

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 and implementation of interventions and initiatives to reduce this mortality gap are urgently needed.

Funding None.

Introduction

Several systematic reviews and meta-analyses have been done to investigate mortality in schizophrenia, occasionally based on more than 100 studies.^{1–5} 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,^{6,7} or on relative risks of or risk factors for cause-specific mortality (eg, suicide and cardiovascular mortality^{8–10}).

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 synthesise 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

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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.

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

seven (1%) were selected for inclusion by one author (CH or AES), and all disagreements were resolved through discussion by these two authors. Reading of full-text papers detected 13 publications that met the inclusion criteria.^{12–24} Two of these publications were conference abstracts^{12,20} for which full-text publications were also available;^{13,21} therefore, 11 relevant studies were represented, nine (82%) presenting information on years of potential life lost and six (55%) on life expectancy (figure 1, table). One paper did not present data on patients with schizophrenia separately, but this information was available from the study authors.²²

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^{12–15,18} or the UK.^{20,21} One Asian study was identified, from Taiwan.²³ From North America, we found one study from the USA¹⁶ and two from different regions of Canada.^{22,24} One study was from Australia¹⁹ and one from Africa in a small Ethiopian cohort.¹⁷ The lowest risk of study bias was attributed to five studies.^{12,13,15,18,19,22} Four studies received one rating for risk of bias^{14,20–23} 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,^{12–15,18} 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),²⁴ 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

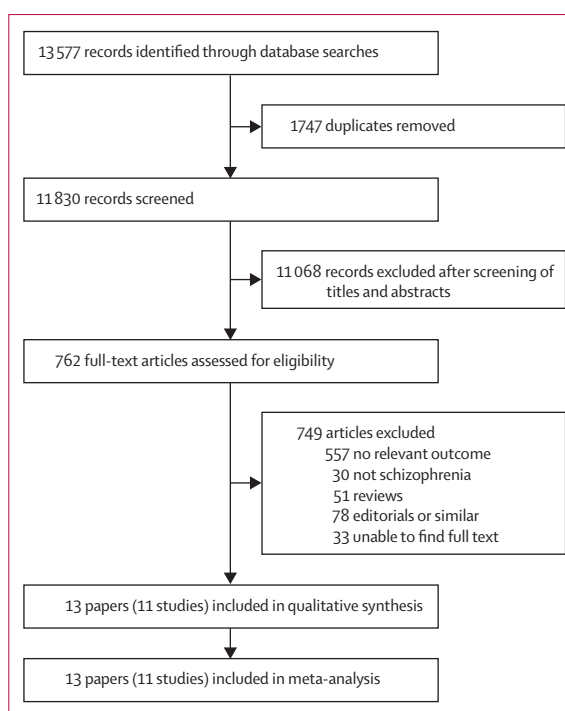


Figure 1: Study selection for meta-analysis

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^{17,19–21,24} 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),^{12–15,18,23} 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.

	Study size weighting in meta-analysis (%)	Study details*	Results for schizophrenia vs general population	Risk of bias†
Chang et al, 2011 ^{20,21}	Years of potential life lost 3.7%, life expectancy 5.3%	UK, London secondary mental health care case register, 2007–09 (n=7018)	Years of potential life lost: men 14.6, women 9.8; life expectancy at birth: men 62.8 years (95% CI 61.6–64.1) vs 77.4 years, women 71.9 (71.0–72.8) vs 81.6 years	Selection ◊◊◊◊; comparability ◊◊; outcome ◊◊ (follow-up was too short)
Fekadu et al, 2015 ¹⁷	Years of potential life lost 0.2%, life expectancy 0.3%	Ethiopia, cohort established 1998–2001 and followed up until 2012 (n=359)	Years of potential life lost 27.7; life expectancy at birth 46.27 years (95% CI 41.92–50.62)	Selection ◊◊◊ (selected group of schizophrenia); comparability ◊◊; outcome ◊◊ (no statement to determine follow-up of cohorts)
Hannerz et al, 2001 ¹⁸	Years of potential life lost 7.3%, life expectancy 10.4%	Sweden, all hospitals 1978–82 (n=13 823)	Remaining life expectancy at age 30 years‡: men 37.1 years vs 45.0 years, women 41.2 years vs 50.7 years	Selection ◊◊◊◊; comparability ◊◊; outcome ◊◊◊
Laursen et al, 2011 ¹⁵	Years of potential life lost 16.6%, life expectancy 23.8%	Denmark, population-based, 2000–06 (n=31 727)	Years of potential life lost: men 18.7, women 16.3; expected age at death, given alive at age 15 years: men 57.8 years (95% CI 57.5–58.1), women 64.6 years (64.1–64.7)	Selection ◊◊◊◊; comparability ◊◊; outcome ◊◊◊
Laursen et al, 2013 ^{12,13§}	Years of potential life lost 10.9%, life expectancy 15.7%	Denmark, Sweden, and Finland, population-based, from Jan 1, 2000, to Jan 1, 2007 (Denmark, n=20 430; Sweden n=24 823; Finland n=20 835)	Years of potential life lost: Denmark men 20.0 and women 16.5, Sweden men 18.9 and women 16.9, Finland men 17.1 and women 15.6; remaining life expectancy at age 15 years: Denmark men 40.7 years and women 48.8 years; Sweden men 44.3 years and women 50.7 years; Finland men 43.6 years and women 51.9 years	Selection ◊◊◊◊; comparability ◊◊; outcome ◊◊◊
Lawrence et al, 2013 ¹⁹	Years of potential life lost 6.9%, life expectancy 9.8%	Population-based, Western Australia, 1985–2005 (1983–87 n=6173; 2003–07 n=13 100)¶	1985 years of potential life lost: men, 14.5 (95% CI 12.4–16.6), women 12.9 (10.6–15.2); life expectancy: men 58.6 years (56.5–60.7) vs 73.1 years, women, 66.5 (64.2–68.7) vs 79.3 years 1995 years of potential life lost: men 10.3 (8.6–12.1), women 11.8 (10.2–13.5); life expectancy: men 60.0 years (58.5–61.5) vs 75.4 years, women 69.5 years (67.9–71.1) vs 81.4 years 2005 years of potential life lost: men 16.4 (14.7–18.0), women 12.5 (10.5–14.5); life expectancy: men 62.7 years (61.1–64.3) vs 79.1 years, women 71.3 years (69.3–73.3) vs 83.8 years	Selection ◊◊◊◊; comparability ◊◊; outcome ◊◊◊
Lêng et al, 2016 ²³	Years of potential life lost 5.5%, life expectancy 7.9%	Taiwan, population-based, 2000–10, followed up until 2011 (n=34 658)	Years of potential life lost: men 15.17, women 9.22; remaining life expectancy at age 20–29 years†: men 35.64 years, women 47.17 years;	Selection ◊◊◊◊; comparability ◊◊; outcome ◊◊ (follow-up was too short)
Lesage et al, 2015 ²²	Years of potential life lost 16.8%, life expectancy 24.1%	Quebec, Canada, population-based, 1999–2012 (n~32 000)	At age 1 year, years of potential life lost 11.35; life expectancy 68.5 years**	Selection ◊◊◊◊; comparability ◊◊; outcome ◊◊ (follow-up was too short)
Morden et al, 2012 ¹⁶	Years of potential life lost 30.2%, life expectancy not reported	USA, Veteran Affairs health system register, fiscal years 2000–07 (n=65 362)	Years of potential life lost per year: 12.8 (2000), 13.2 (2001), 13.8 (2002), 14.4 (2003), 15.0 (2004), 14.8 (2005), 15.3 (2006), and 15.4 (2007)	Selection ◊◊◊ (selected group of schizophrenia); comparability ◊ (years of potential life lost does not control for sex); outcome ◊◊◊
Newman and Bland, 1991 ¹⁴	Years of potential life lost 1.9%, life expectancy 2.7%	Canada, Alberta Mental Health Information System, 1976–85 (n=3623)	Life expectancy: men 56.2 years vs 72.0 years; women 66.1 years vs 79.1 years	Selection ◊◊◊◊; comparability ◊◊; outcome ◊◊◊
Tiihonen et al, 2009 ¹⁴	Years of potential life lost 0, life expectancy 0††	Finland, population-based, 1996–2006 (n=66 881)	At age 20 years, years of potential life lost: 25.0 (1996) and 22.5 (2006); remaining life expectancy: 32.5 years vs 57.7 years (1996) and 37.4 years vs 59.9 (2006)	Selection ◊◊◊◊; comparability ◊ (years of potential life lost does not control for sex); outcome ◊◊◊

Weights within sex-specific or region-specific analyses are not presented in the table. *n=numbers of cases with schizophrenia. †Assessed with the Newcastle-Ottawa Scale: risk is lowest with ◊◊◊◊ for selection, ◊◊ for comparability, and ◊◊◊ for outcome. Reasons for loss of diamonds are given in brackets. ‡Other age groups also reported in paper. §Only Finland included in main analysis because of overlapping samples. ¶Deaths were assessed in 5-year periods and, therefore, the study period did not match that for which data were available. ||Based on personal communication because manuscript included more diagnoses than pure schizophrenia. **Condensed and averaged for both sexes from personal communication. ††Values are zero because study excluded from main analysis due to overlapping samples.

Table: Characteristics of included studies

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^{5,25} and diabetes,^{26,27}

among people with schizophrenia than in the background population. This difference could have several explanations. Second-generation antipsychotics have well established metabolic side-effects.^{28–30} 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 habits³⁶ among individuals with schizophrenia compared with the general population. Additionally, health-seeking behaviour³⁷ is reduced among

people with schizophrenia. A shared genetic disposition for metabolic syndrome or cardiovascular disease and schizophrenia has also been suggested.^{38,39} 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.⁴⁰ 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.^{41,42}

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

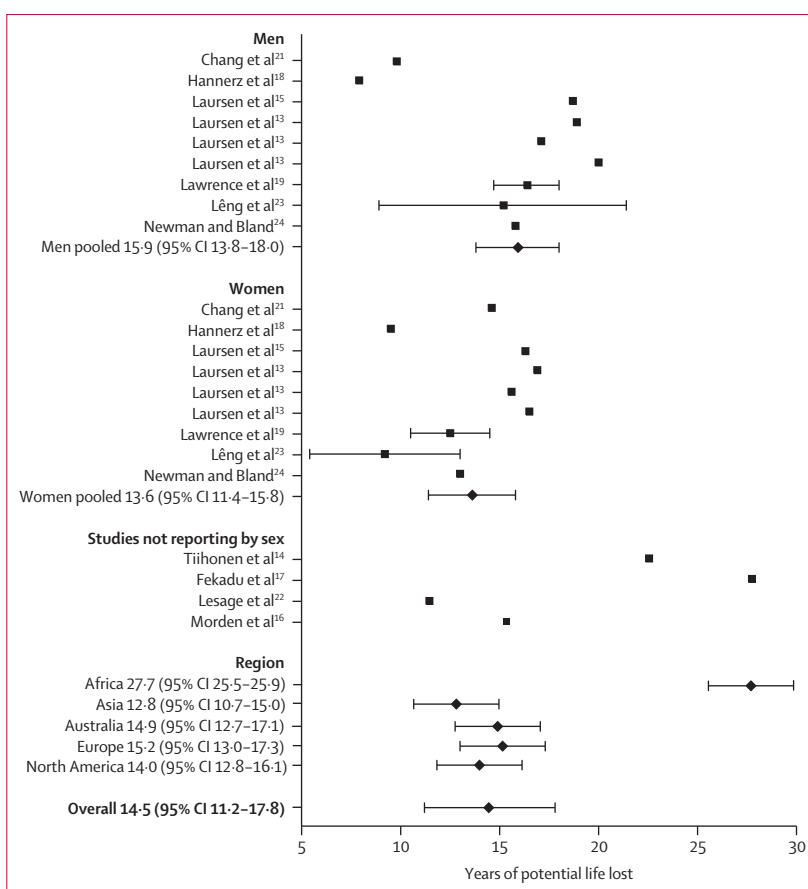


Figure 2: Meta-analysis of years of potential life lost to schizophrenia

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).

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.⁴³

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.¹⁻⁵ Evidently, therefore, many studies on mortality in schizophrenia do not report life expectancy

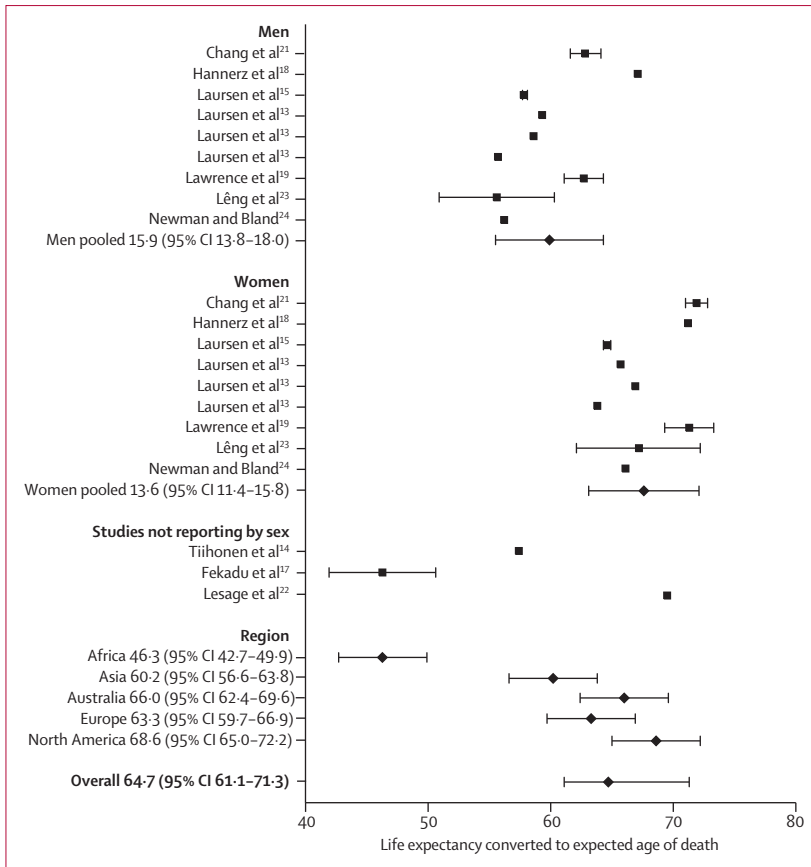


Figure 3: Meta-analysis of life-expectancy converted to expected age of death in schizophrenia
 For overlapping samples, the lowest values were included to provide a conservative estimate. Data are weighted averages and 95% CIs (CIs are only shown if reported in original article).

or years of potential life lost. With more studies reporting these outcomes, a broader representation of countries or identification of subgroups with even more numbers of years of potential life lost might have been possible. Our original protocol included subgroup analyses based on comorbid conditions and other risk factors, but these were not possible. In all the included studies, schizophrenia was diagnosed on the basis of ICD criteria and, therefore, we could not explore whether life expectancy differs according to diagnostic system. This issue might be relevant as, for example, the ICD and DSM definitions of schizophrenia do not fully correspond.⁴⁴ Finally, most studies did not report SEs or CIs around their estimates of years of potential life lost or life expectancy. In these cases, we extrapolated the pooled SE from a fixed-effects meta-analysis of these studies to generate 95% CIs around our own pooled estimates. This approach might have led to both overestimation and underestimation of the true SEs.

Except for the small study from Ethiopia, all those included used hospital data to establish diagnoses of schizophrenia. Thus, all individuals included were seeking or had previously sought treatment. Consequently,

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 I^2 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.

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