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Sex-stratified mortality estimates in people with schizophrenia: a systematic review and meta-analysis of cohort studies of 2,700,825 people with schizophrenia

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Abstract:	The differential influence of sex on premature mortality in schizophrenia is unclear. This study assessed the differences in all-cause and specific cause mortality risks in people with schizophrenia compared to several control groups stratified by sex. We conducted a PRISMA 2020-compliant systematic review and random-effects meta-analysis of cohort studies assessing mortality relative risk (RR) for people with schizophrenia, comparing by sex. We measured publication bias and conducted a quality assessment through the Newcastle-Ottawa scale. We meta-analyzed 43 studies reporting on 2,700,825 people with schizophrenia. Both males and females with schizophrenia had increased all-cause mortality vs. comparison groups (males, RR=2.62, 95%CI 2.35-2.92; females, RR=2.56, 95%CI 2.27-2.87), suicide (males, RR=9.02, 95%CI 5.96-13.67; females, RR=12.09, 95%CI 9.00-16.25), and natural cause mortality (males, RR=2.11, 95%CI 1.88-2.38; females, RR=2.14, 95%CI 1.93-2.38). No statistically significant differences in sex-dependent mortality risk emerged. There was an age-group-dependent increased mortality risk in females < 40 years vs. >/=40 years old (RR=4.23/2.17), and significantly higher risk of death due to neurological disorders (dementia) in males vs. females (RR=5.19/2.40). Increased mortality risks were often associated with specific modifiable risk factors. There were minimal statistically significant differences in sex-dependent mortality risks in people with schizophrenia. However, it revealed areas of targeted intervention efforts.

Eduard Vieta
Editor-in-Chief
European Neuropsychopharmacology

10 June 2024

To Dr. Vieta,

We here submit an original research work, entitled "Sex-stratified mortality estimates in people with schizophrenia: a systematic review and meta-analysis of cohort studies of 2,700,825 people with schizophrenia" for consideration by *European Neuropsychopharmacology*.

In order to further explore the role of sex differences on premature mortality in people with schizophrenia, we performed several subgroup, sensitivity and meta-regression analyses based on a large previous meta-analysis (https://doi.org/10.1002/wps.20994) focusing on cohort studies assessing mortality relative risk (RR) in people with schizophrenia, comparing females and males with schizophrenia with a comparison group (usually the general population).

We meta-analyzed 43 different studies (schizophrenia patients: n=2,700,825; controls: n=730,962,605) to highlight the influence of sex on premature mortality in people with schizophrenia. We found first that both males and females with schizophrenia when compared to comparison groups had increased all-cause mortality, suicide, and natural cause mortality. No statistically significant differences in sex-dependent mortality risk emerged except for higher risk of death due to neurological disorders (dementia-related) in males when compared to females (RR=5.19/2.40). This study also revealed areas of targeted intervention efforts to reduce premature mortality in males and females with schizophrenia.

We confirm that this article is original and has not been published nor considered for publication elsewhere. We have no conflicts of interest to disclose.

We thank you for your consideration of this manuscript.

Sincerely,

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ENP-24-295 Item-By-Item Response to Review

We thank the reviewers for their feedback on this manuscript and are excited to return an improved paper in response to this. All changes have been highlighted in **blue text** below, and tracked changes were made accordingly within the manuscript. We are available for further edits if needed.

Reviewer 1:

Comment 1.0. Solmi and colleagues conducted a systematic review and meta-analysis of sex-stratified mortality estimates in people with schizophrenia. Large-scale previous studies have shown increased all-cause and cause-specific mortality risk for patients with schizophrenia. However, meta-analyses assessing the risk of mortality in schizophrenia across sex have not yet been conducted. The study by Solmi et al. fills this knowledge gap. A meta-analysis confirmed that both males and females with schizophrenia had increased all-cause, suicide, and natural cause mortality, but no statistically significant differences in mortality risk by sex were seen. However, an increased mortality risk in females (less than 40 years vs. more than 40 years old), and a significantly higher risk of death due to neurological disorders (dementia) was identified in males compared to females. Subgroup analysis revealed some interesting features, for example, analysis by continent showed that the risk of suicide-related mortality was 25 times higher in males in Asia compared with a 3.3-fold risk in males from North America. Meta-regression analyzes also revealed some important patterns. In my opinion this is a valuable and rigorously conducted study. The methodology of the meta-analysis is consistent with PRISMA 2020 guidelines. The manuscript is well written and illustrated. The introduction section contains enough relevant literature. The results are generally well presented. The discussion section is well structured and seems sufficient. Supplementary materials also contain quite a lot of useful information. I think this is the rare case where I don't have any suggestions for improving the manuscript.
Response 1.0. We thank Reviewer 1 for taking the time to review our manuscript to improve it prior to publication.

Comment 1.1. When reading the manuscript, I found only minor typos:"whereascomorbid" "trim and fill analyses"- the following term is more correct: "the trim-and-fill analyses".
Response 1.1. These minor typos have been corrected, thank you.

Reviewer 2:

Comment 2.0. This is a systematic review and meta-analysis focusing specifically on the sex-stratified mortality estimates in people with schizophrenia. This review included 43 studies and has examined sex-stratified mortality estimates on all-cause mortality, suicide and natural-cause mortality. The overall results indicated that both males and females with schizophrenia had increased all-cause mortality, suicide and natural-cause mortality relative to the control comparison group. No significant difference in sex-dependent mortality risk was observed, except that there was a higher risk of death due to dementia in males vs

females, as well as an age-dependent increased mortality risk in females (younger than 40 years vs. >=40 years). This topic has not been systematically investigated in previous meta-analysis, The review is comprehensive, and meta-regression, sensitivity and subgroup analyses were performed to explore the sources of heterogeneity, taking into consideration various potential moderators and the nature of the sample (e.g., prevalent and incident, nationwide vs. more restricted sample, underlying physical condition). A few minor points are raised here for further clarification.
Response 2.0. We thank Reviewer 2 for taking the time to review our manuscript and providing points to improve it prior to publication.

Comment 2.1. It is stated in the data analysis section that the effect of treatment with antipsychotic would be examined. However, the findings regarding the antipsychotic treatment effect have not been described in the Results and Discussion sections.
Response 2.1. We had planned to analyze the effect of treatment with antipsychotic on sex differences in mortality, however we did not find any studies. We have added this as a limitation, "**Sixth, no studies analyzed the effect of treatment with an antipsychotic on sex differences in mortality**" (Discussion, paragraph 9).

Comment 2.2. The study included a subgroup analysis by continent. However, it should be noted that the findings of the subgroup analyses were limited by the a very small number of studies in several continents (Africa k=1; North America k=3, Australia k=1). This limitation should be described.
Response 2.2. We agree that this is a limitation worth noting and have since added it to our limitations section, "**Seventh, subgroup analyses were limited by the small number of studies in several continents**" (Discussion, paragraph 9).

Comment 2.3. The results indicated a significant age-dependent increased mortality risk in females with schizophrenia (<40 years vs >=40 years) but not in males with schizophrenia. Are there any possible reasons to explain this finding?
Response 2.3. This is certainly an interesting finding that warrants further discussion. We believe that this may be due to the fact that younger males in the general population (control group) already have elevated risk of mortality (from risk taking behaviour, car crashes, among others). As similar increases in the general population are not seen in younger females in the general population (control group), the RR seems relatively larger in those with schizophrenia. As such we have added the following, "**This finding warrants further investigation, however may be explained due to the fact that younger males in the general population have an elevated risk of mortality (from risk taking behaviour, for instance), and similar increases are not seen in younger females in the general population. As such, the risk may seem relatively larger in those younger females with schizophrenia, but not males, primarily driven by higher mortality rates in the male control group**"(Discussion, paragraph 3).

Citation: https://link.springer.com/article/10.1007/s00406-003-0397-6

Comment 2.4. The study stated that some of the increased mortality risks were associated with specific modifiable risk factors such as smoking and diabetes. However, it seems that smoking has not been investigated in this review?

Response 2.4. Thank you. Although discussed we did not specifically investigate this within our review and have removed it from our conclusion paragraph.

Abstract:248 words
Manuscript:5071 words
Tables:1
Figures:2
eFigures:0
eTables:3
References:83

Sex-stratified mortality estimates in people with schizophrenia: a systematic review and meta-analysis of cohort studies of 2,700,825 people with schizophrenia

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Abstract (248/250 words)

The differential influence of sex on premature mortality in schizophrenia is unclear. This study assessed the differences in all-cause and specific cause mortality risks in people with schizophrenia compared to several control groups stratified by sex. We conducted a PRISMA 2020-compliant systematic review and random-effects meta-analysis of cohort studies assessing mortality relative risk (RR) for people with schizophrenia, comparing by sex. We measured publication bias and conducted a quality assessment through the Newcastle-Ottawa scale. We meta-analyzed 43 studies reporting on 2,700,825 people with schizophrenia. Both males and females with schizophrenia had increased all-cause mortality vs. comparison groups (males, RR=2.62, 95%CI 2.35-2.92; females, RR=2.56, 95%CI 2.27-2.87), suicide (males, RR=9.02, 95%CI 5.96-13.67; females, RR=12.09, 95%CI 9.00-16.25), and natural cause mortality (males, RR=2.11, 95%CI 1.88-2.38; females, RR=2.14, 95%CI 1.93-2.38). No statistically significant differences in sex-dependent mortality risk emerged. There was an age-group-dependent increased mortality risk in females < 40 years vs. >/=40 years old (RR=4.23/2.17), and significantly higher risk of death due to neurological disorders (dementia) in males vs. females (RR=5.19/2.40). Increased mortality risks were often associated with specific modifiable risk factors. There were minimal statistically significant differences in sex-dependent mortality risks in people with schizophrenia. However, it revealed areas of targeted intervention efforts.

Keywords
Schizophrenia; mortality; sex; antipsychotic; systematic review; meta-analysis.

Introduction

Worldwide, across over 200 countries and territories, schizophrenia bears a significant burden due to premature mortality, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs).[1] Over the last decade, this situation has remained largely unchanged[2,3], and the epidemiological and burden estimates are likely underestimated compared to other mental disorders due to its relatively low prevalence.[4]

People with schizophrenia have a considerably shortened lifespan compared to the general population, whereby they are expected to die 15-20 years prematurely.[5–7] Specifically, a recent large-scale systematic review and meta-analysis of 135 prospective, retrospective nationwide, and targeted cohort studies assessing mortality risk among people with schizophrenia compared to the general population or other controls between 1957-2021 established a 152% increased risk in all-cause mortality.[8] For cause-specific mortality risk estimates, people with schizophrenia were at an 876% risk for suicide/injury-poisoning/undetermined non-natural cause risk, 600% risk for pneumonia, 200-300% risk for infectious or endocrine or respiratory or urogenital or diabetes causes, 100-200% risk for alcohol, gastrointestinal or renal or nervous system or cardio-cerebrovascular or any natural causes, and 33-96% risk increase for liver or cerebrovascular, or breast or colon or pancreas or any cancer causes.[8] Further, higher all-cause and suicide-related mortality were observed in incident compared to prevalent schizophrenia, and the use of antipsychotics was found to be associated with lower mortality risk, whereas comorbid substance use disorder elevated mortality risk.[8]

A problematic finding of the meta-analysis was that despite the development and implementation of novel methods to reduce cardiovascular mortality, the mortality gap between people with schizophrenia and the general population has increased over time.[8] This finding suggests that although the general population has benefitted from these interventions, those with schizophrenia have done so to a lesser extent.[9] Contributing to this mortality gap is also the limited access to cancer screening[10] and treatment of cardiovascular disorders[11] experienced by those with severe mental illness, including those with schizophrenia.

Despite the acknowledged increased mortality rate observed in patients with schizophrenia as compared to the general population[12], to our knowledge, no meta-analysis currently exists which explores whether mortality risk and mitigating or risk factors in people with schizophrenia differ across sex. It is imperative that these disparities in mortality by sex be determined in order to provide the foundation for future data-guided studies aimed at determining potential underlying causes, which will allow for the implementation of targeted programs to address and harness potentially sex-divergent risk and protective factors. Therefore, in the current systematic review and meta-analysis, we aimed to assess differences in all-cause and specific cause mortality risks in people with schizophrenia compared to several control groups stratified by biological sex.

Methods

Search

We used identical methods[8] of the published PRISMA 2020-compliant[13] systematic review, which searched Medline, PubMed, and PsycINFO for relevant records indexed up to September 9, 2021. The following search key was used as well as a manual search: (schizophrenia AND (mortal* OR death* OR fatal*)) NOT (animals [mesh] NOT humans [mesh]). The PRISMA 2020 checklist is available in the supplementary material.

Inclusion and exclusion criteria

The inclusion criteria were: 1) peer-reviewed publications with a cohort study design (prospective or retrospective; nationwide or not); 2) over 70% of participants diagnosed with schizophrenia amongst a minimum of 100 total patients; and 3) quantitative and sex-stratified information available on all-cause and cause-specific mortality risk in schizophrenia versus a control group, or on the association of a factor with those outcomes within a cohort of subjects with schizophrenia. Exclusion criteria were : 1) non-cohort study design; 2) studies without quantitative and sex-stratified data on mortality available; and 3) studies that were not peer-reviewed (such as proceedings, poster abstracts, or posters). There were no restrictions on language or time.

Screening, data extraction, and quality assessment

Four independent raters (GC, LKS, MS, NS) conducted the title, abstract, and full-text screening and extracted the data in duplicate with a third author (CUC) who resolved any conflict. Specific details regarding the overall data extraction procedure are available elsewhere.[8] The Newcastle-Ottawa Scale[14] was used to measure the quality of included studies. Authors were contacted to provide missing data for the relevant original studies.

Outcomes

The primary outcome of this meta-analysis was all-cause mortality, with secondary outcomes focused on mortality due to: 1) suicide; 2) natural causes; and 3) other specific-cause mortality.

Data analysis

Main analyses examined incident plus prevalent cohorts of people with schizophrenia together versus any control group, comparing results by sex. We conducted a random-effects meta-analysis[15] calculating the pooled risk ratio (RR). We pooled raw numbers, odds ratio, RR, hazard ratio, and SMR in the same analyses, given the study design, population, and outcomes were homogeneous across studies. The events of interest were rare (i.e., <10%). We preferred adjusted effect sizes over non-adjusted ones or raw data. I^2 and Q-test as used to measure the extent of heterogeneity[16,17] calculating the pooled RR.

Sources of heterogeneity were explored with meta-regression, sensitivity and subgroup analyses. Exploratory random-effects meta-regression analyses were conducted using follow-up time, median study year, number of variables adjusted for, mean age, gender, and sample size as moderator variables. Sensitivity analyses were conducted in studies comparing schizophrenia with the general population, and in studies matching control groups by underlying physical conditions, as well as in incident and prevalent schizophrenia samples. Subgroup analyses were also conducted by use of nationwide versus more restricted samples, Newcastle-Ottawa Scale quality score, adjustment of results, mean age of the sample, incident or prevalent sample, and antipsychotic class prescribed. We chose to analyze the effect of treatment with antipsychotics using subgroups (by class or formulation or specific medication) as the unit of analysis, instead of using the pooled result of the overall study as the unit of analysis, since a single study might have reported on several different antipsychotic subgroups. Comprehensive Meta Analysis Version 2.0 was used for all analyses.[18] Figures were created in R (version 4.3.2) with the meta package[19].

Results

Study Characteristics

Figure 1 illustrates the study selection process. The initial search yielded 8,345 studies of which 5,769 titles and abstracts were excluded, leaving 600 full-texts for assessment. Altogether, 43 studies met inclusion criteria in our meta-analysis after full-text review, reporting on 2,700,825 patients with schizophrenia.

Table 1 summarizes individual study characteristics. The breakdown of study countries of origin was as follows: Europe (k = 28), Asia (k =10), North America (k =3), and Africa (k = 1) and Australia (k = 1). Thirty-four studies (79.1%) reported on prevalent schizophrenia samples while nine studies (20.9%) reported on incident schizophrenia samples.

All-cause and cause-specific mortality in males and females with schizophrenia, and subgroup analyses by sex

Figure 2 summarizes mortality all-cause and cause-specific mortality relative risk in people with schizophrenia versus any control group, incident plus prevalent schizophrenia, by sex (eTable 1). Both males and females with schizophrenia had increased all-cause mortality risk (males, k=36, RR=2.62, 95%CI 2.35-2.92; females, k=35, RR=2.56, 95%CI 2.27-2.87), suicide (males, k=15, RR=9.02, 95%CI 5.96-13.67; females, k=15, RR=12.09, 95%CI 9.00-16.25), and natural cause mortality (males, k=26, RR=2.11, 95%CI 1.88-2.38; females, k=26, RR=2.14, 95%CI 1.93-2.38).

eTable 1 summarizes relative risk of all-cause and cause-specific mortality in males and females with schizophrenia compared with the general population.

Regarding secondary outcomes, for males/females respectively, the relative risk for cause-specific death were as follows: study-defined natural cause mortality (RR=2.38/2.67), cardio-cerebrovascular disease (RR=2.18/2.32), cardiovascular (RR=2.21/2.33), cerebrovascular (RR=1.56/1.61), diabetes (RR=2.56/3.29), any respiratory disease (RR=3.67/3.69), chronic obstructive pulmonary disease (RR=3.60/3.12), any cancer (RR=1.23/1.43), breast cancer (RR=1.81, females only), colon cancer (RR=not significant/1.95), haematological cancer (RR=not significant, males only), liver cancer (RR=not significant/1.41), lung cancer (RR=not significant/not significant), pancreas cancer (RR=1.30/1.42), prostate cancer (RR=1.35, males only), endocrine disease (RR=2.72/6.12), gastrointestinal disease (RR=3.18/2.47), any infectious disease (RR=6.36/4.04), pneumonia (RR=5.56/7.46), any injury (RR=2.71/3.47), accidents (RR=2.72/3.42), poisoning (RR=8.00/12.01), liver disease (RR=1.56/1.72), any neurological disease (dementia) (RR=5.19/2.40), urogenital disease (RR=3.76/2.93), renal failure (RR=2.67/2.67), alcohol-related disease (RR=2.28/3.24), homicide (RR=not significant/not significant), undetermined non-natural (RR=5.36/7.98), other non-specified cause (RR=2.53/2.42).

While, as shown above, a significant increase in mortality relative risk only emerged in males, or in females was seen in neurological disease (dementia) in men (RR=5.19 vs 2.40 in females). In subgroup analyses by sex, no significant difference emerged between males and females, apart from death due to neurological disorder (dementia) (eTable 2).

Sensitivity analyses

Results of main analyses were largely confirmed in sensitivity analyses in incident or prevalent schizophrenia with few exceptions (eTable 1), i.e. an increased risk of all-cause and cause-specific mortality emerged for the vast majority of comparisons. The only exception was as follows: all-cause mortality in prevalent samples (k = 4, RR=1.837, 95%CI 1.351-2.498, males; k = 3, RR=1.640, 95%CI 0.955-2.819, females).

Also, when focusing on control groups matched by underlying physical condition, a general increased all-cause and cause-specific mortality risk was confirmed, with the following few exceptions (eTable 1): diabetes and all-cause mortality in prevalent samples (k = 2, RR=1.409, 95%CI 0.981-2.024, males; k = 2, RR=1.411, 95%CI 0.733-2.717, females).

Subgroup analyses

Results of subgroup analyses are reported in eTable 2. We here briefly report results in incident plus prevalent schizophrenia versus any control group. In subgroup analyses by continent, a significant difference across continents emerged, in males and/or females respectively, as follows: for all-cause mortality (from RR=6.27 Africa to RR=2.78 North America, males; no significant difference in females), for suicide (from RR=25.38 in Asia to RR=3.32 in North America, males; from RR=14.88 in Asia to RR=7.56 in North America, females), and for natural cause (from RR=3.43 North America to RR=1.95 in Asia, males; no significant difference in females). Significant differences emerged also across countries for all-cause mortality, suicide, and natural cause mortality in both males and females (eTable 2).

Comparing estimates from adjusted versus non-adjusted analyses yielded no differences in both males and females for all-cause and natural cause mortality, but for suicide unadjusted studies yielded significantly larger estimates in both males (RR=20.09 unadjusted, RR=5.11 adjusted) and females (RR=21.57 unadjusted, RR=8.2 adjusted) (eTable 2).

Considering mean age below 40 or 40 or more, a significantly larger all-cause mortality risk emerged for the younger than older females (RR=4.23 versus RR=2.17), but not in males, and no difference emerged for suicide (females only). Similarly, a significantly higher all-cause mortality risk emerged for incident versus prevalent schizophrenia in both males (RR=3.68 versus RR=2.57) and females (RR=3.67 versus RR=2.51) , yet no differences merged for suicide or death due to natural cause.

Largely, no difference emerged comparing estimates from nationwide or other cohort studies, high versus lower quality studies in both males and females (eTable 2), or in other subgroup analyses.

Meta-regression

Detailed meta-regression results are available in eTable 3. Considering people with schizophrenia versus any or versus specific control group, incident plus prevalent schizophrenia, the following significant moderators emerged.

For all-cause mortality, more recent study years increased mortality risk in males with prevalent schizophrenia versus the general population (beta=0.009, 95%CI=0.002-0.015), and larger sample size increased mortality risk in females with incident plus prevalent, and prevalent schizophrenia versus any control group, as well as versus the general population (beta<0.001 for all moderators).

For suicide, higher quality of studies increased mortality risk in females with prevalent schizophrenia versus the general population (beta=0.51, 95%CI=0.1-0.92). A larger number of variables that the analyses were adjusted for reduced mortality risk in males and females with incident plus prevalent (beta=-0.33, 95%CI=-0.51, -0.15, males; beta=-0.26, 95%CI=-0.42, -0.09, females) and prevalent (beta=-0.33, 95%CI=-0.58, -0.08, males; beta=-0.24, 95%CI=-0.47, -0.01, females) schizophrenia versus the general population.

For natural cause mortality, more significant moderators were identified. Longer follow-up time reduced mortality risk in males (incident plus prevalent schizophrenia) and females (incident plus prevalent and prevalent schizophrenia) versus any control group, and versus the general population in males (incident schizophrenia), and females (incident plus prevalent schizophrenia) (all beta=-0.02).

More recent study year, versus any control group, increased mortality risk in males and females with incident plus prevalent schizophrenia (both beta=0.01), as well as versus the general population, both in males and females with incident plus prevalent (beta=0.01, 95%CI=0.003-0.02, males; beta=0.01, 95%CI=0.003-0.02, females) and with incident schizophrenia (beta=0.02, 95%CI=0.002-0.03, males; beta=0.03, 95%CI=0.01-0.04, females).

Higher quality of study increased natural cause mortality risk versus any control group and versus the general population, in incident plus prevalent, and in incident or prevalent schizophrenia (beta ranging from 0.11 to 0.23).

Higher number of variables that the analyses were adjusted for increased mortality risk in females with incident schizophrenia versus the general population (beta=0.15, 95%CI=0.07-0.23).

Finally, sample size increased mortality risk in females with incident schizophrenia versus the general population (beta<0.01). No significant moderator was found for any other outcome in males or females with schizophrenia versus any or specific control groups.

Discussion

While within mental disorders, schizophrenia is associated with one of the highest mortality risks and years of potential life lost, surpassed only by substance use disorders and eating disorders[7], and while his mortality risk is substantially higher than in the general population, the differential impact according to sex has not been meta-analyzed so far.[20] This meta-analysis of 43 cohort studies compared more than 2.7 million people with schizophrenia from five different continents with respective control groups in the general population or with matched physical health conditions, reporting mortality risk estimates by sex. Notably, while in the original meta-analysis 135 studies including 4,536,447 people with schizophrenia were included[8], less than one third of the studies and reporting on only little more than half of the overall sample considered sex when analyzing and reporting mortality risk. In those studies reporting on sex-stratified mortality, a similarly increased risk of all-cause mortality compared to the general populations was found in the incident and prevalence sample in both males (2.6-fold) and females (2.5-fold) with schizophrenia. These all-cause mortality risk estimates were also very close to the overall results (2.52-fold) when pooling data from studies with and without sex-related mortality[7], indicating that this subgroup of studies reporting on mortality by sex were generally relatively representative of the overall results. When matching control groups by underlying physical conditions, a general increase in all-cause and cause-specific mortality was still found both in males and females. In addition, when compared to the general population, males and females with schizophrenia were at greater risk of specific-cause mortality for suicide (males=9.0-fold males, females=12.0-fold); natural causes (males=2.1-fold males, females=2.1-fold); and study-defined natural cause mortality (males=2.38-fold, females=2.67-fold).

The relative increase in mortality in people with schizophrenia when compared to the general population was greater in incident populations (i.e. earlier phase of illness) than prevalent populations (i.e. chronic phase of illness), underscoring the need for and value of early identification of increased mortality risk and adequate mitigation. No difference was found between ages in both male and female groups for suicide or death due to natural causes. Generally, when comparing males and

females with schizophrenia to each other with respect to risks of mortality, there was largely no differences found between males and females with the exception of neurological diseases (dementia related mortality). The lack of a difference found in general can be potentially attributed to people with schizophrenia experiencing discrimination from healthcare providers barriers that limit access to primary care, which are systemic issues that act against people with schizophrenia regardless of sex.[10,11,21,22]

However, some interesting variations based on sex were noted. Interestingly, all-cause mortality was higher in females <40 years old compared to females >/=40 years old, while such age-group dependent mortality risk increase was not observed in younger males with schizophrenia. This finding warrants further investigation, however may be explained due to the fact that younger males in the general population have an elevated risk of mortality (from risk taking behaviour, for instance), and similar increases are not seen in younger females in the general population.[23] As such, the risk may seem relatively larger in those younger females with schizophrenia, but not males, primarily driven by higher mortality rates in the male control group. Moreover, male sex was associated with a significantly higher mortality risk due to neurological disorders (dementia) (males: RR=5.19 vs. females: RR=2.40). Males were at greater risk of dementia related mortality compared to females. This difference in dementia related mortality between males and females with schizophrenia could be related to potentially earlier onset of dementia in males with schizophrenia which is further perpetuated by aspects of smoking and substance use.[24,25] Furthermore, barriers faced by people with schizophrenia are compounded by a neurocognitive disease such as dementia.

In terms of disease-specific mortality, males with schizophrenia had higher diabetes-related mortality (2.5-fold) compared to the general population, while this was not the case for females. The greater diabetes-related mortality compared to the general population might be due to multiple factors, i.e. a predisposition to weight gain and diabetes in those with schizophrenia, sedentary lifestyle, and the side effects of the antipsychotic medications used to treat schizophrenia[26,27]. A common side effect of antipsychotic medications is weight gain and decreased glycemic control which as a result increases risk of diabetes in people with schizophrenia.[28–30] This increased risk of diabetes is further compounded by decreased medical attention received by people with schizophrenia and poor self care which contributes to this increased risk of diabetes related mortality.[22,31–33] Furthermore, females are at higher risk of stopping antipsychotic use which would decrease the weight gain and glycemic control issues associated with antipsychotic use thus increasing the risk of mortality in males with schizophrenia when compared to females[34,35].

On the other hand, females had higher colorectal cancer-related mortality (1.9-fold) and liver malignancy-related mortality (1.4-fold) compared to the general population. The higher rates of colorectal cancer-related and liver malignancy-related mortality is consistent with the general increased rate of malignancy-related mortality in people with schizophrenia compared to the general population. This discrepancy can be attributed to factors including people with schizophrenia less likely to seek medical attention, comorbid substance use, specifically smoking, and disparities in healthcare treatment.[10,11,24,25,31,36] When comparing specific-cause mortality in males and females with schizophrenia, no significant differences emerged between males and females. Given these increased disease specific-mortality rates in males and females with schizophrenia when compared to the general population, mental health care providers need to facilitate physical health care as part of a comprehensive and multi-disciplinary care model.[37]

Further subgroup analysis by continent showed a significant difference across continents in mortality risks in males and females with schizophrenia. The greatest difference was seen for risk of

suicide-specific mortality was 25-fold increased risk in males in Asia compared to the 3.3-fold increased risk in males from North America. This increased risk of suicide- specific mortality was also seen in females whereby females in Asia had a 14-fold increased risk of death by suicide compared to a 7.5-fold increased risk in females from North America. The vast differences in rates of mortality between continents in people with schizophrenia are influenced by various socioeconomic and psychosocial factors, including access to care, stigma and discrimination towards people with mental illness, lack of mental health care policies, and gender inequity.[38–40] These findings highlight the disparity in treatment and care for people living with schizophrenia. Therefore, it is important for both males and females with schizophrenia to be screened for risk of suicide and physical health conditions[7,41].

In regards to our meta-regression analyses, for all-cause mortality, larger sample sizes moderated larger relative risks in females with schizophrenia. Larger sample sizes and longer follow-up times can detect smaller differences and are generally more reliable and the increased risk of mortality becomes more apparent. The greater sample sizes may also reflect sex-specific factors in health outcomes not seen in smaller samples. For suicide-related mortality, larger number of variables that were adjusted for during the analyses moderated smaller relative risk in both males and females with schizophrenia. This finding highlights the importance of reducing the confounding effects of other variables apart from schizophrenia itself when determining risk of suicide. For natural-cause mortality, it was most notably found that longer follow-up time moderated smaller relative risks in males and females with schizophrenia compared to the general population. This finding could be used to hypothesize that longer follow-up periods with people with schizophrenia may reduce their risk of mortality by keeping them engaged with the mental health and healthcare system in general. However, the evidence on the impact of follow-up and engagement with psychiatric care on mortality in people with schizophrenia is not clear, requiring further investigation.

The strengths of this meta-analysis are the large number of studies (n=43) that met criteria for inclusion, the large number of patients with schizophrenia (2,700,825) and general population controls (730,962,605), and the high quality of the studies included with robust and consistent results even after trim-and-fill analyses. Future studies should focus on larger sample sizes, longitudinal follow-up, standardization of outcomes in reporting mortality, and more robust methods to further elucidate the factors influencing mortality in the schizophrenia population.

Despite the numerous strengths of this meta-analysis, its results must be interpreted within its limitations. First, the non-randomized nature of the observational cohort studies cannot imply causality. Given that mortality in longitudinal studies is relatively rare and of late-onset, and given the constraints of RCTs that include relatively fewer individuals and could potentially exclude many real-world cohorts, modest follow-up durations, high number of dropouts, and exclusion of the more severely mentally and physically ill, RCTs do not represent the best or most feasible study design to establish mortality risk as well as aggravating and protective factors. Longitudinal cohort studies and more specifically nationwide database studies are a more appropriate option compared to RCTs. Nevertheless, there is evidence that RCTs in schizophrenia are a reliable and fairly representative source of data in schizophrenia, at least for the relative ranking of antipsychotic efficacy and tolerability[42]. Nevertheless, people with relevant physical and psychiatric comorbidities and with active suicidality or recent suicide attempt are generally excluded from RCTs, likely reducing mortality estimates vastly in RCTs. Second, although we were able to include 43 individual studies with a large number of individuals with schizophrenia and an even larger number of patients from the general population, some findings were based on subgroup analyses of five or fewer studies. In order to best identify and evaluate specific factors that increase or decrease the existing mortality gap,

additional studies with sex-stratifired results are of particular importance. Third, the inconsistent definition of age groups among the included studies limited our ability to comprehensively analyze the effects of age on all-cause and specific-cause mortality risks. Given that age is one of the most relevant risk factors for mortality overall, reporting of age in both categorical and continuous nature in future studies would clearly be beneficial. Fourth, in some cases the number of the general population control group was not quantified, but instead studies used regional or nationwide control groups restricted to certain time periods and/or age groups. Imprecision may have been introduced as a result of our estimation of the general population based on census based (sub)population numbers at the time of data collection. Fifth, various metrics were used between studies to report mortality. Imprecision may have also been introduced as a result of pooling results using combined risk estimates with different characteristics. However, imprecision was likely low, given that mortality is a relatively rare event, all included studies used the same cohort design, and all studies evaluated the same population of interest. Sixth, no studies analyzed the effect of treatment with an antipsychotic on sex differences in mortality. Seventh, subgroup analyses were limited by the small number of studies in several continents. Lastly, although there was a preference in using risk estimates with an adjusted estimate for potential confounders, we also included unadjusted risk estimates and adjustments that may not have included all/most relevant covariates associated with mortality risk. However, the scope of this meta-analysis was not to isolate the genetic or narrowly illness-related effects of schizophrenia on mortality risk. Instead, we focused on estimating the differential risk of all-cause and cause-specific mortality in individuals with schizophrenia by sex as well as based on different psychological, social, behavioural, and environmental backgrounds compared to the general population and other control groups. Therefore, the potential residual confounding from a statistical standpoint would represent the reality of individuals living with schizophrenia and ensures the generalizability of our findings.

Conclusion

This meta-analysis assessed the all-cause and cause-specific mortality risks in males and females with schizophrenia compared to the general population and other control groups using a large sample and comprehensive approach. Our findings demonstrated that both males and females with schizophrenia experience increased risks of all-cause and cause-specific mortality compared to the general population and focusing on reported aggravating and protective factors. No statistical significant difference in sex-dependent mortality risk emerged except for males being at a significantly higher risk of death due to neurological disorders (dementia). The results of this mortality gap in males and females with schizophrenia were based on data from high-quality studies that were robust and confirmed in multiple subgroup and meta-regression analyses. Most notably, some of the increased mortality risks were associated with specific modifiable risk factors such as diabetes. These modifiable factors highlight the multidisciplinary approach required in treating people with schizophrenia that involves routine clinician monitoring and patient education. Future studies should focus on larger sample sizes, longitudinal follow-up, and more robust study methodology, reporting results overall and in sex-stratified analyses, to further elucidate factors influencing mortality in this vulnerable population.

Disclosures

MS received honoraria/has been a consultant for AbbVie, Angelini, Lundbeck, Otsuka.

IB received consulting fees from Gedeon Richter and Janssen/Janssen-Cilag; speaker's honoraria from Gedeon Richter, Hikma Pharmaceuticals, Janssen/Janssen-Cilag, KRKA, Lundbeck and Medichem Pharmaceuticals Inc. by Unilab; received research grant from Gedeon Richter; royalties from Oxford University Press.

JT has participated in research projects funded by grants from Janssen-Cilag to his employing institution; he has been a consultant to HLS Therapeutics, Janssen, Orion, Teva, and WebMed Global and received lecture fees from Janssen, Lundbeck and Otsuka.

PG received during the last 5 years fees for presentations at congresses or participation in scientific boards from Biogen, Janssen, Lundbeck, Merk, Otsuka, Richter and Viatris.

R.E.N. has, within the past 3 years, been an investigator for Compass Pharmaceuticals, Janssen-Cilag, Sage and Boehringer-Ingelheim for clinical trials; has received speaking fees from Lundbeck, Teva Pharmaceuticals, Janssen-Cilag and Otsuka Pharmaceuticals; and has acted as advisor to Lundbeck and Janssen-Cilag.

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HT has participated in research projects funded by grants from Janssen-Cilag to her employing institution; and she has received lecture fees from Gedeon Richter, Janssen, Lundbeck and Otsuka.

MF received honoraria for his speaker activity from the American Society of Clinical Psychopharmacology (ASCP) and served as a consultant for Angelini, Otsuka, Lundbeck, Sanofi-Aventis, and Boehringer Ingelheim.

BS is on the Editorial Board of Ageing Research Reviews, Mental Health and Physical Activity, The Journal of Evidence Based Medicine, and The Brazilian Journal of Psychiatry. Brendon has received honorarium from a co-edited book on exercise and mental illness (Elsevier), and unrelated advisory work from ASICS, in addition to honorarium and stock options at FitXR LTD.

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EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Beckley-Psytech, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, HMNC, Idorsia, Johnson & Johnson, Lundbeck, Luye Pharma, Medincell, Merck, Newron, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva, and Viatris, outside the submitted work.

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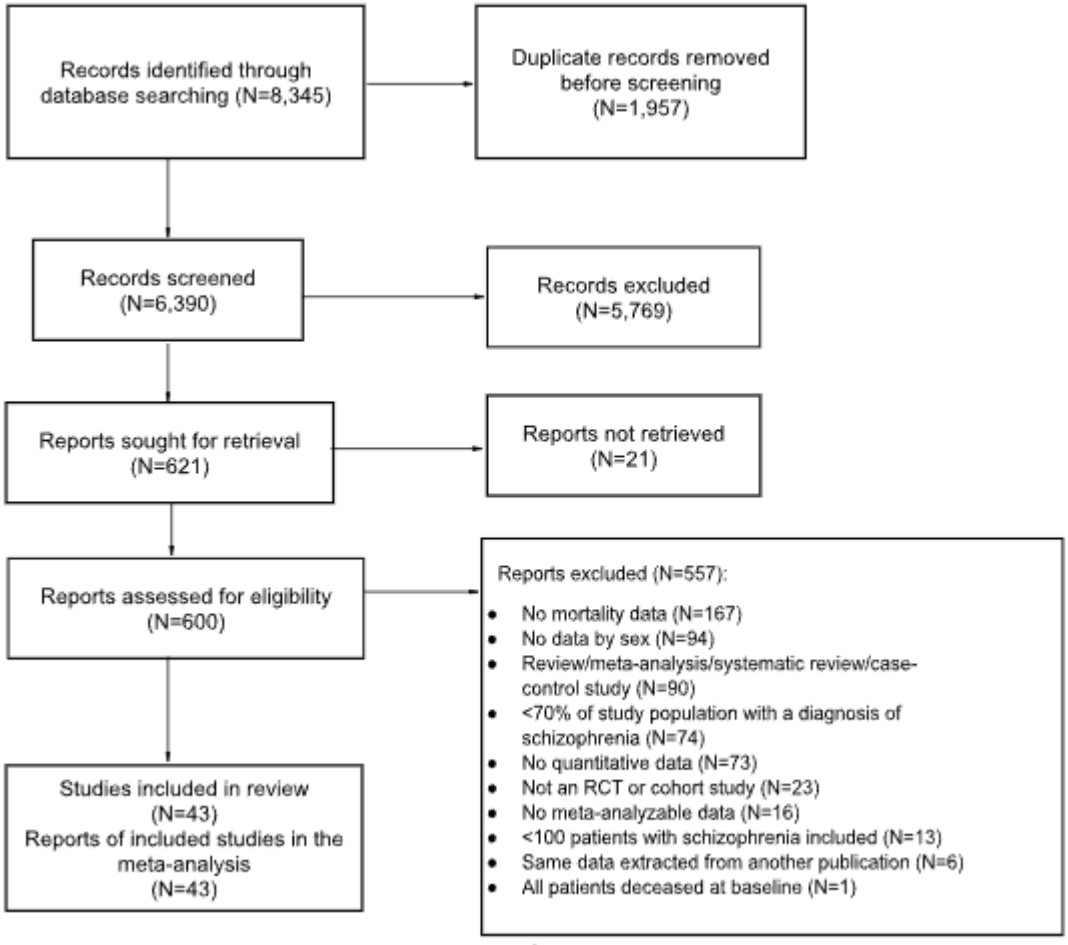


Figure 1: PRISMA Diagram

Table 1: Included studies reporting on risk of all-cause and specific-cause mortality in schizophrenia versus control group, and on mitigating/risk factors

	Country	Years	Comparison	Incident/ prevalent	Number of patients (F / M)	Number of controls (F / M)	Mortality outcomes	NOS
Alleback & Wistedt[43]	Sweden	1971-1981	Schizophrenia vs. general population	P	618 / 572	7,739 / 7,163	All-cause, suicide, various specific causes, undetermined	9
Amaddeo et al[44]	Italy	1982-1991	Schizophrenia vs. general population	P	37,948 / 27,211	189,381 / 136,059	All-cause	9
Bitter et al[45]	Hungary	2005-2013	Schizophrenia vs. general population	P	147 / 209	1,184,709/1,684,383	All-cause	9
Black & Fisher[46]	US	1970-1988	Schizophrenia vs. general population	P	1602 / 1570	2,869,448	All-cause, natural, undetermined	9
Brown et al[47]	UK	1981-2006	Schizophrenia vs. general population	P	157 / 213	24,328,853	All-cause, suicide, natural, various specific causes, undetermined	9
Chen et al[48]	Taiwan	1998-2004	Schizophrenia vs. general population	I	2259 / 3256	18,723	All-cause, natural, undetermined	9
Crump et al[49]	Sweden	2001-2008	Schizophrenia vs. general population	P	10,825 / 14,534	2,944,592 / 3,953,505	All-cause, injury, other	9
Fors et al[50]	Sweden	1991-2000	Schizophrenia vs. general population	P	109 / 146	545 / 730	All-cause, natural, cardiovascular, undetermined	9
Girardi et al[51]	Italy	2008-2018	Schizophrenia vs. general population	P	6,342 / 6,654	2,384,858 / 2,502,146	Suicide, natural, various specific causes	9
Haugland et al[52]	US	1975-1978	Schizophrenia vs. general population	P	175 / 176	NA	All-cause	9

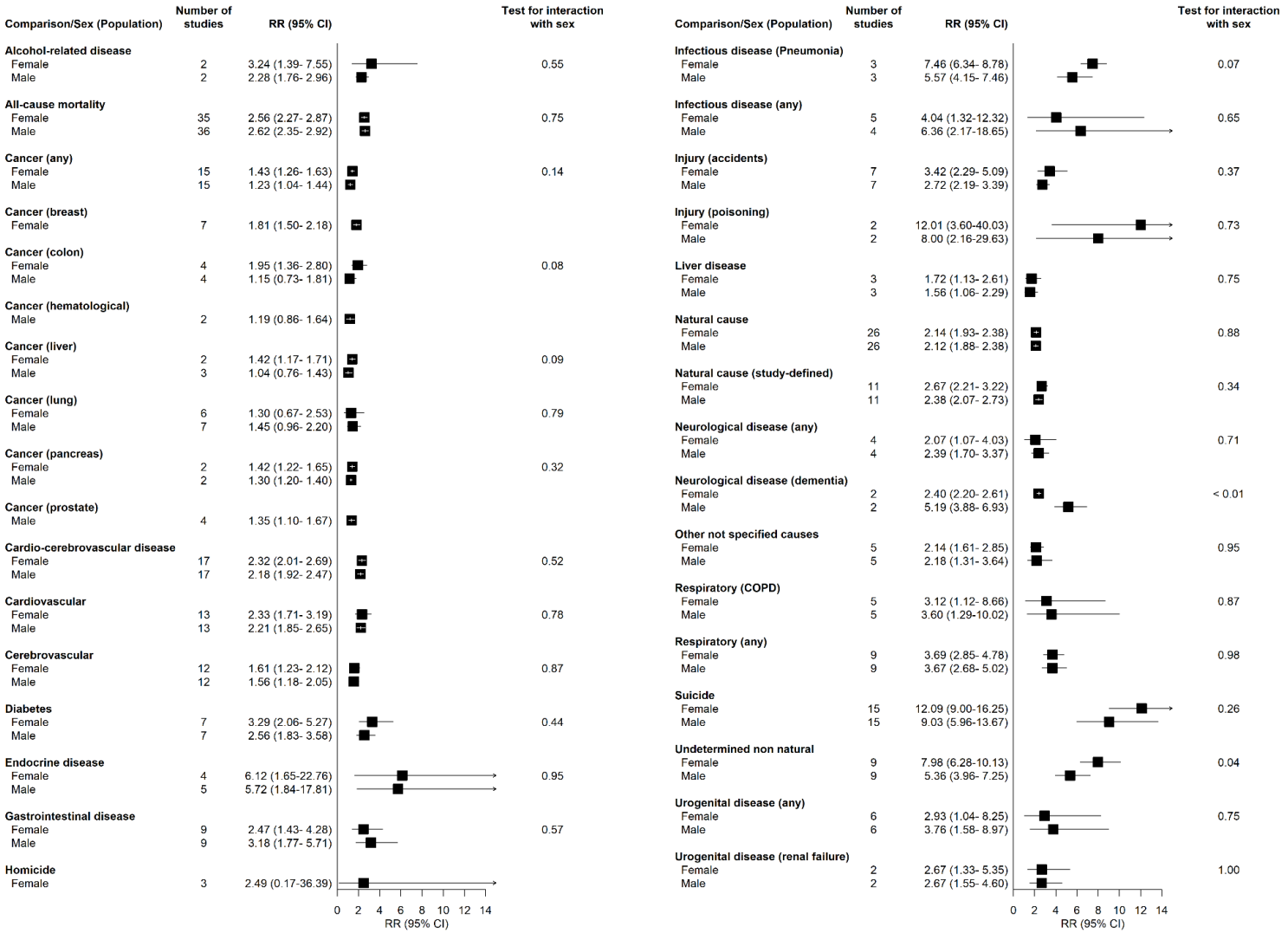
Hayes et al[53]	UK	2000-2014	Schizophrenia vs. general population	P	8,499 / 13,998	82,884 / 136,503	All-cause, suicide, cardiovascular	9
Hellemose et al[54]	Denmark	1970-2011	Schizophrenia vs. general population	I	6,628 / 10,902	1,015,478 / 1,670,299	Other	9
Kiviniemi et al[55]	Finland	1995-2001	Schizophrenia vs. general population	I	3,188 / 4,403	2,147,212 / 2,965,197	All-cause, suicide, natural, various specific causes, undetermined	9
Kurdyak et al[56]	Canada	2007-2010	Schizophrenia vs. general population	I	5,053 / 8,332	9,422,349 / 16,267,908	All-cause, suicide, injury, other	9
Lahti et al[57]	Finland	1969-2004	Schizophrenia vs. general population	I	87 / 117	5,431 / 7,304	Cardio-cerebrovascular	9
Laursen et al[58]	Denmark, Finland, Sweden	2000-2007	Schizophrenia vs. general population	P	29,406 / 36,682	4,452,796 / 5,359,840	All-cause, natural, cardio-cerebrovascular, undetermined	9
Laursen et al[59]	Denmark	1995-2007	Schizophrenia vs. general population	P	4,269 / 11,810	644,704 / 1,783,814	Natural	9
Meesters et al[60]	The Netherlands	2008-2012	Schizophrenia vs. general population	P	113 / 44	18,454 / 7,177	All-cause	9
Mortensen & Juel[61]	Denmark	1957-1986	Schizophrenia vs. general population	P	3,202 / 2,976	1,289,507 / 1,198,493	All-cause, suicide, natural, various specific causes	6
Mortensen & Juel[62]	Denmark	1970-1987	Schizophrenia vs. general population	I	3,948 / 5,658	978,416 / 1,582,584	All-cause, suicide, natural, various specific causes	6
Newman & Bland[63]	Canada	1976-1985	Schizophrenia vs. general population	P	1,501 / 2,122	927,198 / 1,310,802	All-cause, suicide, natural, various specific causes	6
Nielsen et al[64]	Denmark	1980-2010	Schizophrenia vs. general population	P	6,826 / 8,148	603,253 / 708,166	All-cause	9

Olfson et al[65]	US	2001-2007	Schizophrenia vs. general population	I	528,120 / 610,733	80,065,984 / 92,490,016	All-cause, suicide, natural, various specific causes	9
Olfson et al[66]	US	2007-2016	Schizophrenia vs. general population	P	317,892 / 350,943	158,052,108 / 152,859,057	Suicide, other non-natural	9
Ösby et al[67]	Sweden	1973-1995	Schizophrenia vs. general population	I	3,855 / 3,929	887,505 / 904,711	All-cause, suicide, natural, various specific causes, undetermined	9
Pan et al[68]	Taiwan	2005-2008 2010-2013	Schizophrenia vs. general population	P	44,097 / 51,535 49,608 / 54,953	10,524,575 / 12,299,793 10,824,574 / 11,990,865	All-cause, suicide, natural, various specific causes	9
Ran et al[69]	China	1994-2004	Schizophrenia vs. general population	P	267 / 233	65,715 / 57,347	All-cause, suicide, injury, natural	9
Talaslahti et al[70]	Finland	1992-2008	Schizophrenia vs. general population	P	6,504 / 2,957	646,922 / 294,119	All-cause, suicide, natural, various specific causes	9
Tanskanen et al[5]	Finland	1984 1994 2014	Schizophrenia vs. general population	P	159,858	16,701,991	Suicide, natural, cardiovascular, other	9
Teferra et al[71]	Ethiopia	2001-2005	Schizophrenia vs. general population	P	55 / 252	12,250 / 56,128	All-cause	9
Tornianen et al[72]	Sweden	2006-2010	Schizophrenia vs. general population	I	4,970 / 8,054	9,483 / 15,836	All-cause, suicide, various specific causes	9
Tran et al[73]	France	1993-2003	Schizophrenia vs. general population	P	1,236 / 2,198	21,279,600 / 37,830,400	Cardiovascular	9
Westman et al[74]	Sweden	1987-2010	Schizophrenia vs. general population	P	46,911	10,631,817	All-cause, suicide, injury, cardio-cerebrovascular, other	9

Yung et al[75]	China	2006-2016	Schizophrenia vs. general population	P	435 / 382	4,350 / 3,820	All-cause, cerebrovascular	9
Yung et al[76]	Hong Kong	2006-2016	Schizophrenia vs. general population	P	24,103 / 22,793	3,830,650 / 3,622,454	All-cause, various specific causes	9
Zilber et al[77]	Israel	1978-1983	Schizophrenia vs. general population	P	9,282	NA	All-cause, suicide, natural, various specific causes	9
Babidge et al[78]	Australia	1988-1998	Schizophrenia vs. non-schizophrenia homeless	P	0 / 455	0 / 253	All-cause	9
Bodén et al[79]	Sweden	1997-2010	Schizophrenia vs. general population with acute myocardial infarction	P	199 / 342	76,734 / 131,875	All-cause, cardiovascular	9
Chan et al[80]	Hong Kong	2001-2016	Schizophrenia vs. general population with diabetes mellitus	P	3,895 / 3,096	38,266 / 30,416	All-cause, diabetes mellitus	9
Crump et al[6]	Sweden	2003-2009	Schizophrenia vs. general population with ischemic heart disease or cancer	P	3,490 / 4,787	3,123,494 / 2,966,063	All-cause	9
Toender et al[81]	Denmark	1999-2017	Schizophrenia vs. general population with diabetes mellitus	P	1,004	184,470	All-cause, diabetes mellitus, other	9
Liu et al[82]	China	2006-2010	Schizophrenia with vs. without disability	P	4,195 / 3,433	1,045,768 / 855,809	All-cause	9
Oh et al[83]	Korea	2003-2017	Schizophrenia with vs. without antipsychotics	P	39,511 / 37,628	5,011 / 4,773	All-cause, suicide, various specific causes	9

Abbreviations: NOS – Newcastle-Ottawa scale, I – incident, P – prevalent, NA – not available

Figure 2. Relative risk of all-cause and cause-specific mortality in persons with prevalent plus incident schizophrenia, versus any control group, by sex.



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eFigures:0
eTables:3
References:83

Sex-stratified mortality estimates in people with schizophrenia: a systematic review and meta-analysis of cohort studies of 2,700,825 people with schizophrenia

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Abstract (248/250 words)

The differential influence of sex on premature mortality in schizophrenia is unclear. This study assessed the differences in all-cause and specific cause mortality risks in people with schizophrenia compared to several control groups stratified by sex. We conducted a PRISMA 2020-compliant systematic review and random-effects meta-analysis of cohort studies assessing mortality relative risk (RR) for people with schizophrenia, comparing by sex. We measured publication bias and conducted a quality assessment through the Newcastle-Ottawa scale. We meta-analyzed 43 studies reporting on 2,700,825 people with schizophrenia. Both males and females with schizophrenia had increased all-cause mortality vs. comparison groups (males, RR=2.62, 95%CI 2.35-2.92; females, RR=2.56, 95%CI 2.27-2.87), suicide (males, RR=9.02, 95%CI 5.96-13.67; females, RR=12.09, 95%CI 9.00-16.25), and natural cause mortality (males, RR=2.11, 95%CI 1.88-2.38; females, RR=2.14, 95%CI 1.93-2.38). No statistically significant differences in sex-dependent mortality risk emerged. There was an age-group-dependent increased mortality risk in females < 40 years vs. >/=40 years old (RR=4.23/2.17), and significantly higher risk of death due to neurological disorders (dementia) in males vs. females (RR=5.19/2.40). Increased mortality risks were often associated with specific modifiable risk factors. There were minimal statistically significant differences in sex-dependent mortality risks in people with schizophrenia. However, it revealed areas of targeted intervention efforts.

Keywords
Schizophrenia; mortality; sex; antipsychotic; systematic review; meta-analysis.

Introduction

Worldwide, across over 200 countries and territories, schizophrenia bears a significant burden due to premature mortality, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs).[1] Over the last decade, this situation has remained largely unchanged[2,3], and the epidemiological and burden estimates are likely underestimated compared to other mental disorders due to its relatively low prevalence.[4]

People with schizophrenia have a considerably shortened lifespan compared to the general population, whereby they are expected to die 15-20 years prematurely.[5–7] Specifically, a recent large-scale systematic review and meta-analysis of 135 prospective, retrospective nationwide, and targeted cohort studies assessing mortality risk among people with schizophrenia compared to the general population or other controls between 1957-2021 established a 152% increased risk in all-cause mortality.[8] For cause-specific mortality risk estimates, people with schizophrenia were at an 876% risk for suicide/injury-poisoning/undetermined non-natural cause risk, 600% risk for pneumonia, 200-300% risk for infectious or endocrine or respiratory or urogenital or diabetes causes, 100-200% risk for alcohol, gastrointestinal or renal or nervous system or cardio-cerebrovascular or any natural causes, and 33-96% risk increase for liver or cerebrovascular, or breast or colon or pancreas or any cancer causes.[8] Further, higher all-cause and suicide-related mortality were observed in incident compared to prevalent schizophrenia, and the use of antipsychotics was found to be associated with lower mortality risk, whereas comorbid substance use disorder elevated mortality risk.[8]

A problematic finding of the meta-analysis was that despite the development and implementation of novel methods to reduce cardiovascular mortality, the mortality gap between people with schizophrenia and the general population has increased over time.[8] This finding suggests that although the general population has benefitted from these interventions, those with schizophrenia have done so to a lesser extent.[9] Contributing to this mortality gap is also the limited access to cancer screening[10] and treatment of cardiovascular disorders[11] experienced by those with severe mental illness, including those with schizophrenia.

Despite the acknowledged increased mortality rate observed in patients with schizophrenia as compared to the general population[12], to our knowledge, no meta-analysis currently exists which explores whether mortality risk and mitigating or risk factors in people with schizophrenia differ across sex. It is imperative that these disparities in mortality by sex be determined in order to provide the foundation for future data-guided studies aimed at determining potential underlying causes, which will allow for the implementation of targeted programs to address and harness potentially sex-divergent risk and protective factors. Therefore, in the current systematic review and meta-analysis, we aimed to assess differences in all-cause and specific cause mortality risks in people with schizophrenia compared to several control groups stratified by biological sex.

Methods

Search

We used identical methods[8] of the published PRISMA 2020-compliant[13] systematic review, which searched Medline, PubMed, and PsycINFO for relevant records indexed up to September 9, 2021. The following search key was used as well as a manual search: (schizophrenia AND (mortal* OR death* OR fatal*)) NOT (animals [mesh] NOT humans [mesh]). The PRISMA 2020 checklist is available in the supplementary material.

Inclusion and exclusion criteria

The inclusion criteria were: 1) peer-reviewed publications with a cohort study design (prospective or retrospective; nationwide or not); 2) over 70% of participants diagnosed with schizophrenia amongst a minimum of 100 total patients; and 3) quantitative and sex-stratified information available on all-cause and cause-specific mortality risk in schizophrenia versus a control group, or on the association of a factor with those outcomes within a cohort of subjects with schizophrenia. Exclusion criteria were : 1) non-cohort study design; 2) studies without quantitative and sex-stratified data on mortality available; and 3) studies that were not peer-reviewed (such as proceedings, poster abstracts, or posters). There were no restrictions on language or time.

Screening, data extraction, and quality assessment

Four independent raters (GC, LKS, MS, NS) conducted the title, abstract, and full-text screening and extracted the data in duplicate with a third author (CUC) who resolved any conflict. Specific details regarding the overall data extraction procedure are available elsewhere.[8] The Newcastle-Ottawa Scale[14] was used to measure the quality of included studies. Authors were contacted to provide missing data for the relevant original studies.

Outcomes

The primary outcome of this meta-analysis was all-cause mortality, with secondary outcomes focused on mortality due to: 1) suicide; 2) natural causes; and 3) other specific-cause mortality.

Data analysis

Main analyses examined incident plus prevalent cohorts of people with schizophrenia together versus any control group, comparing results by sex. We conducted a random-effects meta-analysis[15] calculating the pooled risk ratio (RR). We pooled raw numbers, odds ratio, RR, hazard ratio, and SMR in the same analyses, given the study design, population, and outcomes were homogeneous across studies. The events of interest were rare (i.e., <10%). We preferred adjusted effect sizes over non-adjusted ones or raw data. I^2 and Q-test as used to measure the extent of heterogeneity[16,17] calculating the pooled RR.

Sources of heterogeneity were explored with meta-regression, sensitivity and subgroup analyses. Exploratory random-effects meta-regression analyses were conducted using follow-up time, median study year, number of variables adjusted for, mean age, gender, and sample size as moderator variables. Sensitivity analyses were conducted in studies comparing schizophrenia with the general population, and in studies matching control groups by underlying physical conditions, as well as in incident and prevalent schizophrenia samples. Subgroup analyses were also conducted by use of nationwide versus more restricted samples, Newcastle-Ottawa Scale quality score, adjustment of results, mean age of the sample, incident or prevalent sample, and antipsychotic class prescribed. We chose to analyze the effect of treatment with antipsychotics using subgroups (by class or formulation or specific medication) as the unit of analysis, instead of using the pooled result of the overall study as the unit of analysis, since a single study might have reported on several different antipsychotic subgroups. Comprehensive Meta Analysis Version 2.0 was used for all analyses.[18] Figures were created in R (version 4.3.2) with the meta package[19].

Results

Study Characteristics

Figure 1 illustrates the study selection process. The initial search yielded 8,345 studies of which 5,769 titles and abstracts were excluded, leaving 600 full-texts for assessment. Altogether, 43 studies met inclusion criteria in our meta-analysis after full-text review, reporting on 2,700,825 patients with schizophrenia.

Table 1 summarizes individual study characteristics. The breakdown of study countries of origin was as follows: Europe (k = 28), Asia (k =10), North America (k =3), and Africa (k = 1) and Australia (k = 1). Thirty-four studies (79.1%) reported on prevalent schizophrenia samples while nine studies (20.9%) reported on incident schizophrenia samples.

All-cause and cause-specific mortality in males and females with schizophrenia, and subgroup analyses by sex

Figure 2 summarizes mortality all-cause and cause-specific mortality relative risk in people with schizophrenia versus any control group, incident plus prevalent schizophrenia, by sex (eTable 1). Both males and females with schizophrenia had increased all-cause mortality risk (males, k=36, RR=2.62, 95%CI 2.35-2.92; females, k=35, RR=2.56, 95%CI 2.27-2.87), suicide (males, k=15, RR=9.02, 95%CI 5.96-13.67; females, k=15, RR=12.09, 95%CI 9.00-16.25), and natural cause mortality (males, k=26, RR=2.11, 95%CI 1.88-2.38; females, k=26, RR=2.14, 95%CI 1.93-2.38).

eTable 1 summarizes relative risk of all-cause and cause-specific mortality in males and females with schizophrenia compared with the general population.

Regarding secondary outcomes, for males/females respectively, the relative risk for cause-specific death were as follows: study-defined natural cause mortality (RR=2.38/2.67), cardio-cerebrovascular disease (RR=2.18/2.32), cardiovascular (RR=2.21/2.33), cerebrovascular (RR=1.56/1.61), diabetes (RR=2.56/3.29), any respiratory disease (RR=3.67/3.69), chronic obstructive pulmonary disease (RR=3.60/3.12), any cancer (RR=1.23/1.43), breast cancer (RR=1.81, females only), colon cancer (RR=not significant/1.95), haematological cancer (RR=not significant, males only), liver cancer (RR=not significant/1.41), lung cancer (RR=not significant/not significant), pancreas cancer (RR=1.30/1.42), prostate cancer (RR=1.35, males only), endocrine disease (RR=2.72/6.12), gastrointestinal disease (RR=3.18/2.47), any infectious disease (RR=6.36/4.04), pneumonia (RR=5.56/7.46), any injury (RR=2.71/3.47), accidents (RR=2.72/3.42), poisoning (RR=8.00/12.01), liver disease (RR=1.56/1.72), any neurological disease (dementia) (RR=5.19/2.40), urogenital disease (RR=3.76/2.93), renal failure (RR=2.67/2.67), alcohol-related disease (RR=2.28/3.24), homicide (RR=not significant/not significant), undetermined non-natural (RR=5.36/7.98), other non-specified cause (RR=2.53/2.42).

While, as shown above, a significant increase in mortality relative risk only emerged in males, or in females was seen in neurological disease (dementia) in men (RR=5.19 vs 2.40 in females). In subgroup analyses by sex, no significant difference emerged between males and females, apart from death due to neurological disorder (dementia) (eTable 2).

Sensitivity analyses

Results of main analyses were largely confirmed in sensitivity analyses in incident or prevalent schizophrenia with few exceptions (eTable 1), i.e. an increased risk of all-cause and cause-specific mortality emerged for the vast majority of comparisons. The only exception was as follows: all-cause mortality in prevalent samples (k = 4, RR=1.837, 95%CI 1.351-2.498, males; k = 3, RR=1.640, 95%CI 0.955-2.819, females).

Also, when focusing on control groups matched by underlying physical condition, a general increased all-cause and cause-specific mortality risk was confirmed, with the following few exceptions (eTable 1): diabetes and all-cause mortality in prevalent samples (k = 2, RR=1.409, 95%CI 0.981-2.024, males; k = 2, RR=1.411, 95%CI 0.733-2.717, females).

Subgroup analyses

Results of subgroup analyses are reported in eTable 2. We here briefly report results in incident plus prevalent schizophrenia versus any control group. In subgroup analyses by continent, a significant difference across continents emerged, in males and/or females respectively, as follows: for all-cause mortality (from RR=6.27 Africa to RR=2.78 North America, males; no significant difference in females), for suicide (from RR=25.38 in Asia to RR=3.32 in North America, males; from RR=14.88 in Asia to RR=7.56 in North America, females), and for natural cause (from RR=3.43 North America to RR=1.95 in Asia, males; no significant difference in females). Significant differences emerged also across countries for all-cause mortality, suicide, and natural cause mortality in both males and females (eTable 2).

Comparing estimates from adjusted versus non-adjusted analyses yielded no differences in both males and females for all-cause and natural cause mortality, but for suicide unadjusted studies yielded significantly larger estimates in both males (RR=20.09 unadjusted, RR=5.11 adjusted) and females (RR=21.57 unadjusted, RR=8.2 adjusted) (eTable 2).

Considering mean age below 40 or 40 or more, a significantly larger all-cause mortality risk emerged for the younger than older females (RR=4.23 versus RR=2.17), but not in males, and no difference emerged for suicide (females only). Similarly, a significantly higher all-cause mortality risk emerged for incident versus prevalent schizophrenia in both males (RR=3.68 versus RR=2.57) and females (RR=3.67 versus RR=2.51) , yet no differences merged for suicide or death due to natural cause.

Largely, no difference emerged comparing estimates from nationwide or other cohort studies, high versus lower quality studies in both males and females (eTable 2), or in other subgroup analyses.

Meta-regression

Detailed meta-regression results are available in eTable 3. Considering people with schizophrenia versus any or versus specific control group, incident plus prevalent schizophrenia, the following significant moderators emerged.

For all-cause mortality, more recent study years increased mortality risk in males with prevalent schizophrenia versus the general population (beta=0.009, 95%CI=0.002-0.015), and larger sample size increased mortality risk in females with incident plus prevalent, and prevalent schizophrenia versus any control group, as well as versus the general population (beta<0.001 for all moderators).

For suicide, higher quality of studies increased mortality risk in females with prevalent schizophrenia versus the general population (beta=0.51, 95%CI=0.1-0.92). A larger number of variables that the analyses were adjusted for reduced mortality risk in males and females with incident plus prevalent (beta=-0.33, 95%CI=-0.51, -0.15, males; beta=-0.26, 95%CI=-0.42, -0.09, females) and prevalent (beta=-0.33, 95%CI=-0.58, -0.08, males; beta=-0.24, 95%CI=-0.47, -0.01, females) schizophrenia versus the general population.

For natural cause mortality, more significant moderators were identified. Longer follow-up time reduced mortality risk in males (incident plus prevalent schizophrenia) and females (incident plus prevalent and prevalent schizophrenia) versus any control group, and versus the general population in males (incident schizophrenia), and females (incident plus prevalent schizophrenia) (all beta=-0.02).

More recent study year, versus any control group, increased mortality risk in males and females with incident plus prevalent schizophrenia (both beta=0.01), as well as versus the general population, both in males and females with incident plus prevalent (beta=0.01, 95%CI=0.003-0.02, males; beta=0.01, 95%CI=0.003-0.02, females) and with incident schizophrenia (beta=0.02, 95%CI=0.002-0.03, males; beta=0.03, 95%CI=0.01-0.04, females).

Higher quality of study increased natural cause mortality risk versus any control group and versus the general population, in incident plus prevalent, and in incident or prevalent schizophrenia (beta ranging from 0.11 to 0.23).

Higher number of variables that the analyses were adjusted for increased mortality risk in females with incident schizophrenia versus the general population (beta=0.15, 95%CI=0.07-0.23).

Finally, sample size increased mortality risk in females with incident schizophrenia versus the general population (beta<0.01). No significant moderator was found for any other outcome in males or females with schizophrenia versus any or specific control groups.

Discussion

While within mental disorders, schizophrenia is associated with one of the highest mortality risks and years of potential life lost, surpassed only by substance use disorders and eating disorders[7], and while his mortality risk is substantially higher than in the general population, the differential impact according to sex has not been meta-analyzed so far.[20] This meta-analysis of 43 cohort studies compared more than 2.7 million people with schizophrenia from five different continents with respective control groups in the general population or with matched physical health conditions, reporting mortality risk estimates by sex. Notably, while in the original meta-analysis 135 studies including 4,536,447 people with schizophrenia were included[8], less than one third of the studies and reporting on only little more than half of the overall sample considered sex when analyzing and reporting mortality risk. In those studies reporting on sex-stratified mortality, a similarly increased risk of all-cause mortality compared to the general populations was found in the incident and prevalence sample in both males (2.6-fold) and females (2.5-fold) with schizophrenia. These all-cause mortality risk estimates were also very close to the overall results (2.52-fold) when pooling data from studies with and without sex-related mortality[7], indicating that this subgroup of studies reporting on mortality by sex were generally relatively representative of the overall results. When matching control groups by underlying physical conditions, a general increase in all-cause and cause-specific mortality was still found both in males and females. In addition, when compared to the general population, males and females with schizophrenia were at greater risk of specific-cause mortality for suicide (males=9.0-fold males, females=12.0-fold); natural causes (males=2.1-fold males, females=2.1-fold); and study-defined natural cause mortality (males=2.38-fold, females=2.67-fold).

The relative increase in mortality in people with schizophrenia when compared to the general population was greater in incident populations (i.e. earlier phase of illness) than prevalent populations (i.e. chronic phase of illness), underscoring the need for and value of early identification of increased mortality risk and adequate mitigation. No difference was found between ages in both male and female groups for suicide or death due to natural causes. Generally, when comparing males and

females with schizophrenia to each other with respect to risks of mortality, there was largely no differences found between males and females with the exception of neurological diseases (dementia related mortality). The lack of a difference found in general can be potentially attributed to people with schizophrenia experiencing discrimination from healthcare providers barriers that limit access to primary care, which are systemic issues that act against people with schizophrenia regardless of sex.[10,11,21,22]

However, some interesting variations based on sex were noted. Interestingly, all-cause mortality was higher in females <40 years old compared to females >/=40 years old, while such age-group dependent mortality risk increase was not observed in younger males with schizophrenia. This finding warrants further investigation, however may be explained due to the fact that younger males in the general population have an elevated risk of mortality (from risk taking behaviour, for instance), and similar increases are not seen in younger females in the general population.[23] As such, the risk may seem relatively larger in those younger females with schizophrenia, but not males, primarily driven by higher mortality rates in the male control group. Moreover, male sex was associated with a significantly higher mortality risk due to neurological disorders (dementia) (males: RR=5.19 vs. females: RR=2.40). Males were at greater risk of dementia related mortality compared to females. This difference in dementia related mortality between males and females with schizophrenia could be related to potentially earlier onset of dementia in males with schizophrenia which is further perpetuated by aspects of smoking and substance use.[24,25] Furthermore, barriers faced by people with schizophrenia are compounded by a neurocognitive disease such as dementia.

In terms of disease-specific mortality, males with schizophrenia had higher diabetes-related mortality (2.5-fold) compared to the general population, while this was not the case for females. The greater diabetes-related mortality compared to the general population might be due to multiple factors, i.e. a predisposition to weight gain and diabetes in those with schizophrenia, sedentary lifestyle, and the side effects of the antipsychotic medications used to treat schizophrenia[26,27]. A common side effect of antipsychotic medications is weight gain and decreased glycemic control which as a result increases risk of diabetes in people with schizophrenia.[28–30] This increased risk of diabetes is further compounded by decreased medical attention received by people with schizophrenia and poor self care which contributes to this increased risk of diabetes related mortality.[22,31–33] Furthermore, females are at higher risk of stopping antipsychotic use which would decrease the weight gain and glycemic control issues associated with antipsychotic use thus increasing the risk of mortality in males with schizophrenia when compared to females[34,35].

On the other hand, females had higher colorectal cancer-related mortality (1.9-fold) and liver malignancy-related mortality (1.4-fold) compared to the general population. The higher rates of colorectal cancer-related and liver malignancy-related mortality is consistent with the general increased rate of malignancy-related mortality in people with schizophrenia compared to the general population. This discrepancy can be attributed to factors including people with schizophrenia less likely to seek medical attention, comorbid substance use, specifically smoking, and disparities in healthcare treatment.[10,11,24,25,31,36] When comparing specific-cause mortality in males and females with schizophrenia, no significant differences emerged between males and females. Given these increased disease specific-mortality rates in males and females with schizophrenia when compared to the general population, mental health care providers need to facilitate physical health care as part of a comprehensive and multi-disciplinary care model.[37]

Further subgroup analysis by continent showed a significant difference across continents in mortality risks in males and females with schizophrenia. The greatest difference was seen for risk of

suicide-specific mortality was 25-fold increased risk in males in Asia compared to the 3.3-fold increased risk in males from North America. This increased risk of suicide- specific mortality was also seen in females whereby females in Asia had a 14-fold increased risk of death by suicide compared to a 7.5-fold increased risk in females from North America. The vast differences in rates of mortality between continents in people with schizophrenia are influenced by various socioeconomic and psychosocial factors, including access to care, stigma and discrimination towards people with mental illness, lack of mental health care policies, and gender inequity.[38–40] These findings highlight the disparity in treatment and care for people living with schizophrenia. Therefore, it is important for both males and females with schizophrenia to be screened for risk of suicide and physical health conditions[7,41].

In regards to our meta-regression analyses, for all-cause mortality, larger sample sizes moderated larger relative risks in females with schizophrenia. Larger sample sizes and longer follow-up times can detect smaller differences and are generally more reliable and the increased risk of mortality becomes more apparent. The greater sample sizes may also reflect sex-specific factors in health outcomes not seen in smaller samples. For suicide-related mortality, larger number of variables that were adjusted for during the analyses moderated smaller relative risk in both males and females with schizophrenia. This finding highlights the importance of reducing the confounding effects of other variables apart from schizophrenia itself when determining risk of suicide. For natural-cause mortality, it was most notably found that longer follow-up time moderated smaller relative risks in males and females with schizophrenia compared to the general population. This finding could be used to hypothesize that longer follow-up periods with people with schizophrenia may reduce their risk of mortality by keeping them engaged with the mental health and healthcare system in general. However, the evidence on the impact of follow-up and engagement with psychiatric care on mortality in people with schizophrenia is not clear, requiring further investigation.

The strengths of this meta-analysis are the large number of studies (n=43) that met criteria for inclusion, the large number of patients with schizophrenia (2,700,825) and general population controls (730,962,605), and the high quality of the studies included with robust and consistent results even after trim-and-fill analyses. Future studies should focus on larger sample sizes, longitudinal follow-up, standardization of outcomes in reporting mortality, and more robust methods to further elucidate the factors influencing mortality in the schizophrenia population.

Despite the numerous strengths of this meta-analysis, its results must be interpreted within its limitations. First, the non-randomized nature of the observational cohort studies cannot imply causality. Given that mortality in longitudinal studies is relatively rare and of late-onset, and given the constraints of RCTs that include relatively fewer individuals and could potentially exclude many real-world cohorts, modest follow-up durations, high number of dropouts, and exclusion of the more severely mentally and physically ill, RCTs do not represent the best or most feasible study design to establish mortality risk as well as aggravating and protective factors. Longitudinal cohort studies and more specifically nationwide database studies are a more appropriate option compared to RCTs. Nevertheless, there is evidence that RCTs in schizophrenia are a reliable and fairly representative source of data in schizophrenia, at least for the relative ranking of antipsychotic efficacy and tolerability[42]. Nevertheless, people with relevant physical and psychiatric comorbidities and with active suicidality or recent suicide attempt are generally excluded from RCTs, likely reducing mortality estimates vastly in RCTs. Second, although we were able to include 43 individual studies with a large number of individuals with schizophrenia and an even larger number of patients from the general population, some findings were based on subgroup analyses of five or fewer studies. In order to best identify and evaluate specific factors that increase or decrease the existing mortality gap,

additional studies with sex-stratifired results are of particular importance. Third, the inconsistent definition of age groups among the included studies limited our ability to comprehensively analyze the effects of age on all-cause and specific-cause mortality risks. Given that age is one of the most relevant risk factors for mortality overall, reporting of age in both categorical and continuous nature in future studies would clearly be beneficial. Fourth, in some cases the number of the general population control group was not quantified, but instead studies used regional or nationwide control groups restricted to certain time periods and/or age groups. Imprecision may have been introduced as a result of our estimation of the general population based on census based (sub)population numbers at the time of data collection. Fifth, various metrics were used between studies to report mortality. Imprecision may have also been introduced as a result of pooling results using combined risk estimates with different characteristics. However, imprecision was likely low, given that mortality is a relatively rare event, all included studies used the same cohort design, and all studies evaluated the same population of interest. Sixth, no studies analyzed the effect of treatment with an antipsychotic on sex differences in mortality. Seventh, subgroup analyses were limited by the small number of studies in several continents. Lastly, although there was a preference in using risk estimates with an adjusted estimate for potential confounders, we also included unadjusted risk estimates and adjustments that may not have included all/most relevant covariates associated with mortality risk. However, the scope of this meta-analysis was not to isolate the genetic or narrowly illness-related effects of schizophrenia on mortality risk. Instead, we focused on estimating the differential risk of all-cause and cause-specific mortality in individuals with schizophrenia by sex as well as based on different psychological, social, behavioural, and environmental backgrounds compared to the general population and other control groups. Therefore, the potential residual confounding from a statistical standpoint would represent the reality of individuals living with schizophrenia and ensures the generalizability of our findings.

Conclusion

This meta-analysis assessed the all-cause and cause-specific mortality risks in males and females with schizophrenia compared to the general population and other control groups using a large sample and comprehensive approach. Our findings demonstrated that both males and females with schizophrenia experience increased risks of all-cause and cause-specific mortality compared to the general population and focusing on reported aggravating and protective factors. No statistical significant difference in sex-dependent mortality risk emerged except for males being at a significantly higher risk of death due to neurological disorders (dementia). The results of this mortality gap in males and females with schizophrenia were based on data from high-quality studies that were robust and confirmed in multiple subgroup and meta-regression analyses. Most notably, some of the increased mortality risks were associated with specific modifiable risk factors such as ~~smoking and~~ diabetes. These modifiable factors highlight the multidisciplinary approach required in treating people with schizophrenia that involves routine clinician monitoring and patient education. Future studies should focus on larger sample sizes, longitudinal follow-up, and more robust study methodology, reporting results overall and in sex-stratified analyses, to further elucidate factors influencing mortality in this vulnerable population.

Disclosures

MS received honoraria/has been a consultant for AbbVie, Angelini, Lundbeck, Otsuka.

IB received consulting fees from Gedeon Richter and Janssen/Janssen-Cilag; speaker's honoraria from Gedeon Richter, Hikma Pharmaceuticals, Janssen/Janssen-Cilag, KRKA, Lundbeck and Medichem Pharmaceuticals Inc. by Unilab; received research grant from Gedeon Richter; royalties from Oxford University Press.

JT has participated in research projects funded by grants from Janssen-Cilag to his employing institution; he has been a consultant to HLS Therapeutics, Janssen, Orion, Teva, and WebMed Global and received lecture fees from Janssen, Lundbeck and Otsuka.

PG received during the last 5 years fees for presentations at congresses or participation in scientific boards from Biogen, Janssen, Lundbeck, Merk, Otsuka, Richter and Viatris.

R.E.N. has, within the past 3 years, been an investigator for Compass Pharmaceuticals, Janssen-Cilag, Sage and Boehringer-Ingelheim for clinical trials; has received speaking fees from Lundbeck, Teva Pharmaceuticals, Janssen-Cilag and Otsuka Pharmaceuticals; and has acted as advisor to Lundbeck and Janssen-Cilag.

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RIGH has received fees for lecturing from Boehringer-Ingelheim, EASD, Eli Lilly, Encore, Liberum, Novo Nordisk, ROVI and funding for conference attendance from Novo Nordisk and Eli Lilly.

HT has participated in research projects funded by grants from Janssen-Cilag to her employing institution; and she has received lecture fees from Gedeon Richter, Janssen, Lundbeck and Otsuka.

MF received honoraria for his speaker activity from the American Society of Clinical Psychopharmacology (ASCP) and served as a consultant for Angelini, Otsuka, Lundbeck, Sanofi-Aventis, and Boehringer Ingelheim.

BS is on the Editorial Board of Ageing Research Reviews, Mental Health and Physical Activity, The Journal of Evidence Based Medicine, and The Brazilian Journal of Psychiatry. Brendon has received honorarium from a co-edited book on exercise and mental illness (Elsevier), and unrelated advisory work from ASICS, in addition to honorarium and stock options at FitXR LTD.

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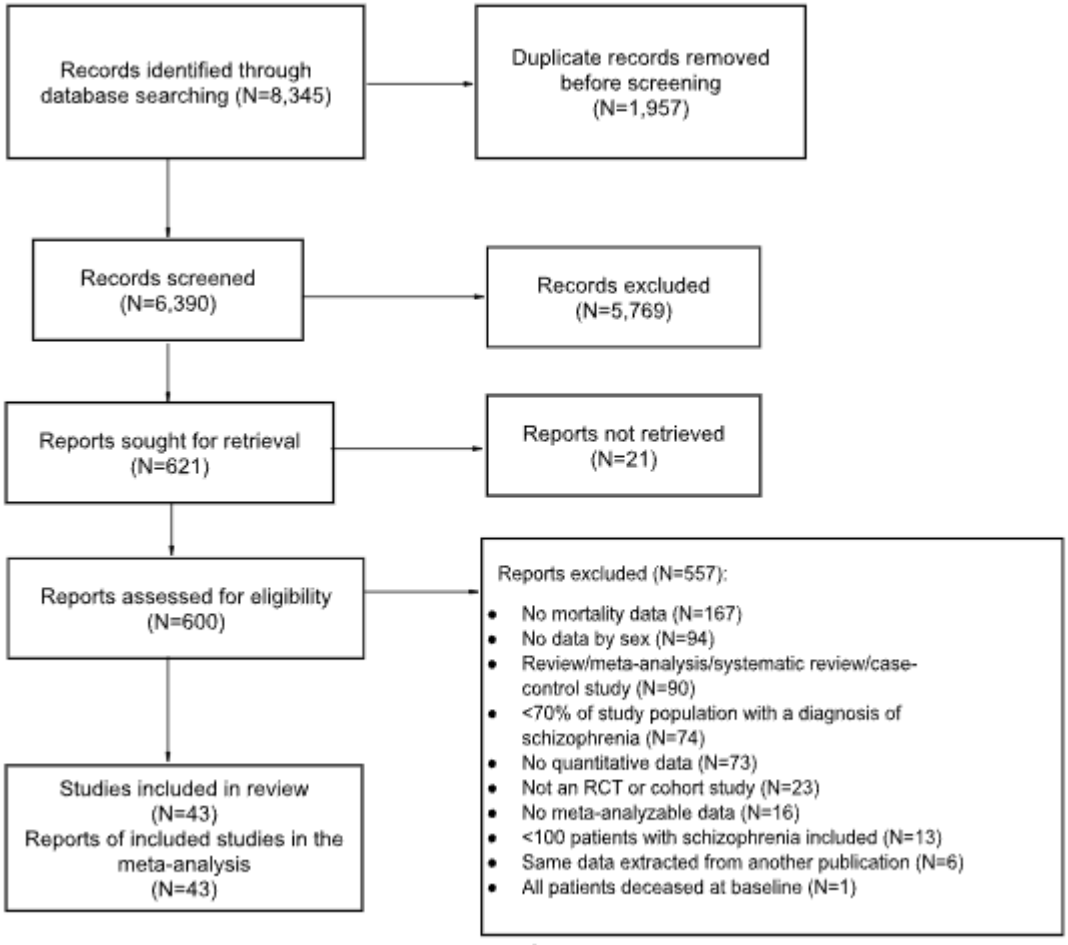

Figure 1: PRISMA Diagram

Table 1: Included studies reporting on risk of all-cause and specific-cause mortality in schizophrenia versus control group, and on mitigating/risk factors

	Country	Years	Comparison	Incident/ prevalent	Number of patients (F / M)	Number of controls (F / M)	Mortality outcomes	NOS
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Amaddeo et al[44]	Italy	1982-1991	Schizophrenia vs. general population	P	37,948 / 27,211	189,381 / 136,059	All-cause	9
Bitter et al[45]	Hungary	2005-2013	Schizophrenia vs. general population	P	147 / 209	1,184,709/1,684,383	All-cause	9
Black & Fisher[46]	US	1970-1988	Schizophrenia vs. general population	P	1602 / 1570	2,869,448	All-cause, natural, undetermined	9
Brown et al[47]	UK	1981-2006	Schizophrenia vs. general population	P	157 / 213	24,328,853	All-cause, suicide, natural, various specific causes, undetermined	9
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Girardi et al[51]	Italy	2008-2018	Schizophrenia vs. general population	P	6,342 / 6,654	2,384,858 / 2,502,146	Suicide, natural, various specific causes	9
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Lahti et al[57]	Finland	1969-2004	Schizophrenia vs. general population	I	87 / 117	5,431 / 7,304	Cardio-cerebrovascular	9
Laursen et al[58]	Denmark, Finland, Sweden	2000-2007	Schizophrenia vs. general population	P	29,406 / 36,682	4,452,796 / 5,359,840	All-cause, natural, cardio-cerebrovascular, undetermined	9
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Mortensen & Juel[61]	Denmark	1957-1986	Schizophrenia vs. general population	P	3,202 / 2,976	1,289,507 / 1,198,493	All-cause, suicide, natural, various specific causes	6
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Abbreviations: NOS – Newcastle-Ottawa scale, I – incident, P – prevalent, NA – not available

Figure 2. Relative risk of all-cause and cause-specific mortality in persons with prevalent plus incident schizophrenia, versus any control group, by sex.

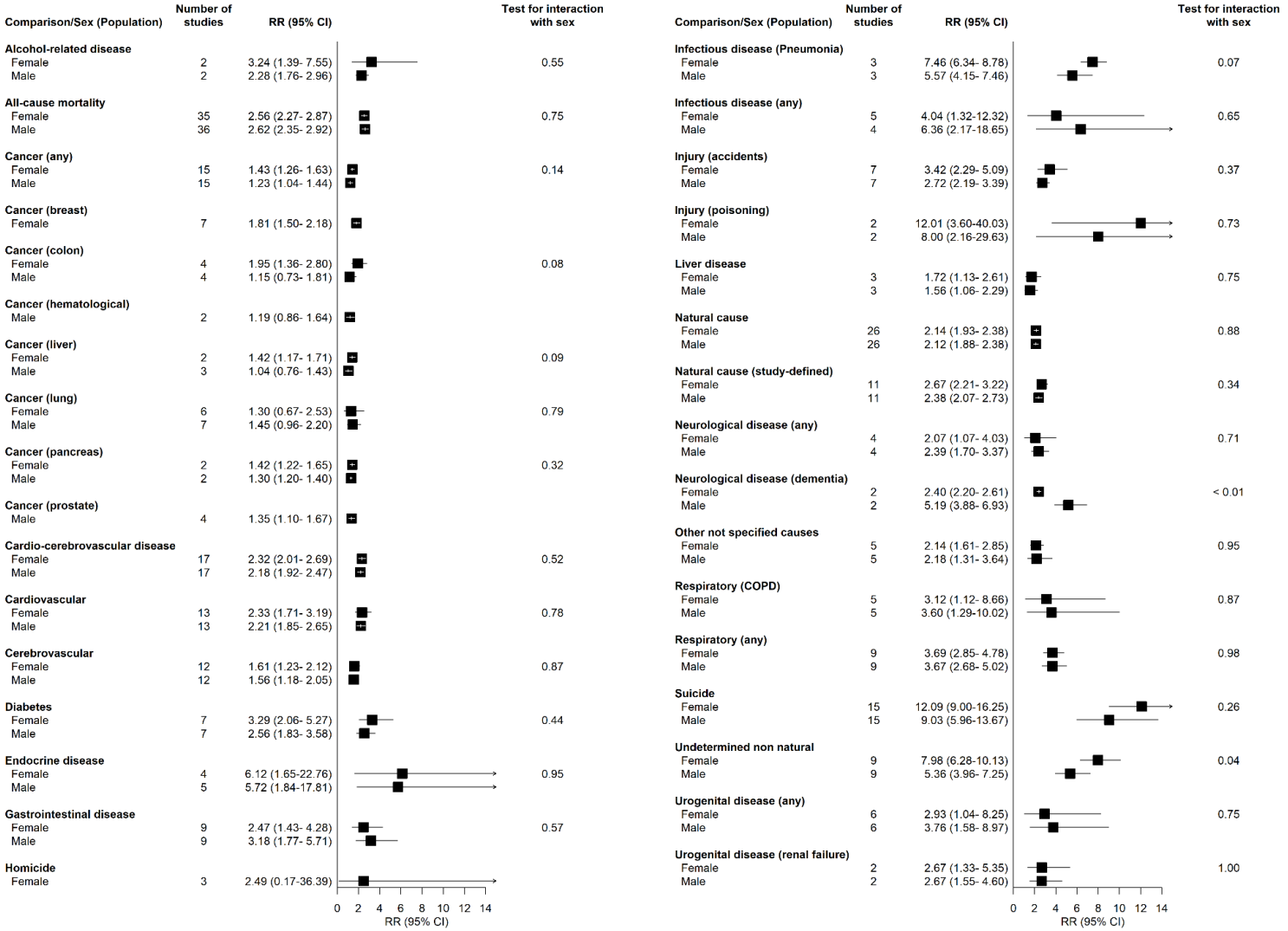

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Figure 1

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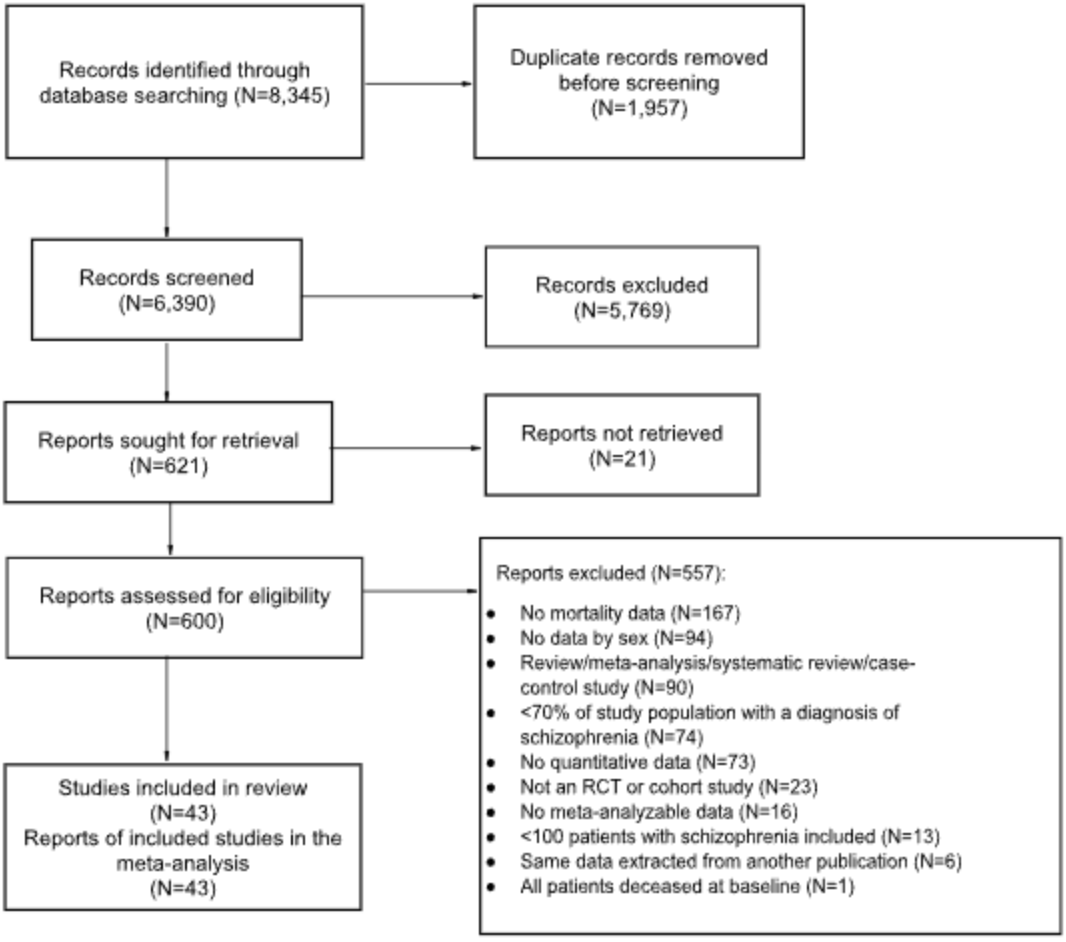
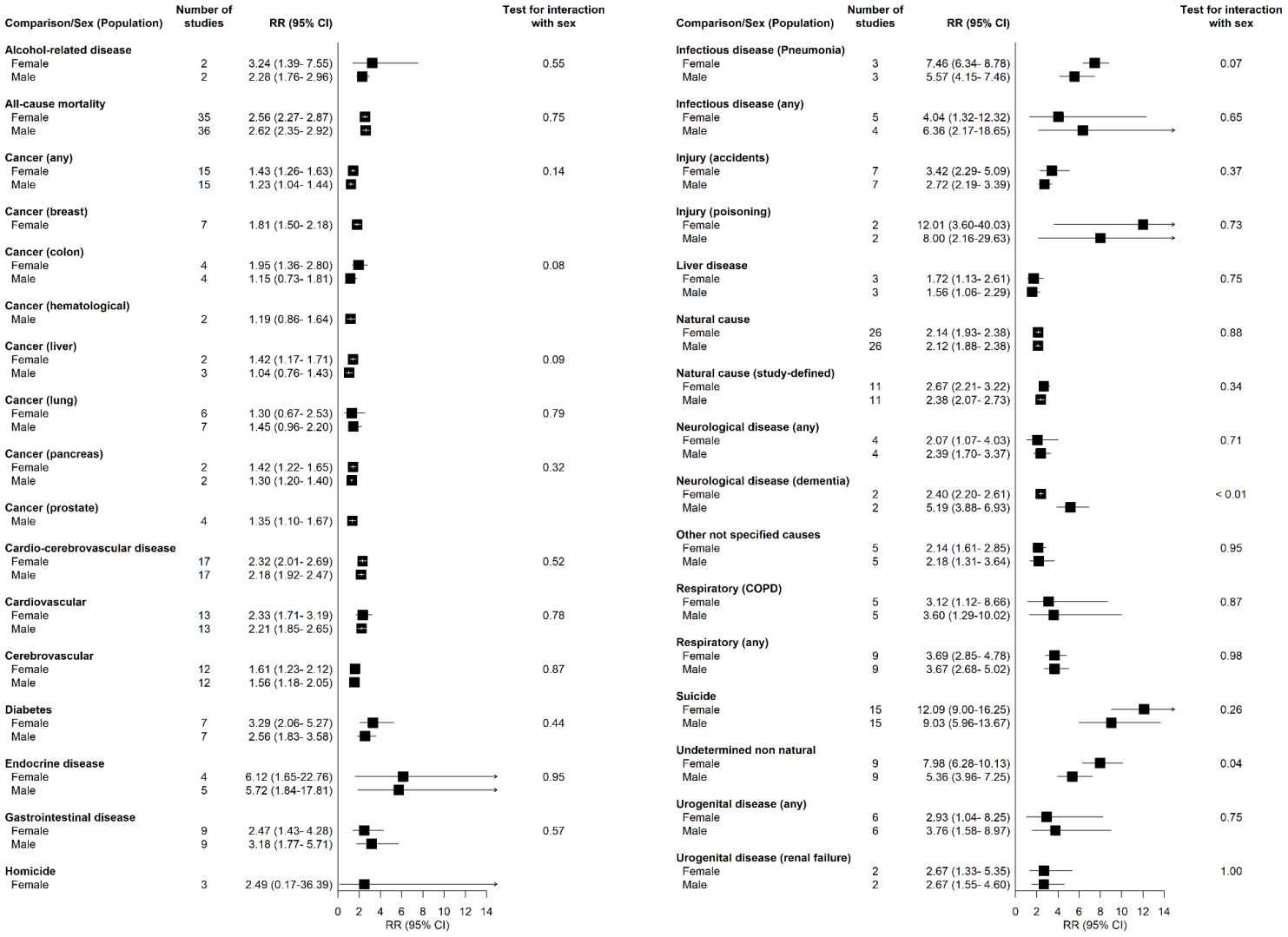


Figure 1: PRISMA Diagram

Figure 2

Click here to access/download;Figure (300 dpi and editable format);Figure 2.docx

Figure 2. Relative risk of all-cause and cause-specific mortality in persons with prevalent plus incident schizophrenia, versus any control group, by sex.



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Marco Solmi and Christoph U. Correll designed the study. Giovanni Croatto undertook the statistical analysis. Nicholas Fabiano, Stanley Wong, and Arnav Gupta wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Disclosures

MS received honoraria/has been a consultant for AbbVie, Angelini, Lundbeck, Otsuka.

IB received consulting fees from Gedeon Richter and Janssen/Janssen-Cilag; speaker's honoraria from Gedeon Richter, Hikma Pharmaceuticals, Janssen/Janssen-Cilag, KRKA, Lundbeck and Medichem Pharmaceuticals Inc. by Unilab; received research grant from Gedeon Richter; royalties from Oxford University Press.

JT has participated in research projects funded by grants from Janssen-Cilag to his employing institution; he has been a consultant to HLS Therapeutics, Janssen, Orion, Teva, and WebMed Global and received lecture fees from Janssen, Lundbeck and Otsuka.

PG received during the last 5 years fees for presentations at congresses or participation in scientific boards from Biogen, Janssen, Lundbeck, Merk, Otsuka, Richter and Viatris.

R.E.N. has, within the past 3 years, been an investigator for Compass Pharmaceuticals, Janssen-Cilag, Sage and Boehringer-Ingelheim for clinical trials; has received speaking fees from Lundbeck, Teva Pharmaceuticals, Janssen-Cilag and Otsuka Pharmaceuticals; and has acted as advisor to Lundbeck and Janssen-Cilag.

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BS is on the Editorial Board of Ageing Research Reviews, Mental Health and Physical Activity, The Journal of Evidence Based Medicine, and The Brazilian Journal of Psychiatry. Brendon has received honorarium from a co-edited book on exercise and mental illness (Elsevier), and unrelated advisory work from ASICS, in addition to honorarium and stock options at FitXR LTD.

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