Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis

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Summary

Background Several studies and meta-analyses have shown that mortality in people with schizophrenia is higher than that in the general population but have used relative measures, such as standardised mortality ratios. We did a systematic review and meta-analysis to estimate years of potential life lost and life expectancy in schizophrenia, which are more direct, absolute measures of increased mortality.

Methods We searched MEDLINE, PsycINFO, Embase, Cinahl, and Web of Science for published studies on years of potential life lost and life expectancy in schizophrenia. Data from individual studies were combined in meta-analyses as weighted averages. We did subgroup analyses for sex, geographical region, timing of publication, and risk of bias (estimated with the Newcastle-Ottawa Scale).

Findings We identified 11 studies in 13 publications covering all inhabited continents except South America (Africa n=1, Asia n=1, Australia n=1, Europe n=7, and North America n=3) that involved up to 247 603 patients. Schizophrenia was associated with a weighted average of 14·5 years of potential life lost (95% CI 11·2–17·8), and was higher for men than women (15·9, 13·8–18·0 vs 13·6, 11·4–15·8). Loss was least in the Asian study and greatest in Africa. The overall weighted average life expectancy was 64·7 years (95% CI 61·1–71·3), and was lower for men than women (59·9 years, 95% CI 55·5–64·3 vs 67·6 years, 63·1–72·1). Life expectancy was lowest in Asia and Africa. Timing of publication and risk of bias had little effect on results.

Interpretation The effects of schizophrenia on years potential life lost and life expectancy seem to be substantial and not to have lessened over time. Development of implementation and interventions to reduce this mortality gap are urgently needed.

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Introduction

Several systematic reviews and meta-analyses have been done to investigate mortality in schizophrenia, occasionally based on more than 100 studies.1–3 These analyses have typically focused on establishing the pooled standardised mortality ratio, which measures mortality relative to that in the background population. Other approaches have been to focus on predictors of increased mortality within populations with schizophrenia,4,5 or on relative risks of or risk factors for cause-specific mortality (eg, suicide and cardiovascular mortality6–8). Relative measures of mortality are useful, but can be difficult to interpret. Small variations in rates of rare outcomes result in high relative risks because estimates are dependent on the baseline risks. Furthermore, mortality is difficult to understand without knowing the length of follow-up. At the population level, life expectancy is often used as a measure of mortality and health status. Life expectancy at birth for a given year is defined as the mean length of time a person born in that year would live if he or she were exposed to the age-specific mortality for that year. Life expectancy may also be calculated at any given age, and is defined as the mean remaining number of years a person would expect to live given that he or she has already survived to that age. Thus, life expectancy can be calculated for a population before anyone has died, whereas average age of death may be derived only from observed deaths. Use of life expectancy allows comparisons of subpopulations. For instance, the magnitude of difference between life expectancy of people with schizophrenia and the background population would be termed years of potential life lost due to schizophrenia.

We are unaware of any studies that have systematically reviewed the literature specifically for life expectancy or years of potential life lost in patients with schizophrenia. Similarly, whether or how these factors vary over time or geographical location have not been established. We did a systematic review and meta-analysis in which we aimed to identify studies and synthesize their findings on life expectancy and years of potential life lost in people with schizophrenia. If applicable, we aimed to stratify the findings by sex, geographical location, comorbid disorders, other risk factors, timing of publication, and risk of bias in included studies.

Methods

Search strategy

Before we started literature searches, we registered the protocol for this systematic review at PROSPERO, number CRD42016043673. On July 29, 2016, we searched MEDLINE (through PubMed), PsycINFO, Embase, Cinahl, and Web of Science, without restrictions on year
Articles

Research in context

Evidence before this study
On July 29, 2016, we searched PubMed, PsycINFO, Embase, Cinahl, and Web of Science for reviews and meta-analyses of mortality in patients with schizophrenia. We placed no restrictions on year, country, or language of publication. We identified 11 relevant studies and meta-analyses (including some that assessed >100 studies). All papers reported standardised mortality ratios, predictors of mortality in schizophrenia, or predictors of cause-specific mortality. No papers summarised results with absolute measures of mortality, such as years of potential life lost or life expectancy.

Added value of this study
We quantified years of potential life lost to schizophrenia and life expectancy in people with schizophrenia. Although there was some variation between samples, we estimate that people with schizophrenia lose 13–15 years of potential life, and that life expectancy is about 60 years for men and 68 years for women. These values seemed not to have improved over time.

Implications of all the available evidence
The excess mortality in schizophrenia highlights the importance of developing and implementing interventions to reduce the number of years of potential life lost.

do of publication, geographical location, or language of publication. In PubMed, we used the search term (“Schizophrenia”[Mesh] OR “Mental Disorders”[Majr]) AND (“Mortality”[Mesh] OR “Life Expectancy”[Mesh] OR “Survival rate”[Mesh] OR “Mortality, Premature”[Mesh]). In Embase, we used the search term (exp schizophrenia/ OR *mental disease/) AND (exp mortality/ OR exp life expectancy/ OR exp survival rate/ OR exp premature mortality/). In PsycINFO, we used the search term (exp schizophrenia/ OR *Mental Disorders) AND (exp ‘Death and Dying’/ OR exp life expectancy/ OR exp Mortality Rate/). In Cinahl, we used the search term ((MH “Schizophrenia+”) OR (MM “Mental Disorders”)) AND ((MH “Mortality+”) OR (MM “Life Expectancy”) OR (MM “Survival”)). In Web of Science, we used the search term (TOPIC: (schizophrenia) OR Title: (“mental dis*”)) AND (TOPIC: (“MORTALITY”) OR TOPIC: (“LIFE EXPECTANCY”) OR TOPIC: (“SURVIVAL RATE”) OR TOPIC: (“PREMATURE MORTALITY”)).

Inclusion criteria
We included studies that reported data on years of potential life lost or life expectancy in patients diagnosed as having schizophrenia according to ICD (any version), DSM (any version), or the Research Diagnostic Criteria. If schizophrenia was reported as part of a larger group of disorders (eg, psychotic or mental disorders), we contacted the authors to obtain schizophrenia-specific estimates. We included only original data. We did not apply any language restrictions or other exclusion criteria to the studies.

Study selection
One author (CH) initially screened the titles of retrieved papers to exclude those that were obviously irrelevant. Two authors (CH and AES) screened the abstracts and full texts of the remaining papers to determine which should be included. Discrepancies were registered and discussed by these two authors to try to reach a decision. If no consensus could be reached, the two remaining authors (JJM and MN) could act as arbiters.

Data extraction
The following data were extracted from the included studies: diagnostic system, total number, age, and sex of patients, study country or region, study period, source of data, and years of potential life lost and life expectancy (overall and within subgroups). We contacted authors to request data if background variables, years of potential life lost, or life expectancy were missing from the publication. Risk of bias was established with the Newcastle-Ottawa Scale.11

Synthesis of data
Distributions of life expectancy and years of potential life lost are presented graphically. Most studies did not report measures of uncertainty (eg, SEs or CIs) around their estimates of life expectancy or years of potential life lost. We could not, therefore, use the usual variance-based approaches to calculate study weights. Instead, we calculated averaged values weighted by size of the individual study populations. From the studies without SEs or CIs, we extrapolated the pooled SE from a fixed effects meta-analysis, which we used to generate CIs around the estimated weighted averages. For studies that reported CIs, we converted these to SEs before inclusion in the fixed effects meta-analysis. Weighted averages were estimated and forest plots were drawn with Stata version 13.1. The random-effects models used to estimate CIs were generated with Comprehensive Meta-Analysis version 3.3.070. We did subanalyses for sex, geographical region, timing of publication, and low versus high risk of bias. In the main synthesis of data on life expectancy, we pooled estimates regardless of the age at which they were calculated. In studies that reported remaining life expectancy at a given age, we added this age to the estimate to obtain an expected age at death.

Results
We identified 11830 unique entries in bibliographical databases, from which 762 entries remained after removal of obviously irrelevant papers (figure 1). All but...
The studies involved 302,691 patients with schizophrenia, the diagnosis of which was based on ICD criteria in all studies. Some geographical areas were represented by more than one study, which could have meant that patients were included more than once in our dataset. If we allowed only one study per geographical area, the studies included involved 179,260 patients with schizophrenia when the smaller studies were used and 247,603, when the larger studies were used. All inhabited continents were represented except for South America. All European studies were from either the Nordic countries\(^2\) or the UK.\(^1\) One Asian study was identified, from Taiwan.\(^2\) From North America, we found one study from the USA\(^2\) and two from different regions of Canada.\(^1,2\) One study was from Australia\(^6\) and one from Africa in a small Ethiopian cohort.\(^7\) The lowest risk of study bias was attributed to five studies.\(^1,2,11,13,18\) Four studies received one rating for risk of bias\(^1,2,20,21\) and two received two ratings for risk of bias (table). Estimates of years of potential life lost were presented at various ages in some studies and, therefore, for the main analyses we chose the younger age groups. For studies that had potentially overlapping populations,\(^2,11,13,18,19,22\) we used the lower estimates for years of potential life lost in the main analysis as a conservative approach. The overall weighted average for years of potential life lost to schizophrenia was 14.5 (95% CI 11.2–17.8; figure 2). Our conservative estimates for men and women were similar to the overall value (figure 2). The higher estimates from the overlapping samples increased the estimates by 3–5 years (data not shown). When findings were stratified by geographical region, years of potential life lost in Australia, Europe, and North America were similar to the overall value, whereas fewer years were lost in the Asian study and more years were lost in the African study (figure 2). The highest quality studies showed nearly the same results as the overall analysis, but roughly 2 more years of potential life were lost in the studies with bias ratings (data not shown). One study was published earlier than the others (1991 vs 2000 or later),\(^2\) and reported 15.8 (95% CI 13.7–17.9) years of potential life lost for men and 13.00 (10.8–15.2) for women, which were similar to the pooled values for these subgroups (figure 2). Results did not differ substantially if years of potential life lost were estimated at birth, around the usual age of diagnosis of schizophrenia, or at other ages (data not shown).

Including each country or region only once, and using the highest available life expectancies, the overall weighted average life expectancy for people with schizophrenia was 64.7 years (95% CI 61.1–71.3, figure 3). For men, life expectancy was nearly 8 years shorter than for women. When assessed by geographical region, values did not differ substantially from the overall value for Australia, Europe, or North America, whereas that for Asia was somewhat lower and for Africa was substantially lower (figure 3). Studies with increased risk of bias yielded similar life expectancies to those with low risk of bias (61.5 years, 95% CI 57.9–65.1 vs 63.4, 59.8–67.0). In the study published in 1991, the estimated life expectancy at birth was 56.2 years for men and 66.1 years for women, both of which were only marginally lower than the estimates in the full sample. This study did not report CIs or SEs for these estimates. When the higher estimates from overlapping samples were used, weighted averages of life expectancy were reduced by 3–4 years (data not shown). Conversely, the four studies that allowed for calculation of life expectancy at birth\(^2,10,20,24\) yielded weighted averages that were around 3–4 years higher (data not shown). Finally, using only studies that estimated years of potential life lost around the expected age of onset of schizophrenia (defined as 15–30 years),\(^2,10,20,24\) we estimated that the average weighted life expectancy was 62.6 years (95% CI 59.0–66.2) overall, 59.3 (54.9–63.7) for men, and 66.8 (62.4–71.3) for women.

### Figure 1: Study selection for meta-analysis

![Study selection for meta-analysis](https://example.com/fig1.png)
Discussion

In most analyses, schizophrenia was associated with 13–15 years of potential life lost. Also, in most analyses, more years of potential life were lost for men with schizophrenia than for women with schizophrenia. Our findings are consistent with the robust literature that has focused on causes of premature death in schizophrenia. For example, several studies have shown more somatic disorders, such as cardiovascular disease\(^{13,19}\) and diabetes\(^{20,21}\) among people with schizophrenia than in the background population. This difference could have several explanations. Second-generation antipsychotics have well established metabolic side-effects.\(^{22,23}\) Furthermore, several studies have indicated increased frequency of tobacco smoking,\(^{31,32}\) alcohol misuse and use of illicit substances,\(^{33,34}\) sedentary behaviour,\(^{35}\) and poor dietary habits\(^{36}\) among individuals with schizophrenia compared with the general population. Additionally, health-seeking behaviour\(^ {27}\) is reduced among people with schizophrenia compared with the general population. This difference could have several explanations. Second-generation antipsychotics have well established metabolic side-effects.\(^{22,23}\) Furthermore, several studies have indicated increased frequency of tobacco smoking,\(^{31,32}\) alcohol misuse and use of illicit substances,\(^{33,34}\) sedentary behaviour,\(^{35}\) and poor dietary habits\(^{36}\) among individuals with schizophrenia compared with the general population. Additionally, health-seeking behaviour\(^ {27}\) is reduced among people with schizophrenia compared with the general population. This difference could have several explanations. Second-generation antipsychotics have well established metabolic side-effects.\(^{22,23}\) Furthermore, several studies have indicated increased frequency of tobacco smoking,\(^{31,32}\) alcohol misuse and use of illicit substances,\(^{33,34}\) sedentary behaviour,\(^{35}\) and poor dietary habits\(^{36}\) among individuals with schizophrenia compared with the general population. Additionally, health-seeking behaviour\(^ {27}\) is reduced among
people with schizophrenia. A shared genetic disposition for metabolic syndrome or cardiovascular disease and schizophrenia has also been suggested. Finally, the risk of suicide is increased by as much as 22 times among people with schizophrenia compared with in the general population, especially within 1 year of the first hospital admission. Consequently, a reduction in suicide risk and improved quality of care could have notable effects on years of potential life lost to schizophrenia.

We found some indication of regional differences, although some regions were represented by only one study each. The study from Asia suggested notably fewer years of potential life lost to schizophrenia than in Australia and North America. In Europe, years of potential life lost ranged from the high end of the estimates in Australia and North America to much higher in one analysis (20.3 years). The African study showed a strikingly high estimate at 27.7 years of potential life lost. Given low numbers of countries represented, however, reasons for differences are difficult to assess, although access to health care and lifestyle factors might contribute, and the variations might just be random fluctuations.

Risk of study bias and timing of publication did not seem to affect estimated years of potential life lost. The latter is perhaps surprising because studies estimating standardised mortality ratios or similar for schizophrenia have documented increases in these estimates over time.

Most studies reported either life expectancy at birth or at a given age, in which case we added the age in question to the estimate for synthesis. Generally, life expectancy was around 60 years, and possibly lower, for men and around 68 years for women. Life expectancy estimated around the typical ages of onset of schizophrenia was approximately 5 years lower than that calculated in the overall synthesis. Estimating life expectancy at birth for a population with schizophrenia is potentially biased. Since the whole population is eventually diagnosed as having schizophrenia, all people are essentially rendered immortal until the time of diagnosis. Consequently, life expectancy based on age of onset might be shorter (and years of potential life lost greater) than for estimates made at birth.

Life expectancy seemed to differ by region. The lowest life expectancy (46-3 years) was seen in the African study, whereas life expectancy was highest in North America and Australia. This distribution is similar to that for life expectancy in the general population and, therefore, might not be related to schizophrenia. Risk of study bias had no effect on life expectancy. Although life expectancy was lowest in the earliest published paper, this finding probably reflects the general trend of increasing life expectancy over time and might not be related to schizophrenia.

Publication bias in the traditional sense—ie, analyses of data that were not published because they did not confirm the hypotheses of the authors—is probably unlikely, at least by reasons of competing interests, such as funding. Of note, for all relevant conference abstracts we identified, full papers were available in peer-reviewed journals. However, an important issue is whether there are, for instance, geographical regions from which no relevant data have been published. We found no studies from South America, and only one study from each of Asia, Africa, and Australia. As such, while perhaps not related to publication bias, the validity of our meta-analysis results outside the regions of Europe and North America, and possibly Australia, is unclear.

Taiwan, where the population is 23.5 million, represents only around 0.5% of the 4.4 billion people living in Asia. Finally, similar reductions in life expectancy might be seen in populations with other psychiatric disorders, as previous studies have indicated that increased mortality is associated with all types of severe mental illness.

This meta-analysis had some important limitations. First, it was based on only 11 studies, whereas some reviews and meta-analyses of standardised mortality ratios and similar parameters have included more than 100 studies. Evidently, therefore, many studies on mortality in schizophrenia do not report life expectancy
we could not assess whether life expectancy or years of potential life lost differed between patients seeking and those not seeking treatment. However, given that lifetime rates of undiagnosed schizophrenia are probably very low, this issue might not be a major concern. Finally, most of the studies we included reported cause-specific relative measures of mortality, but none assessed years of potential life lost by causes of death.

Many meta-analyses report $P$ statistics for heterogeneity. However, most of the studies we included did not report variance or related measures of uncertainty. Thus, although we found substantial heterogeneity for years of potential life lost and life expectancy (figures 2, 3), this could not be formally quantified. Heterogeneity might arise for a variety of reasons. One potentially important reason is differences in the mean age at first diagnosis of schizophrenia between countries or regions. Except for the study from Africa, though, the pooled results for years of potential life lost and life expectancy were similar in all geographical regions, which suggests that this factor was probably not an important bias in this meta-analysis.

Finally, life expectancy and years of potential life lost provide general indices of the force of mortality in specific groups, and are particularly affected by deaths in young people. From a service planning perspective, however, premature deaths in both the elderly and the young warrant attention. Thus, we did not weight or discount our estimates for age.45

In the studies we assessed, schizophrenia was associated with at least 13–15 years of potential life lost, with men losing more years to schizophrenia than women. We found no indication that this loss had lessened over time, which highlights the importance of developing and implementing interventions and initiatives to reduce the excess mortality.

Contributors
All authors developed the protocol, designed the search strategy, and defined the inclusion criteria. CH and AES did the literature search and screened papers for inclusion. CH extracted data and did the meta-analyses in close collaboration with AES. CH assessed the risk of study bias and prepared the first draft of the manuscript. AES, JJM, and MN made critical and substantial revisions, based on which, CH did further analyses. All authors approved the final version of the manuscript.

Declaration of interests
We declare that we have no competing interests.

References

Figure 3: Meta-analysis of life-expectancy converted to expected age of death in schizophrenia
For overlapping samples, the lowest values were included to provide a conservative estimate. Data are weighted averages and 95% CIs (CIs are only shown if reported in original article).