.83). The Cochran Q test found a marginally acceptable level of heterogeneity ($Q_{36}=50.72$; $P=.06$). We undertook several post hoc analyses to explore potential sources of variation (eg, published vs unpublished diagnostic criteria, cohorts based on first-episode patients vs all patients, cohorts based on inpatient and/or outpatient samples, sites clustered according to World Health Organization regions, and SMRs attributable to suicide sorted by decade). However, none of the post hoc comparisons resulted in significantly different SMR distributions (data not shown).

COMMENT

People with schizophrenia have a substantially increased risk of death compared with the general population. Overall, people with schizophrenia have 2.5 times the risk of dying. This review was able to extract data from 37 studies that were conducted in 25 countries. As predicted, the distribution of all-cause SMRs showed prominent variability.

Confirming the hypothesis that the relative mortality risk associated with schizophrenia is increasing, we found that SMRs have increased in a linear fashion during the 3 decades examined in this study. This finding is consistent with earlier studies.[4,17] Considering that (1) CFRs for schizophrenia did not significantly differ among the decades and (2) age-standardized mortality rates are generally decreasing in most nations,[74-76] these findings suggest that people with schizophrenia have not fully benefited from the improvements in health outcomes available to the general population. The SMRs are ratio measures and thus reflect differential mortality. If mortality rates in the general population decrease over time at a faster rate than those for people with schizophrenia, then SMRs for people with schizophrenia will increase over time. The evidence from the current study suggests that this differential mortality gap has widened over time.

Mental health services have advanced in many parts of the world during the past few decades. Apart from a different mix of community-based care, the introduction of the second-generation antipsychotic medications in the early 1990s was initially found to be associated with better quality of life and reduced risk of relapse.[77-79] More recent trials have questioned the clinical superiority of second-generation antipsychotic medication,[80,81] and concern is now widespread about the adverse effects associated with these medications.[82] In particular, compared with typical antipsychotics, several of the second-generation antipsychotics are more likely to cause weight gain and metabolic syndrome.[83] Because the metabolic syndrome is associated with a 2-

Table 1. SMRs for Schizophrenia by Cause of Death for All Persons

Causes of Death	No. of SMRs	Quantile					Mean (SD)	Geometric Mean
		10%	25%	Median	75%	90%		
All-Cause and Middle-Level Categories								
All-cause (*ICD-9* codes 001-799/E800-E999)	38	1.18	1.87	2.58	3.64	5.76	2.98 (1.75)	2.68
All-natural cause (*ICD-9* codes 001-799)	6	0.99	1.04	2.41	2.90	4.10	2.31 (1.18)	2.03
All-unnatural cause (*ICD-9* codes E800-E999)	3	5.56	5.56	7.50	12.73	12.73	8.60 (3.71)	8.10
Natural Causes, Cause Specific								
Cardiovascular diseases (*ICD-9* codes 390-429)	7	1.11	1.40	1.79	2.49	3.60	2.01 (0.83)	1.88
Cerebrovascular diseases (*ICD-9* codes 430-438)	3	0.61	0.61	0.69	1.30	1.30	0.87 (0.38)	0.82
Digestive diseases (*ICD-9* codes 520-579)	5	1.79	2.24	2.38	2.50	17.50	5.28 (6.84)	3.34
Endocrine diseases (*ICD-9* codes 250-259)	3	2.20	2.20	2.63	11.66	11.66	5.50 (5.34)	4.07
Infectious diseases (*ICD-9* codes 001-139)	3	1.60	1.60	4.29	7.80	7.80	4.56 (3.11)	3.77
Genitourinary diseases (*ICD-9* codes 580-629)	3	1.54	1.54	3.70	4.29	4.29	3.18 (1.45)	2.90
Neoplastic diseases (*ICD-9* codes 140-239)	7	0.71	1.00	1.37	2.01	2.40	1.44 (0.60)	1.33
Nervous diseases (*ICD-9* codes 345-349)	4	1.60	1.95	4.22	6.57	7.00	4.26 (2.70)	3.55
Respiratory diseases (*ICD-9* codes 460-519)	6	2.20	2.39	3.19	3.80	9.30	4.01 (2.66)	3.51
Other diseases (*ICD-9* codes 1-389/630-799)	3	1.45	1.45	2.00	3.40	3.40	2.28 (1.01)	2.14
Unnatural Causes, Cause Specific								
Accident (*ICD-9* codes E800-E949)	6	1.20	1.63	1.73	5.10	8.40	3.30 (2.88)	2.51
Suicide (*ICD-9* codes E950-E959)	10	0.66	5.90	12.86	21.43	174.25	43.47 (95.11)	16.13

Abbreviations: ICD-9, *International Classification of Diseases, Ninth Revision (ICD-9)*; SMRs, standardized mortality ratios.

Table 2. SMRs for Schizophrenia of All-Cause Mortality by Economic Development Status for All Persons[a]

Economic Development Status	No. of SMRs	Quantile					Mean (SD)	Geometric Mean
		10%	25%	Median	75%	90%		
Least developed countries	4	1.88	1.89	2.02	2.75	3.36	2.32 (0.70)	2.25
Emerging economy countries	6	1.04	1.31	2.19	5.98	8.43	3.52 (3.03)	2.57
Developed countries	28	1.18	1.97	2.79	3.74	5.69	2.96 (1.52)	2.77

Abbreviation: SMRs, standardized mortality ratios.
[a] $F_{2,34} = 0.30$; $P = .74$.

to 3-fold increase in cardiovascular mortality and a 2-fold increase in all-cause mortality,[84] these adverse effects would be expected to contribute to even higher SMRs in the next few decades.[85,86] Unfortunately, we are unable to explore the role of atypical medications as a contributing factor for the increasing SMRs associated with schizophrenia (eg, deaths related to clozapine-induced agranulocytosis or deaths related to atypical antipsychotic-induced weight gain). Adverse health outcomes associated with weight gain and/or metabolic syndrome (eg, myocardial infarction, cerebrovascular accidents, or cancer) may take decades to fully emerge. Thus, it seems likely that studies undertaken in the 1990s (ie, the most recent studies included in this review) would capture only a small fraction of the eventual burden of mortality associated with the adverse effect profile of the second-generation antipsychotic medications. In light of the rising secular trends in SMRs already identified by this review, the prospect of further increases in mortality risks for schizophrenia is alarming.

In keeping with the findings of Harris and Barraclough[11] and Simpson,[10] we found no significant sex difference in all-cause SMRs. Thus, although many well-documented sex differences exist in the epidemiological features of schizophrenia,[19,87,88] the increased risk of mortality associated with schizophrenia affects men and women equally.

Of the specific-cause SMRs, suicide was associated with the highest estimate: 12 times greater than expected from the general population. In keeping with previous reviews, the SMRs associated with many different types of natural causes of death were elevated in people with schizophrenia. Curiously, the category neoplastic disorder had one of the lowest median SMRs (1.37). Although the median was still greater than 1, several record linkage studies[89] have suggested that cancers may be significantly less prevalent in people with schizophrenia. The current review examines only mortality, and studies that examine morbidity would be better able to explore this issue.[90]

We found no significant difference in SMRs among sites when sorted by economic status. However, this meta-analysis identified just 3 studies[53,58,61] that provided discrete SMRs from the least developed and emerging economy countries; thus, caution should be exercised in the interpretation of this finding. Furthermore, a single derived variable was used to define economic status, which was applied at the ecological level.

What factors have contributed to the differential mortality risk associated with schizophrenia? Many demo-
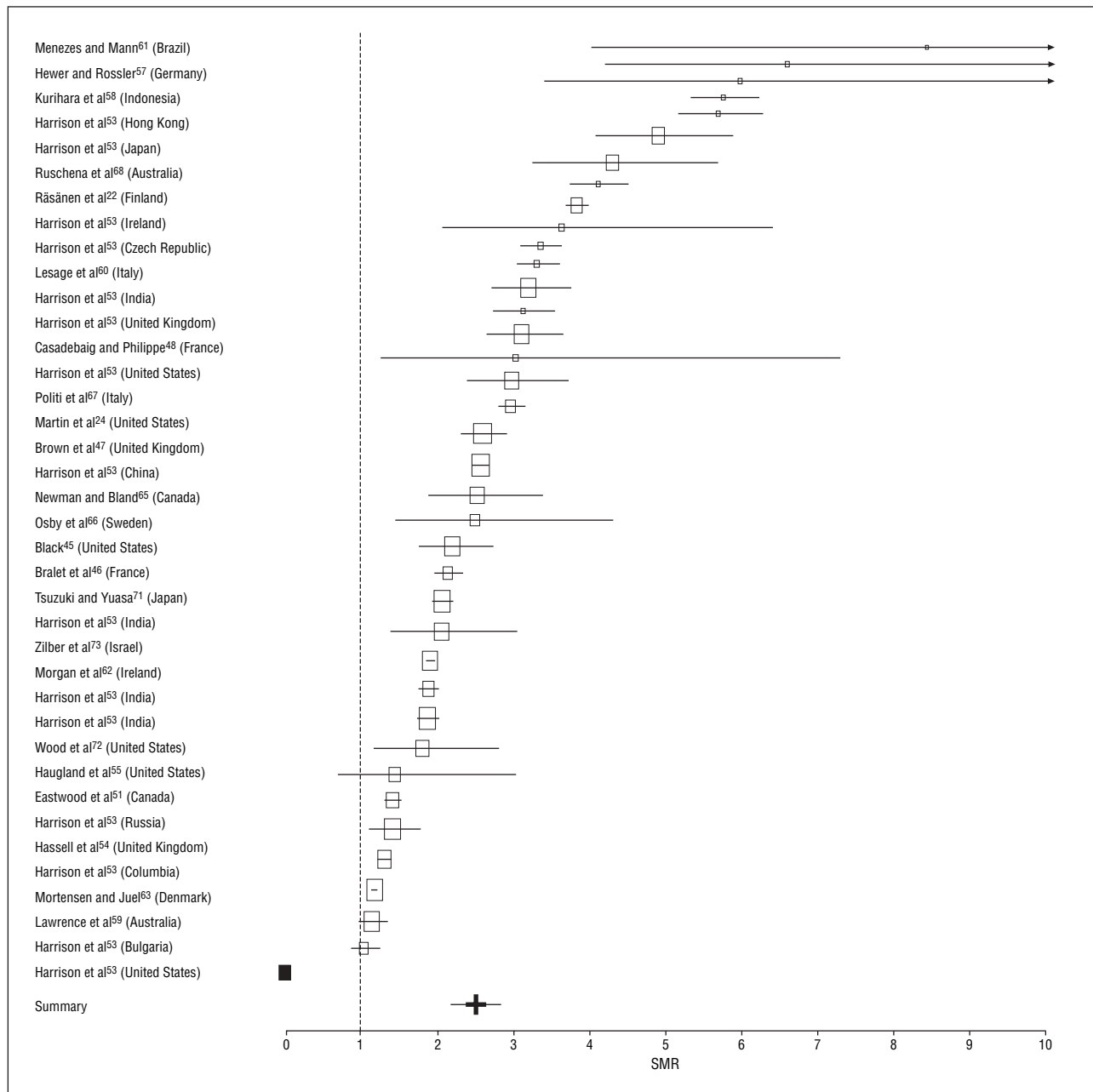
Figure 2. Forest plot of standardized mortality ratios (SMRs) for all-cause mortality in people with schizophrenia. Individual SMRs and the pooled estimate are shown with 95% confidence intervals (error bars). For each of the individual studies, the central open box symbol indicates the relative weighting on the pooled estimate (larger symbols indicate greater influence on the summary estimate). Standard errors cannot be calculated when the SMR is 0; thus, these values do not contribute to the pooled value. The upper 95% confidence limits for 3 studies extend beyond 10 (indicated with right arrow symbol). See also Supplementary Table S3 at www.qcmhr.uq.edu.au/epi.

graphic, clinical, political, and cultural factors mediate pathways and barriers to health care in general (eg, availability of services, stigma, and disease profiles).[91] With respect to schizophrenia, the onset of the illness can result in a cascade of unhealthy lifestyle factors that elevate the risk of various somatic diseases and consequently increase the risk of death. People with schizophrenia are thought to be less inclined to seek health care, to consume less medical care, to engage in high-risk behaviors, and to be less compliant with their treatments.[82,90,92] However, in addition to factors that operate on the pathway to care, schizophrenia and its associated comorbid somatic conditions may be downstream expressions of common genetic or environmental factors.[92,93] For example, it is feasible that polymorphisms in genes may increase the susceptibility to both schizophrenia and diabetes[94] or that de novo germline mutations across many generations could result in an increased risk of schizophrenia[95] and a wide range of adverse health outcomes. Prenatal nutritional disruptions may equally affect brain development and general metabolic functioning.[96,97] Although the current review cannot address these issues directly, the worsening SMRs associated with schizophrenia noted in recent decades

suggest that this already disadvantaged group is not benefiting from the improved health of the community in an equitable fashion. A systematic approach to monitoring and treating the physical health needs of people with schizophrenia is clearly warranted.[98]

Several important caveats to this review should be noted. Publication bias is always an issue in systematic reviews. We endeavored to address this by obtaining data from all available sources, including those from electronic databases, citations and authors, and publications in languages other than English. Factors such as the reliability of psychiatric diagnoses and admission practices (between sites and across time) could contribute to the variability identified in this systematic review. The reliability of the categorization of cause of death is also a cause for concern. With respect to specific-cause mortality, changes in the coding rules for the *ICD-9* and between-site variability in the application of these rules also need to be taken into account.[99,100] However, these issues do not affect all-cause SMRs (which were used for the main analyses in this review). The current study found a higher all-cause SMR (median SMR, 2.58; pooled meta-analysis SMR, 2.50) compared with the 2 previous reviews, which reported all-cause SMRs of 1.51[4] and 1.57.[11] The 2 previous systematic reviews were based on studies published before 1995[11] and 1996[4] compared with the current systematic review, which included 18 additional studies published after 1995.

In conclusion, compared with the general population, people with schizophrenia have a 2- to 3-fold increased risk of dying. Suicide contributes to the increased mortality associated with schizophrenia; however, people with schizophrenia have increased mortality risks attributable to a wide range of somatic conditions. The increased mortality risk affects both sexes equally. Substantial variation occurs in all-cause SMRs among sites. In recent decades, the differential mortality gap associated with schizophrenia has been increasing. It is sobering to reflect on this paradox of schizophrenia treatment. As we become better at detecting and treating the core symptoms of schizophrenia, patients have worsening SMRs. Given the potential for an even greater disease burden as a result of the introduction of second-generation antipsychotic medications, research aimed at optimizing the physical health of people with schizophrenia needs to be undertaken with a sense of urgency.

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