Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors

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People with schizophrenia die 15-20 years prematurely. Understanding mortality risk and aggravating/attenuating factors is essential to reduce this gap. We conducted a systematic review and random-effects meta-analysis of prospective and retrospective, nationwide and targeted cohort studies assessing mortality risk in people with schizophrenia versus the general population or groups matched for physical comorbidities or groups with different psychiatric disorders, also assessing moderators. Primary outcome was all-cause mortality risk ratio (RR); key secondary outcomes were mortality due to suicide and natural causes. Other secondary outcomes included any other specific-cause mortality. Publication bias, subgroup and meta-regression analyses, and quality assessment (Newcastle-Ottawa Scale) were conducted. Across 135 studies spanning from 1957 to 2021 (schizophrenia: N=4,536,447; general population controls: N=1,115,600,059; other psychiatric illness controls: N=3,827,955), all-cause mortality was increased in people with schizophrenia versus any non-schizophrenia control group (RR=2.52, 95% CI: 2.38-2.68, n=79), with the largest risk in first-episode (RR=7.43, 95% CI: 4.02-13.75, n=2) and incident (i.e., earlier-phase) schizophrenia (RR=3.52, 95% CI: 3.09-4.00, n=7) versus the general population. Specific-cause mortality was highest for suicide or injury-poisoning or undetermined non-natural cause (RR=9.76-8.42), followed by pneumonia among natural causes (RR=7.00, 95% CI: 6.79-7.23), decreasing through infectious or endocrine or respiratory or urogenital or diabetes causes (RR=3 to 4), to alcohol or gastrointestinal or renal or nervous system or cardio-cerebrovascular or all natural causes (RR=2 to 3), and liver or cerebrovascular, or breast or colon or pancreas or any cancer causes (RR=1.33 to 1.96). All-cause mortality increased slightly but significantly with median study year (beta=0.0009, 95% CI: 0.001-0.02, p=0.02). Individuals with schizophrenia <40 years of age had increased all-cause and suicide-related mortality compared to those ≥40 years old, and a higher percentage of females increased suicide-related mortality risk in incident schizophrenia samples. All-cause mortality was higher in incident than prevalent schizophrenia (RR=3.52 vs. 2.86, p=0.009). Comorbid substance use disorder increased all-cause mortality (RR=1.62, 95% CI: 1.47-1.80, n=3). Antipsychotics were protective against all-cause mortality versus no antipsychotic use (RR=0.71, 95% CI: 0.59-0.84, n=11), with largest effects for second-generation long-acting injectable antipsychotics (SGA-LAIs) (RR=0.39, 95% CI: 0.27-0.56, n=3), clozapine (RR=0.43, 95% CI: 0.34-0.55, n=3), any LAI (RR=0.47, 95% CI: 0.39-0.58, n=2), and any SGA (RR=0.53, 95% CI: 0.44-0.63, n=4). Antipsychotics were also protective against natural cause-related mortality, yet first-generation antipsychotics (FGAs) were associated with increased mortality due to suicide and natural cause in incident schizophrenia. Higher study quality and number of variables used to adjust the analyses moderated larger natural-cause mortality risk, and more recent study year moderated larger protective effects of antipsychotics. These results indicate that the excess mortality in schizophrenia is associated with several modifiable factors. Targeting comorbid substance abuse, long-term maintenance antipsychotic treatment and appropriate/earlier use of SGA-LAIs and clozapine could reduce this mortality gap.

Key words: Schizophrenia, psychosis, mortality, suicide, first-episode schizophrenia, antipsychotics, comorbidity, substance use disorder, cardiovascular disease, physical health, long-acting injectable antipsychotics, clozapine

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Schizophrenia is associated with one of the highest mortality risks of all psychiatric disorders[1]. While it is well recognized that individuals with this disorder die prematurely compared to the general population, reasons for the estimated life expectancy gap of 15-20 years are less clear[2].

Modifiable risk factors reportedly associated with greater and earlier mortality in individuals with schizophrenia include poorer lifestyle behaviors, reduced access to physical care, frequent comorbid illnesses, and use – or lack thereof – of antipsychotic medications[3,4]. However, it is unclear whether mortality risk changes in new-onset incident cases or evolves in established prevalent cases. A larger mortality gap has been reported in younger people, not only for suicide but also for physical health causes[5].

In a nationwide study from Finland that compared 34,809-42,712 individuals with schizophrenia with 3,877,129-4,515,838 people from the general population between 1984 and 2014, the higher all-cause standardized mortality ratio for those with schizophrenia compared to the general population remained stable during the 30 years of follow-up (1984=2.6; 2014=2.7)[6]. However, in a Danish nationwide cohort study, the standardized mortality gap appeared to be increasing by 0.03 annually between 1995 and 2014[7].

There is growing evidence supporting the protective effect of antipsychotic treatment versus non-use of antipsychotics in people with schizophrenia[8-10]. Notably, although antipsychotics have been associated with adverse cardiometabolic effects that can increase the risk of cardiovascular death[11-14] – which represents the largest absolute risk for mortality associated with schizophrenia[15-19] – antipsychotic use versus non-use has not been

associated with a greater risk of hospitalization for any physical disease (hazard ratio, HR=1.00, 95% CI: 0.98-1.03), including cardiovascular disorders (HR=1.00, 95% CI: 0.92-1.07)[10]. Rather, antipsychotic use versus non-use has been associated with a significantly decreased risk for death from cardiovascular illness in individuals with schizophrenia (HR=0.62, 95% CI: 0.57-0.67)[10].

This apparent paradox has been explained by healthier lifestyle behaviors, less psychosis-related stress/cortisol increase, and better help-seeking behaviors in antipsychotic-treated individuals. Recently, adherence versus non-adherence to antipsychotics has also been associated with decreased discontinuation risk of antidiabetics (adjusted hazard ratio, aHR=0.56, 95% CI: 0.47-0.66), statins (aHR=0.61, 95% CI: 0.53-0.70), antihypertensives (aHR=0.63, 95% CI: 0.56-0.71), and beta-blockers (aHR=0.79, 95% CI: 0.73-0.87) in within-subject analyses[20].

Additionally, among antipsychotic medications, differential risk attenuation of mortality risk in individuals with schizophrenia has been described[8-10]. For example, a Swedish prospective nationwide study on a register-based cohort followed for a median of 5.7 years reported an approximately 33% reduced mortality risk among individuals who received long-acting injectable antipsychotics (LAIs) compared with equivalent oral antipsychotics[9]. This greater protective effect of LAIs versus oral antipsychotics was substantiated in a Taiwanese nationwide cohort study with a median of 14 years of follow-up, which reported a 34% decreased all-cause mortality risk with LAIs, with an even stronger protective effect (i.e., 47% decreased mortality risk) in subjects switched to an LAI within the first two years of diagnosis of schizophrenia[8].

Finally, use of clozapine, one of the agents with the highest cardiometabolic risk burden[21,22], has also been associated with decreased all-cause mortality risk, such as in a Finnish nationwide database study with a median of 14.1 years of follow-up, where all-cause mortality was reduced by 61% and cardiovascular death risk was decreased by 45% versus non-use of antipsychotics[10]. Consistent with the previously noted association between antipsychotic use and adherence to cardiometabolic treatments, clozapine was associated with the largest reduction among all second-generation antipsychotics (SGAs) regarding discontinuation of statins, antidiabetics and beta-blockers[20].

Increased mortality in individuals with schizophrenia appears to be associated to a large degree with comorbid physical conditions and unhealthy lifestyle behaviors. These individuals have higher rates of cardiovascular risk factors than the general population, including (components of) metabolic syndrome[13] and diabetes[14], as well as sedentary behavior[2] and smoking[23], yet are less likely to receive education regarding smoking cessation and may not receive preventive or acute care for comorbid illnesses comparable to patients without schizophrenia[24-27]. Moreover, in addition to increased cardiovascular risk factors, individuals with schizophrenia also receive lower quality of care for cardiovascular disease[28].

The role of antipsychotics in specific-cause mortality in schizophrenia has not been definitively clarified, and there is still an ongoing debate regarding whether antipsychotic agents reduce overall mortality largely due to decreasing suicide-related mortality risk, while tending to increase natural-cause mortality risk owing to their adverse impact on cardiac repolarization, body weight and other cardiometabolic risk factors[4,29,30], a risk that may be aggravated in older age[31].

To the best of our knowledge, there has been no large-scale, comprehensive meta-analysis that has included several control groups, most relevant specific causes of mortality and antipsychotic treatments, as well as an analysis of factors aggravating or attenuating mortality in individuals with schizophrenia. Most of the prior meta-analyses included fewer than 30 studies. Many studies focused either on one specific causative factor (such as suicide, cardiovascular disease, or use of specific antipsychotic agents) or included schizophrenia among other severe mental illnesses.

To fill this gap, we performed a systematic review and meta-analysis examining risk of all-cause and specific-cause mortality in individuals with schizophrenia versus several control groups, as well as factors associated with increased or attenuated mortality risk in these persons, focusing also on representativeness of the sample, study quality and time trends.

METHODS

Search methods for identification of studies

We conducted a PRISMA 2020-compliant systematic review[32] searching Medline, PubMed and PsycINFO until September 9, 2021, using the search key (schizophrenia AND (mortal* OR death* OR fatal*)) NOT (animals [mesh] NOT humans [mesh]), and complemented it with manual search. The PRISMA 2020 checklist and abstract checklist are provided in the supplementary information.

Study eligibility criteria

Peer-reviewed publications of a cohort study (prospective or retrospective; nationwide or not) were eligible. We included only studies in which ≥70% of the participants had a diagnosis of schizophrenia and in which a minimum of 100 patients with this diagnosis were recruited. Publications had to include quantified reporting – e.g., odds ratio (OR), risk ratio (RR), HR, or raw numbers – of the relationship between schizophrenia diagnosis versus control group and any type of mortality. When a risk or protective factor was present that defined a subgroup of people with schizophrenia, such as cardiac illness or diabetes or substance use disorder comorbidity, only studies where the schizophrenia and control group were matched on that risk or protective factor were included.

We excluded non-cohort studies, such as case-control studies, reviews, meta-analyses and systematic reviews. Publications were also excluded if they did not provide mortality data, quanti-

tative data, or if the data were not meta-analyzable. Publications that contained non-peer-reviewed data (such as proceedings, poster abstracts or posters) were not considered. No language or time restrictions were applied.

Four independent raters (GC, LKS, MS, NS) selected studies and extracted outcome data as well as information on potential effect modifiers. The Newcastle-Ottawa Scale[33] was used to classify quality/risk of bias. When discrepancies occurred, a further rater (CUC) was consulted. Original study authors were contacted to provide missing data.

Outcomes

The primary outcome was RR of all-cause mortality in individuals with schizophrenia versus any control group. Key secondary outcomes were mortality due to suicide and natural causes. Additional secondary outcomes included other specific-cause mortality.

Analyses examined incident plus prevalent cohorts together and either prevalent or incident cohorts separately. Prevalent cases include all individuals living with schizophrenia within a specified timeframe, regardless of when the person was diagnosed with or developed the condition. Incident cases encompass all individuals who are newly identified within the period of observation as having schizophrenia, or all new cases of schizophrenia. Control groups consisted of the general population, regardless of underlying comorbid physical diseases (from here on, "general population"), or control samples matched by physical disease. Patients with schizophrenia were compared with both control populations combined, and with each one separately, whenever possible.

Extraction methodology

Whenever results for different degrees of adjustment of RR were presented, we always used the result that was adjusted for the largest number of variables. Whenever data for both prevalent and incident cohorts were presented, we extracted both. For studies where data were only presented graphically, we extracted the data from the respective figures. For studies that only provided data on the point estimates but did not include the standard deviation or 95% CI, we imputed the 95% CI as the mean of all studies with the available data.

Whenever only raw mortality data were reported, we calculated the mortality ratio by dividing the mortality rate for schizophrenia subjects by the rate for controls. When authors presented data by narrow or broad definitions, we picked the broad definition, to be more conservative and include as many potential deaths as possible. Whenever data on samples overlapping by at least 50% were reported in different publications, we used the data including 95% CIs from the larger sample.

Whenever a subgroup of patients with schizophrenia with a specific condition was the subject of a study (for example, schizophrenia with type 2 diabetes mellitus), the control group had to have that same condition. Whenever the exact number of the control group was not specified, but rather the group was defined by a region, state or country, we took the size of that population at the midpoint of the study period. When the sample size of the control group in subgroup analyses was not specified, we imputed it by applying the same ratio of the group with schizophrenia (e.g., same male to female ratio). In representative studies, if the control group was not provided, we extracted data from census sources matching the time of study.

Data analysis

We conducted a random-effects meta-analysis[34] and calculated the RR of primary and secondary outcomes. Given that the outcome of interest, mortality, is rare (i.e., less than 10%), and that all included studies used the same design and evaluated the same population of interest, we pooled ORs, RRs, HRs and standardized mortality ratios. When an association measure was not available, we used the raw data (i.e., number of events and sample sizes in schizophrenia and control groups) and calculated the unadjusted RR. When both adjusted and unadjusted effect sizes were available, we prioritized adjusted ones.

I^2 was used to measure heterogeneity[35], and Egger's test to assess publication bias[36]. When Egger's test revealed publication bias (i.e., $p<0.1$), we conducted trim and fill analyses, and calculated the fail-safe number[37].

Sources of heterogeneity were explored with meta-regression, sensitivity and subgroup analyses. Random-effects meta-regression analyses were conducted with 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.

RESULTS

Search results

An initial search retrieved 8,345 abstracts; removal of duplicates resulted in 6,390 abstracts for review. Of these, a total of 135

studies[5-10,38-166] were included, after excluding 463 articles upon full text assessment (see Figure 1, Table 1 and supplementary information). We ultimately included 4,536,447 individuals with schizophrenia who were compared with 1,115,600,059 control subjects from the general population.

Studies compared subjects with schizophrenia (N=3,494,716) versus the general population (N=1,097,856,754) (n=72); schizophrenia subjects (N=29,616) versus general population groups matched for physical comorbidities (N=17,733,923) (n=30); and schizophrenia individuals (N=19,011) versus groups with other mental disorders (N=3,827,955) (n=6). Additionally, 27 studies (N=994,273) investigated the association between present/absent risk/protective factors and mortality within two groups of subjects with schizophrenia.

Studies were conducted in the US (n=20), Denmark (n=19), Taiwan (n=17), Sweden (n=10), Finland (n=9), Canada (n=9), the UK (n=9), China (n=6), Israel (n=5), France (n=4); 3 each in Italy, Hong Kong, the Netherlands, Korea, or multiple countries; 2 each in Australia, Japan and Spain; and one each in Ethiopia, Germany, Hungary, India, Norway and Singapore.

There were 22 (16.3%) prospective and 113 (83.7%) retrospective cohort studies, with 85 (63.0%) being nationwide database studies. Study periods ranged from 1957 to 2021.

Nearly one-third of the studies (32.6%) included in the meta-analysis did not report an age range. When an age range was provided, 23 studies (17.0%) reported the minimal age as >15 years and another 22 studies (16.3%) used >18 years. The remaining 46 studies listed widely heterogeneous age ranges, with upper and lower extremes ranging from 10 to 109 years old.

Altogether, 20 studies (14.8%) exclusively or also included incident (i.e., earlier-phase) cases with schizophrenia, two studies (1.5%) included first-episode patients, and five studies (3.7%) focused on treatment-resistant schizophrenia. Regarding outcomes, 49 studies (36.3%) only reported on all-cause mortality, 25 (18.5%) only on a specific cause of mortality, and 63 (46.7%) on both (see Table 1).

Primary outcome: all-cause mortality

Across 79 studies, schizophrenia was associated with significantly higher all-cause mortality as compared with any control group (RR=2.52, 95% CI: 2.38-2.68, I^2=99.7%) (see Table 2). Patients with schizophrenia had substantially higher all-cause mortality versus the general population (RR=2.94, 95% CI: 2.75-3.13, I^2=99.7%, n=57) (see Table 2 and Figure 2). The association

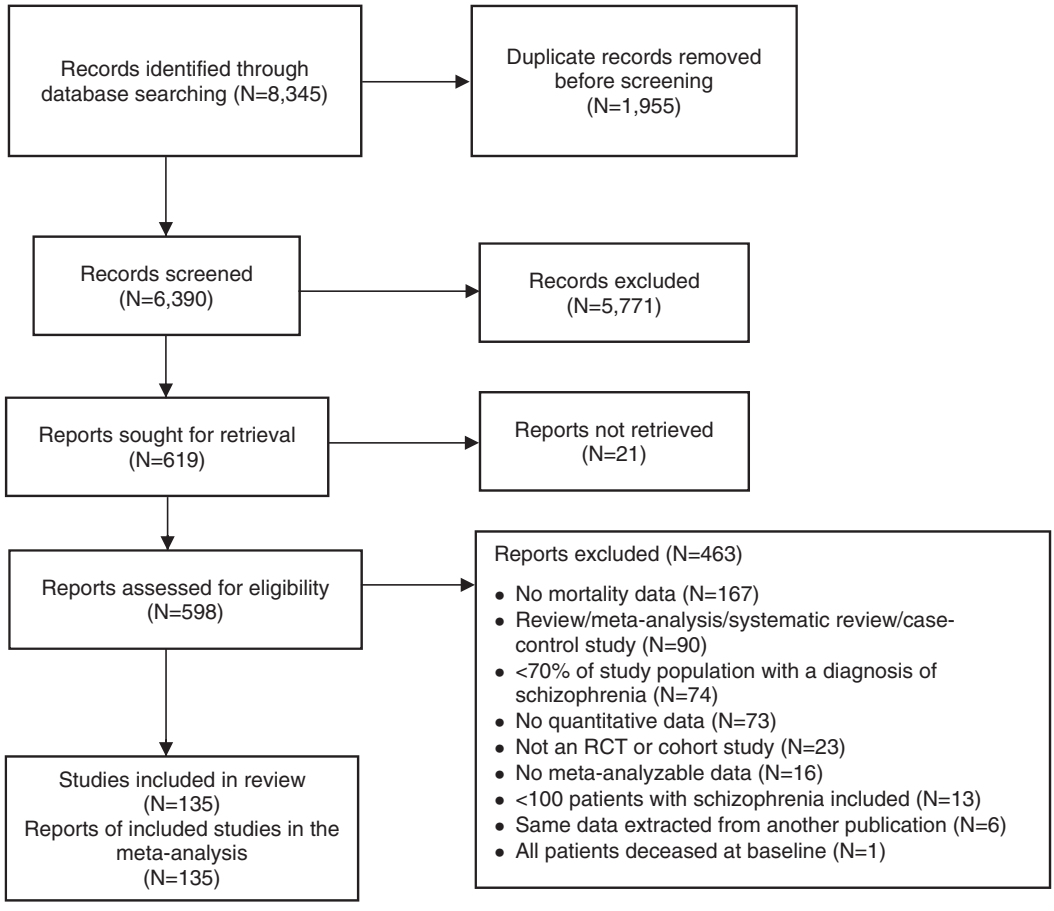

Figure 1 PRISMA flow chart. RCT – randomized controlled trial

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	Number of controls	Mortality outcomes	NOS
Alleback & Wistedt[38]	Sweden	1971-1981	Schizophrenia vs. general population	P	1,190	16,902	All-cause, suicide, various specific causes, undetermined	9
Amaddeo et al[39]	Italy	1982-1991	Schizophrenia vs. general population	P	3,172	153,352	All-cause	9
Attar et al[40]	Denmark	1995-2013	Schizophrenia vs. general population	P	726	2,178	Cardio-cerebrovascular	9
Bagewadi et al[41]	India	2009-2011	Schizophrenia vs. general population	P	325	NA	All-cause	9
Berardi et al[42]	Italy	2008-2017	Schizophrenia vs. general population	P	7,940	4,250,075	All-cause, natural, various specific causes	9
Bitter et al[5]	Hungary	2005-2013	Schizophrenia vs. general population	P	65,165	390,599	All-cause	9
Black & Fisher[43]	US	1970-1988	Schizophrenia vs. general population	P	356	2,869,448	All-cause, natural, undetermined	9
Bouza et al[44]	Spain	2004-2004	Schizophrenia vs. general population	P	16,776	3,951,000	All-cause	9
Bralet et al[45]	France	1991-1999	Schizophrenia vs. general population	P	150	552,303	All-cause	8
Brown et al[46]	UK	1981-2006	Schizophrenia vs. general population	P	370	24,328,853	All-cause, suicide, natural, various specific causes, undetermined	9
Buda et al[47]	US	1934-1974	Schizophrenia vs. general population	P	332	NA	Suicide, natural, various specific causes, undetermined	9
Castagnini et al[48]	Denmark	1995-2008	Schizophrenia vs. general population	I	4,576	3,565,833	All-cause, suicide, natural, various specific causes, undetermined	9
Chan et al[49]	Hong Kong	2006-2016	Schizophrenia vs. general population	I	3,105	13,545	Natural, various specific causes	9
Chen et al[50]	Taiwan	2000-2016	Schizophrenia vs. general population	P	170,322	22,710,322	Cardiovascular	9
Chen et al[51]	Taiwan	1999-2010	Schizophrenia vs. general population	P	7,531	22,547,531	All-cause	9
Chen et al[52]	Taiwan	1998-2004	Schizophrenia vs. general population	I	5,515	24,238	All-cause, natural, undetermined	9
Cheng et al[53]	Taiwan	1998-2008	Schizophrenia vs. general population	P	2,457	22,561,450	All-cause, natural, various specific causes, undetermined	9
Crump et al[54]	Sweden	2001-2008	Schizophrenia vs. general population	P	25,359	6,908,922	All-cause, injury, other	9
Curkendall et al[55]	Canada	1994-1998	Schizophrenia vs. general population	P	3,022	13,110	All-cause, natural	8
Daumit et al[56]	US	1992-2001	Schizophrenia vs. general population	P	2,303	5,171,640	Cardiovascular	8
Dickerson et al[57]	US	1999-2009	Schizophrenia vs. general population	P	517	2,448,017	Natural	7
Dickerson et al[58]	US	1999-2012	Schizophrenia vs. general population	P	710	182,165,000	Natural	9
Enger et al[59]	US	1995-1999	Schizophrenia vs. general population	P	1,920	11,520	All-cause, natural, cardiovascular	9

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

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Fors et al[60]	Sweden	1991-2000	Schizophrenia vs. general population	P	255	1,530	All-cause, natural, cardiovascular, undetermined	9
Gatov et al[61]	Canada	1993-2012	Schizophrenia vs. general population	P	34,338	8,793,478	All-cause	9
Girardi et al[62]	Italy	2008-2018	Schizophrenia vs. general population	P	12,196	9,787,004	Suicide, natural, various specific causes	9
Guan et al[63]	The Netherlands	1999-2007	Schizophrenia vs. general population	P	4,590	23,062	All-cause, suicide, natural, other	9
Haugland et al[64]	US	1975-1978	Schizophrenia vs. general population	P	351	NA	All-cause	9
Hayes et al[65]	UK	2000-2014	Schizophrenia vs. general population	P	22,497	241,884	All-cause, suicide, cardiovascular	9
Heila et al[66]	Finland	1980-1996	Schizophrenia vs. general population	P	58,761	7,314,595	All-cause, suicide	9
Hellemose et al[67]	Denmark	1970-2011	Schizophrenia vs. general population	I	17,530	5,389,084	Other	9
Hennessy et al[68]	US	1993-1996	Schizophrenia vs. general population	P	136,927	29,086	Cardiovascular	7
Hewer & Rössler[69]	Germany	1984-1986	Schizophrenia vs. general population	P	8,927	61,057,927	All-cause, suicide, natural	9
Kilbourne et al[70]	US	1999-2006	Schizophrenia vs. general population	P	22,817	38,859	Cardiovascular	9
Kim et al[71]	Korea	2002-2013	Schizophrenia vs. general population	I	9,387	1,025,340	All-cause	9
Kiviniemi et al[72]	Finland	1995-2001	Schizophrenia vs. general population	I	7,591	5,120,000	All-cause, suicide, natural, various specific causes, undetermined	9
Kredentser et al[73]	Canada	1999-2008	Schizophrenia vs. general population	P	9,038	978,128	All-cause, suicide, natural, various specific causes	9
Kugathasan et al[74]	Denmark	1995-2015	Schizophrenia vs. general population	P	30,210	5,432,821	All-cause, natural, various specific causes	9
Kugathasan et al[75]	UK	2013-2017	Schizophrenia vs. general population	P	36,425	218,297	Various specific causes	9
Kurdyak et al[76]	Canada	2007-2010	Schizophrenia vs. general population	I	13,385	12,851,821	All-cause, suicide, injury, other	9
Lahti et al[77]	Finland	1969-2004	Schizophrenia vs. general population	I	204	12,735	Cardio-cerebrovascular	9
Laursen et al[78]	Denmark, Finland, Sweden	2000-2007	Schizophrenia vs. general population	P	66,088	19,691,360	All-cause, natural, cardio-cerebrovascular, undetermined	9
Laursen et al[79]	Denmark	1992-2006	Schizophrenia vs. general population	P	30,614	8,999,225	Cardiovascular	9
Laursen et al[80]	Denmark	1995-2007	Schizophrenia vs. general population	P	16,079	4,873,115	Natural	9
Lomholt et al[7]	Denmark	1995-2014	Schizophrenia vs. general population	P	38,500	6,176,414	All-cause	9
Luo et al[81]	China	2007-2010	Schizophrenia vs. general population	P	2,071	1,909,205	All-cause	9
Meesters et al[82]	The Netherlands	2008-2012	Schizophrenia vs. general population	P	157	25,788	All-cause	9

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

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Mortensen & Juel[83]	Denmark	1957-1986	Schizophrenia vs. general population	P	6,178	2,494,178	All-cause, suicide, natural, various specific causes	6
Mortensen & Juel[84]	Denmark	1970-1987	Schizophrenia vs. general population	I	9,156	5,131,156	All-cause, suicide, natural, various specific causes	6
Newman & Bland[85]	Canada	1976-1985	Schizophrenia vs. general population	P	3,623	4,479,623	All-cause, suicide, natural, various specific causes	6
Nielsen et al[86]	Denmark	1980-2010	Schizophrenia vs. general population	P	14,974	1,326,393	All-cause	9
Olfson et al[87]	US	2001-2007	Schizophrenia vs. general population	I	1,138,853	173,699,853	All-cause, suicide, natural, various specific causes	9
Olfson et al[88]	US	2007-2016	Schizophrenia vs. general population	P	668,836	311,580,000	Suicide, other non-natural	9
Ösby et al[89]	Sweden	1973-1995	Schizophrenia vs. general population	I	7,784	1,792,216	All-cause, suicide, natural, various specific causes, undetermined	9
Pan et al[90]	Taiwan	2001-2016	Schizophrenia vs. general population	P	170,322	23,000,000	Suicide, other non-natural	9
Pan et al[91]	Taiwan	2005-2008 2010-2013	Schizophrenia vs. general population	P	95,632 104,561	2,292,000 229,200	All-cause, suicide, natural, various specific causes	9
Phillippe et al[92]	France	1993-2002	Schizophrenia vs. general population	P	3,470	33,264,661	All-cause, natural	6
Phillips et al[93]	China	1995-1999	Schizophrenia vs. general population	P	102	19,121	Suicide, natural	9
Ran et al[94]	China	1994-2004	Schizophrenia vs. general population	P	500	123,562	All-cause, suicide, injury, natural	9
Ruschena et al[95]	Australia	1995-1995	Schizophrenia vs. general population	P	25,202	35,361,211	All-cause, suicide, injury, natural, undetermined	7
Talaslahti et al[96]	Finland	1992-2008	Schizophrenia vs. general population	P	9,461	1,891,543	All-cause, suicide, natural, various specific causes	9
Tanskanen et al[6]	Finland	1984 1994 2014	Schizophrenia vs. general population	P	159,858	16,701,991	Suicide, natural, cardiovascular, other	9
Teferra et al[97]	Ethiopia	2001-2005	Schizophrenia vs. general population	P	307	68,685	All-cause	9
Tenback et al[98]	The Netherlands	2006-2008	Schizophrenia vs. general population	P	7,415	105,141	All-cause	9
Tokuda et al[99]	Japan	1987-2004	Schizophrenia vs. general population	P	1,108	190,157	All-cause	9
Tornianen et al[100]	Sweden	2006-2010	Schizophrenia vs. general population	I	48,441	1,032,760	All-cause, suicide, various specific causes	9
Tran et al[101]	France	1993-2003	Schizophrenia vs. general population	P	3,434	3,434	Cardiovascular	9
Westman et al[102]	Sweden	1987-2010	Schizophrenia vs. general population	P	46,911	10,678,728	All-cause, suicide, injury, cardio-cerebrovascular, other	9
Wood et al[103]	US	1972-1976	Schizophrenia vs. general population	P	8,779	235,558	All-cause	9
Yung et al[104]	China	2006-2016	Schizophrenia vs. general population	P	817	8,987	All-cause, cerebrovascular	9
Yung et al[105]	Hong Kong	2006-2016	Schizophrenia vs. general population	P	46,896	7,500,000	All-cause, various specific causes	9

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

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Zilber et al[106]	Israel	1978-1983	Schizophrenia vs. general population	P	9,282	NA	All-cause, suicide, natural, various specific causes	9
Attar et al[107]	Sweden	2000-2018	Schizophrenia vs. general population with acute myocardial infarction	P	1,008	285,325	All-cause	9
Babidge et al[108]	Australia	1988-1998	Schizophrenia vs. no schizophrenia homeless	P	455	708	All-cause	9
Bodén et al[109]	Sweden	1997-2010	Schizophrenia vs. general population with acute myocardial infarction	P	541	209,592	All-cause, cardiovascular	9
Bradford et al[110]	US	2001-2005	Schizophrenia vs. general population with lung cancer	P	835	34,644	All-cause	9
Chan et al[111]	Hong Kong	2001-2016	Schizophrenia vs. general population with diabetes mellitus	P	6,991	75,673	All-cause, diabetes mellitus	9
Chong et al[112]	Singapore	2000-2006	Schizophrenia with vs. without tardive dyskinesia	P	241	561	All-cause, natural, various specific causes	9
Chou et al[113]	Taiwan	2000-2008	Schizophrenia vs. no schizophrenia with cancer	P	1,131	6,377	All-cause	9
Chou et al[114]	Taiwan	2000-2008	Schizophrenia vs. general population with pneumonia	P	6,040	13,878	All-cause	9
Closson et al[115]	Canada	1998-2012	Schizophrenia vs. general population with HIV	P	835	13,331	All-cause	9
Crump et al[116]	Sweden	2003-2009	Schizophrenia vs. general population with ischemic heart disease or cancer	P	8,277	6,097,834	All-cause	9
Druss et al[117]	US	1994-1995	Schizophrenia vs. general population with acute myocardial infarction	P	161	88,241	All-cause	9
Fleetwood et al[118]	UK	1991-2014	Schizophrenia vs. no schizophrenia with acute myocardial infarction	P	923	235,310	Cardiovascular	9
Fond et al[119]	France	2020-2020	Schizophrenia vs. general population with COVID	P	823	50,750	COVID	9
Guerrero Fernandez de Alba et al[120]	Spain	2012-2015	Schizophrenia vs. general population with diabetes mellitus	P	931	52,266	All-cause	9
Hauck et al[121]	Canada	2008-2015	Schizophrenia vs. general population with myocardial infarction	P	1,145	108,610	All-cause	9
Jeon et al[122]	Korea	2019-2020	Schizophrenia vs. general population with COVID	P	159	2,976	COVID	9
Kang et al[123]	Taiwan	2002-2004	Schizophrenia vs. general population with stroke	P	485	2,910	Cerebrovascular	9
Kapral et al[124]	Canada	2002-2017	Schizophrenia vs. no schizophrenia with stroke	P	612	52,473	Cerebrovascular, other	9
Kershenbaum et al[125]	UK	2013-2019	Schizophrenia vs. anxiety disorders	P	238	1,115	All-cause	9

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

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Kugathasan et al[126]	Denmark	1995-2015	Schizophrenia vs. general population with myocardial infarction	P	631	101,510	All-cause	9
Kurdyak et al[127]	Canada	2002-2006	Schizophrenia vs. general population with acute myocardial infarction	P	842	71,668	Cardiovascular	9
Laursen et al[128]	Denmark	1998-2008	Schizophrenia vs. general population with stroke	P	3,660	877,507	All-cause, cardiovascular, undetermined	9
Liao et al[129]	Taiwan	2004-2007	Schizophrenia vs. general population with surgery	P	8,967	44,835	Other	9
Mohamed et al[130]	US	2004-2014	Schizophrenia vs. other severe mental illness vs. no severe mental illness with myocardial infarction	P	23,582	6,322,796	Cardiovascular	9
Shen et al[131]	Taiwan	2005-2007	Schizophrenia vs. general population in intensive care unit	P	203	2,239	All-cause	9
Sögaard et al[132]	Denmark	2000-2015	Schizophrenia vs. general population with atrial fibrillation	P	534	2,552,772	Cardiovascular	9
Toender et al[133]	Denmark	1999-2017	Schizophrenia vs. general population with diabetes mellitus	P	1,004	184,470	All-cause, diabetes mellitus, other	9
Tsai et al[134]	Taiwan	1999-2008	Schizophrenia vs. general population with stroke	P	1,377	4,329	All-cause	9
Tsai et al[135]	Taiwan	1999-2010	Schizophrenia vs. general population with osteoporotic fractures	P	30,335	151,675	All-cause	9
Tzur Bitan et al[136]	Israel	2020-2021	Schizophrenia vs. no schizophrenia with COVID	P	25,539	51,078	COVID	8
Wellejus Albertsen et al[137]	Denmark	2000-2013	Schizophrenia vs. general population with acute myocardial infarction	P	1,160	36,685	Cardiovascular	9
Alaräisänen et al[138]	Finland	1997-2005	Schizophrenia vs. other mental disorder	I	100	422	Suicide	9
Dickerson et al[139]	US	1999-2018	Schizophrenia vs. bipolar disorder or major depressive disorder	P	861	1,745	Natural	9
Hayes et al[140]	UK	2007-2010	Schizophrenia vs. bipolar disorder	P	4,270	6,109	All-cause	9
Kodesh et al[141]	Israel	2002-2012	With vs. without very late onset schizophrenia	P	329	94,120	All-cause	9
Chen et al[142]	Taiwan	1998-2008	Schizophrenia on SGA vs. FGA	I	812	1,624	All-cause	9
Cho et al[143]	UK	2008-2015	TRS with vs. without clozapine	TRS	1,025	2,817	All-cause	9
Cullen et al[144]	US	1994-2004	Schizophrenia with or without annual antipsychotic continuity	P	2,132	-	All-cause, suicide, cardiovascular	9
Dickerson et al[145]	US	1999-2004	Schizophrenia with vs. without Toxoplasma	P	358	-	Natural	9

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

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Fontanella et al[146]	US	2006-2013	Schizophrenia with vs. without benzodiazepines with or without antipsychotics	P	5,212	32,694	All-cause, suicide, natural	9
Funayama et al[147]	Japan	1999-2016	Schizophrenia with vs. without catatonia	P	140	1,710	All-cause	9
Hayes et al[148]	UK	2007-2011	TRS with vs. without clozapine	TRS	617	9,437	All-cause	9
Hjorthoj et al[149]	Denmark	1969-2013	Schizophrenia with vs. without substance use disorder	P	29,549	41,470	All-cause, suicide, various specific causes	9
Horsdal et al[150]	Denmark	2000-2012	Schizophrenia with vs. without abnormal C-reactive protein or white blood cell levels	I	208	1,025	All-cause	9
Huang et al[8]	Taiwan	2002-2017	Schizophrenia with oral vs. LAI antipsychotic	I	2,614	2,614	Suicide, natural	9
Kadra et al[151]	UK	2007-2014	Schizophrenia vs. bipolar disorder	P	5,896	7,782	All-cause	9
Kiviniemi et al[152]	Finland	1998-2003	First-episode schizophrenia with or without antipsychotics	I	5,266	6,713	All-cause, suicide, cardiovascular	9
Kugathasan et al[153]	Denmark	1980-2015	Schizophrenia with vs. without physical health multimorbidity	P	9,775	1,798	All-cause	9
Lahteenvuo et al[154]	Finland, Sweden	1972-2007 2006-2016	Schizophrenia with vs. without substance use disorder	P	8,110 4,514	30,860 14,616	Suicide, injury, natural	9
Liu et al[155]	China	2006-2010	Schizophrenia vs. other mental disorders	P	7,628	3,810,782	All-cause	9
Oh et al[156]	Korea	2003-2017	Schizophrenia with vs. without antipsychotics	P	77,139	86,923	All-cause, suicide, various specific causes	9
Pridan et al[157]	Israel	2007-2012	TRS with vs. without clozapine	TRS	43	527	All-cause	9
Ran et al[158]	China	1994-2015	Men vs. women and older vs. younger people with schizophrenia	P	510	123,062	All-cause, suicide, natural, other	9
Strom et al[159]	Multicountry	2002-2006	Schizophrenia on ziprasidone vs. olanzapine	P	9,077	18,154	All-cause, suicide, cardiovascular, other	9
Strømme et al[160]	Norway	2005-2014	Schizophrenia with vs. without antipsychotics	P	101	696	All-cause	9
Stroup et al[161]	US	2001-2009	TRS with vs. without clozapine	TRS	3,123	6,246	All-cause	9
Taipale et al[9]	Sweden	2006-2013	Schizophrenia with vs. without antipsychotics	P I	34,426	-	All-cause	9
Taipale et al[10]	Finland	1996-2015	Schizophrenia with vs. without antipsychotics	P I	62,250	-	All-cause, suicide, cardiovascular	9
Tang et al[162]	Taiwan	2001-2015	Schizophrenia on oral vs. LAI antipsychotics	P	58,615	87,247	Cardiovascular	9

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

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Taub et al[163]	Israel	2012-2014	Schizophrenia on clozapine with vs. without physical illness	P	2,406	1,817	All-cause	9
Tiihonen et al[164]	Finland	2000-2007	Schizophrenia with vs. without antipsychotics, antidepressants or benzodiazepines	I	2,192	2,588	All-cause	9
Wimberley et al[165]	Denmark	1996-2013	TRS with vs. without clozapine	TRS	1,372	2,370	All-cause, suicide, natural, other	9
Wu & Shur-Fen Gau[166]	Taiwan	2001-2012	Schizophrenia with vs. without antipsychotics or benzodiazepines	P	32,512	68,718	All-cause	9

NOS – Newcastle-Ottawa Scale, I – incident, P – prevalent, TRS – treatment-resistant schizophrenia, NA – not available, SGA – second generation antipsychotic, FGA – first generation antipsychotic, LAI – long-acting injectable antipsychotic

was the highest in two studies specifically including individuals with first-episode schizophrenia (RR=7.43, 95% CI: 4.02-13.75, I^2=93.0%), and significantly higher in incident than prevalent schizophrenia (RR=3.52, 95% CI: 3.09-4.00, I^2=97.1%, n=7 vs. RR=2.86, 95% CI: 2.62-3.12, I^2=99.67, n=50, p=0.009) (see Table 2, Figures 3-4 and supplementary information).

Compared with controls matched for physical diseases, the mortality risk of individuals with schizophrenia was attenuated but still significant (RR=1.66, 95% CI: 1.42-1.94, I^2=97.2%, n=22) (see Table 2). Specifically, individuals with schizophrenia had significantly higher mortality compared with controls matched for acute myocardial infarction (RR=1.82, 95% CI: 1.49-2.22, I^2=83.1%, n=6), diabetes mellitus (RR=1.91, 95% CI: 1.08-3.38, I^2=99.4, n=4), and stroke (RR=1.35, 95% CI: 1.22-1.50, I^2=0%, n=2) (see Table 2).

No significantly increased mortality risk emerged when schizophrenia was compared with other psychiatric disorders, except for bipolar disorder (RR=1.26, 95% CI: 1.03-1.53, I^2=25.4%, n=3) (see Table 2).

Regarding risk and protective factors for all-cause mortality, having a substance use disorder comorbid with schizophrenia increased mortality (RR=1.62, 95% CI: 1.47-1.80, I^2=57.4%, n=3) (see Table 2).

Wherever publication bias was detected, we conducted trim and fill analyses, which confirmed the magnitude and significance of the findings in the primary analyses, with a fail-safe N ranging from 545 to 27,164,601 (see also supplementary information).

Key secondary outcomes: suicide-related mortality and natural causes of mortality

Suicide-related mortality

Across 28 studies, schizophrenia was associated with increased mortality by suicide compared with the general population (RR=9.76, 95% CI: 7.60-12.55, I^2=99.5%) (see Table 2 and Figure 2), suggesting that suicide is the greatest relative risk factor for mortality in individuals with schizophrenia. There was a numerically but not statistically significantly greater suicide-related mortality among the incident versus prevalent cohort (RR=12.7, 95% CI: 5.25-30.53, I^2=99.8, n=5 vs. RR=9.28, 95% CI: 7.31-11.78, I^2=98.8%, n=23, p=0.51) (see Table 2, Figures 3-4 and supplementary information).

Wherever publication bias was detected, we conducted trim and fill analyses, which confirmed the magnitude and significance of the primary findings, with a fail-safe N ranging from 25,581 to 229,490 (see also supplementary information).

Natural causes of mortality

Across 59 studies, schizophrenia was associated with higher natural-cause mortality (which excludes mortality due to suicide or accident or poisoning) compared with either the general population or control groups matched for a physical disease (RR=2.00, 95% CI: 1.85-2.15, I^2=99.5%) (see Table 2).

Higher natural-cause mortality was confirmed across 44 studies involving comparisons with the general population (RR=2.16, 95% CI: 1.99-2.36, I^2=99.6%), without differences between incident and prevalent schizophrenia (RR=2.15, 95% CI: 1.86-2.48, I^2=94.6, n=6 vs. RR=2.15, 95% CI: 1.96-2.37, I^2=99.1%, n=38, p=0.939) (see Table 2, Figures 3-4 and supplementary information).

Across 16 studies involving prevalent populations with physical disease-matched controls, natural-cause mortality risk was also significantly increased (RR=1.56, 95% CI: 1.35-1.82, I^2=94.0%), including specifically matched patients with acute myocardial infarction (RR=1.66, 95% CI: 1.24-2.22, I^2=96.4%, n=5) (see Table 2).

Wherever publication bias was detected, we conducted trim

Table 2 All-cause and cause-specific mortality risk in schizophrenia versus control groups

	Incident/ prevalent	N. studies	Risk ratio	95% CI	p	I^2	Egger's p
All-cause mortality							
Schizophrenia vs. any other population	I + P	79	**2.523**	**2.377-2.678**	**0.000**	99.7	0.001
	P	72	**2.432**	**2.253-2.626**	**0.000**	99.591	0.690
First-episode schizophrenia vs. general population	I	2	**7.433**	**4.017-13.754**	**0.000**	92.965	NA
Schizophrenia vs. general population	I + P	57	**2.938**	**2.753-3.135**	**0.000**	99.733	0.050
	I	7	**3.516**	**3.092-3.998**	**0.000**	97.114	0.840
	P	50	**2.859**	**2.622-3.117**	**0.000**	99.669	0.360
Schizophrenia vs. no schizophrenia (all matched)	P	22	**1.664**	**1.425-1.943**	**0.000**	97.226	0.530
Schizophrenia vs. no schizophrenia (matched for acute myocardial infarction)	P	6	**1.821**	**1.491-2.224**	**0.000**	83.146	0.840
Schizophrenia vs. no schizophrenia (matched for diabetes mellitus)	P	4	**1.913**	**1.082-3.380**	**0.026**	99.414	0.500
Schizophrenia vs. no schizophrenia (matched for stroke)	P	2	**1.351**	**1.219-1.498**	**0.000**	0.000	NA
Schizophrenia vs. other mental disorder	I + P	5	2.130	0.648-7.002	0.213	99.349	0.110
	P	5	2.130	0.648-7.002	0.213	99.349	0.110
Schizophrenia vs. bipolar disorder	P	3	**1.257**	**1.031-1.533**	**0.023**	25.362	0.210
Schizophrenia with vs. without substance use disorder	P	3	**1.625**	**1.467-1.799**	**0.000**	57.443	0.680
Mortality due to suicide							
Schizophrenia vs. general population	I + P	28	**9.764**	**7.598-12.549**	**0.000**	99.478	0.030
	I	5	**12.654**	**5.245-30.530**	**0.000**	99.802	0.050
	P	23	**9.281**	**7.311-11.782**	**0.000**	98.793	0.680
Mortality due to natural cause							
Schizophrenia vs. any other population	I + P	59	**1.996**	**1.851-2.153**	**0.000**	99.464	0.020
	P	53	**1.967**	**1.793-2.158**	**0.000**	99.201	0.040
Schizophrenia vs. general population	I + P	44	**2.162**	**1.985-2.355**	**0.000**	99.571	0.004
	I	6	**2.149**	**1.861-2.481**	**0.000**	94.602	0.270
	P	38	**2.154**	**1.961-2.367**	**0.000**	99.182	0.140
Schizophrenia vs. no schizophrenia (all matched)	P	16	**1.565**	**1.346-1.821**	**0.000**	94.001	0.030
Schizophrenia vs. no schizophrenia (matched for acute myocardial infarction)	P	5	**1.659**	**1.238-2.223**	**0.001**	96.379	0.070
Mortality due to cardio-cerebrovascular diseases							
Schizophrenia vs. any other population	I + P	30	**2.028**	**1.678-2.452**	**0.000**	99.470	0.020
Schizophrenia vs. general population	I + P	28	**2.099**	**1.797-2.451**	**0.000**	99.008	0.001
	I	4	**3.470**	**1.792-6.719**	**0.000**	97.883	0.570
	P	24	**1.984**	**1.729-2.275**	**0.000**	97.690	0.210
Schizophrenia vs. no schizophrenia (all matched)	P	2	1.329	0.907-1.946	0.144	97.625	NA
Mortality due to cardiovascular diseases							
Schizophrenia vs. any other population	I + P	25	**2.089**	**1.764-2.474**	**0.000**	99.289	0.020
	P	20	**1.963**	**1.653-2.331**	**0.000**	98.841	0.220
Schizophrenia vs. general population	I + P	19	**2.205**	**1.824-2.666**	**0.000**	99.412	0.050
	I	5	**2.701**	**1.802-4.050**	**0.000**	98.514	0.250
	P	14	**2.058**	**1.680-2.522**	**0.000**	99.120	0.370
Schizophrenia vs. no schizophrenia (all matched)	P	7	**1.855**	**1.392-2.473**	**0.000**	91.665	0.480
Schizophrenia vs. no schizophrenia (matched for acute myocardial infarction)	P	4	**1.847**	**1.515-2.252**	**0.000**	73.575	0.360

Table 2 All-cause and cause-specific mortality risk in schizophrenia versus control groups *(continued)*

	Incident/ prevalent	N. studies	Risk ratio	95% CI	p	I^2	Egger's p
Mortality due to cerebrovascular diseases							
Schizophrenia vs. any other population	I + P	16	**1.458**	**1.168-1.822**	**0.001**	97.435	0.090
	P	11	1.386	0.993-1.936	0.055	98.027	0.260
Schizophrenia vs. general population	I + P	13	**1.598**	**1.250-2.042**	**0.000**	97.748	0.220
	I	5	**1.764**	**1.357-2.292**	**0.000**	72.580	0.090
	P	8	**1.583**	**1.062-2.359**	**0.024**	98.505	0.490
Schizophrenia vs. no schizophrenia (all matched)	P	3	0.972	0.520-1.817	0.929	91.905	0.240
Schizophrenia vs. no schizophrenia (matched for stroke)	P	2	0.724	0.173-3.038	0.659	95.719	NA
Mortality due to diabetes mellitus							
Schizophrenia vs. any other population	I + P	7	**2.512**	**1.623-3.889**	**0.000**	99.121	0.170
	P	6	**2.271**	**1.444-3.572**	**0.000**	98.201	0.920
Schizophrenia vs. general population	I + P	5	**3.159**	**2.420-4.123**	**0.000**	94.848	0.270
	P	4	**2.878**	**1.858-4.458**	**0.000**	94.485	0.630
Schizophrenia vs. no schizophrenia (matched for diabetes mellitus)	P	2	**1.483**	**1.032-2.131**	**0.033**	95.695	NA
Mortality due to any cancer							
Schizophrenia vs. general population	I + P	25	**1.327**	**1.187-1.482**	**0.000**	97.942	0.001
	I	5	1.315	0.982-1.760	0.066	93.121	0.060
	P	20	**1.328**	**1.157-1.524**	**0.000**	97.109	0.420
Mortality due to endocrine diseases							
Schizophrenia vs. general population	I + P	9	**3.802**	**1.750-8.262**	**0.001**	97.438	0.500
	I	3	**4.217**	**1.747-10.179**	**0.001**	76.243	0.390
	P	6	**3.519**	**1.216-10.185**	**0.020**	98.350	0.640
Mortality due to gastrointestinal diseases							
Schizophrenia vs. general population	I + P	12	**2.859**	**2.069-3.950**	**0.000**	96.838	0.930
	I	4	**2.384**	**1.939-2.932**	**0.000**	0.000	0.910
	P	8	**3.060**	**2.046-4.577**	**0.000**	97.959	0.800
Mortality due to any infectious diseases							
Schizophrenia vs. general population	I + P	10	**3.840**	**2.103-7.012**	**0.000**	97.025	0.460
	P	8	**4.344**	**2.228-8.471**	**0.000**	97.679	0.410
Mortality due to any liver diseases							
Schizophrenia vs. general population	I + P	2	**1.964**	**1.899-2.032**	**0.000**	0.000	NA
Mortality due to any neurological diseases							
Schizophrenia vs. general population	I + P	8	**2.347**	**1.942-2.838**	**0.000**	6.879	0.400
	I	4	**1.972**	**1.126-3.452**	**0.018**	25.381	0.270
	P	4	**2.435**	**2.245-2.641**	**0.000**	0.000	0.840
Mortality due to any respiratory diseases							
Schizophrenia vs. general population	I + P	15	**3.748**	**2.989-4.699**	**0.000**	97.563	0.790
	I	4	**3.267**	**2.365-4.515**	**0.000**	60.784	0.430
	P	11	**3.860**	**2.963-5.029**	**0.000**	98.217	0.720
Mortality due to any urogenital diseases							
Schizophrenia vs. general population	I + P	9	**3.328**	**2.062-5.372**	**0.000**	98.032	0.640
	P	7	**3.752**	**2.183-6.450**	**0.000**	98.518	0.560

Significant values of risk ratio are highlighted in bold. I – incident, P – prevalent, TRS – treatment-resistant schizophrenia, FGA – first-generation antipsychotic, SGA, second-generation antipsychotic, LAI – long-acting injectable antipsychotic, NA – not available

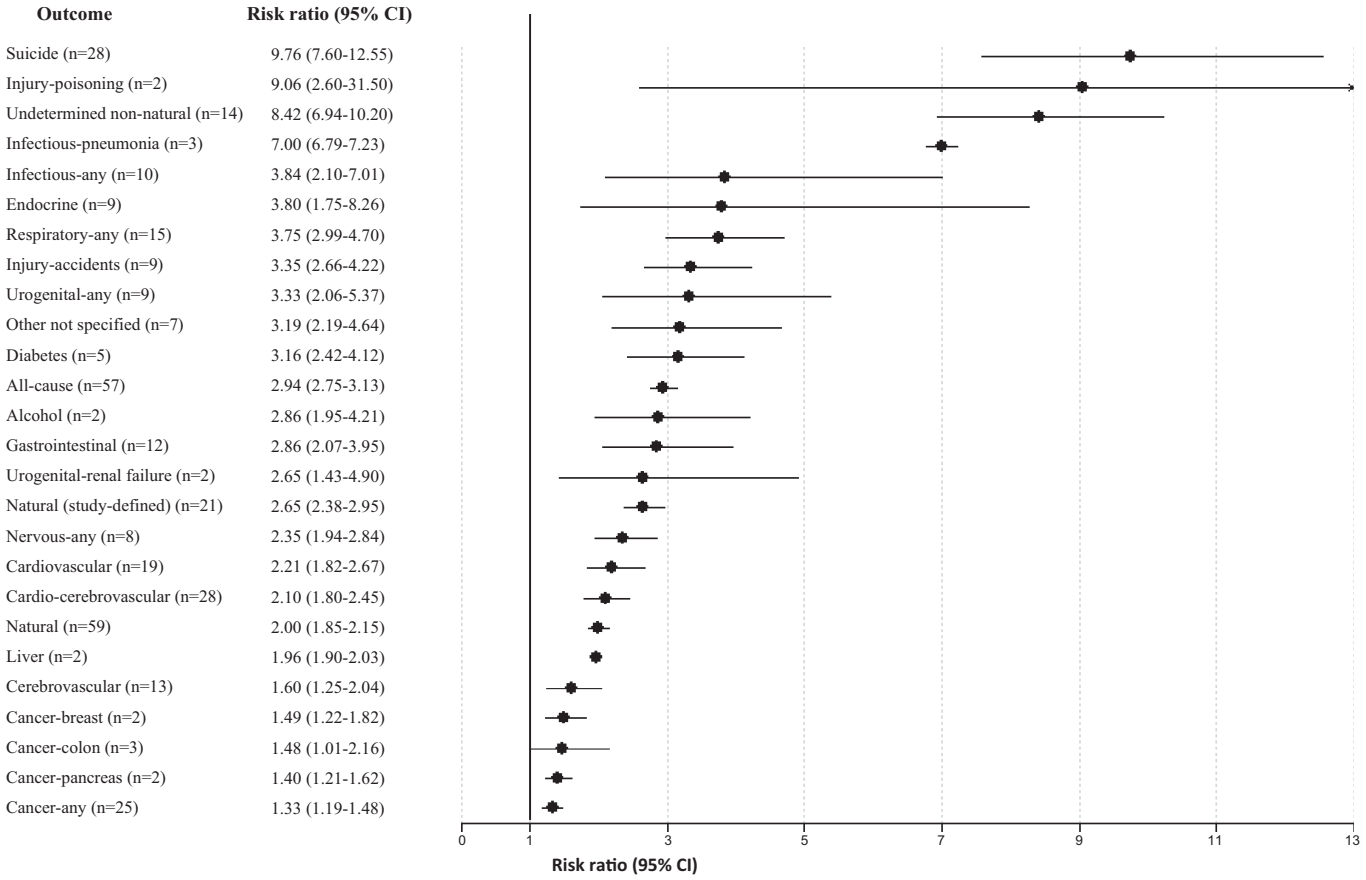

Figure 2 Significant findings for all-cause and cause-specific mortality risk in incident plus prevalent schizophrenia versus the general population

and fill analyses, which confirmed the magnitude and significance of the primary findings (with a fail-safe N ranging from 235 to 282,469), except for a slight reduction of the effect size in comparison with physical disease-matched controls (four studies trimmed, RR=1.35, 95% CI: 1.17-1.56) (see also supplementary information).

Additional secondary outcomes: other specific-cause mortality

Cardiovascular and/or cerebrovascular diseases

Across 30 studies, schizophrenia was associated with higher cardio-cerebrovascular-related mortality compared with either the general population or control groups matched for a physical illness (RR=2.03, 95% CI: 1.68-2.45, I^2=99.5%) (see Table 2). Separating causes, higher mortality from cardiovascular diseases (RR=2.09, 95% CI: 1.76-2.47, I^2=99.3%, n=25) as well as from cerebrovascular diseases (RR=1.46, 95% CI: 1.17-1.82, I^2=97.4%, n=16) was observed among individuals with schizophrenia (see Table 2).

Comparing schizophrenia with the general population, significant findings emerged for the composite mortality outcome (RR=2.10, 95% CI: 1.80-2.45, I^2=99.0%, n=28), as well as for mortality due to cardiovascular diseases (RR=2.21, 95% CI: 1.82-2.67, I^2=99.4%, n=19) and to cerebrovascular diseases (RR=1.60, 95% CI: 1.25-2.04, I^2=97.7%. n=13). Mortality due to cardio-cerebrovascular diseases was substantially higher in incident (RR=3.47, 95% CI: 1.79-6.72, I^2=97.9%, n=4) than in prevalent schizophrenia (RR=1.98, 95% CI: 1.73-2.27, I^2=97.7%, n=24) (see Table 2 and Figure 2).

Compared with physical disease-matched controls, patients with schizophrenia had significantly higher mortality from cardiovascular diseases (RR=1.86, 95% CI: 1.39-2.47, I^2=91.7%, n=7), including cohorts that were specifically matched for acute myocardial infarction (RR=1.85, 95% CI: 1.52-2.25, I^2=73.6%, n=4) (see Table 2).

Other specific causes

Individuals with schizophrenia had significantly higher mortality than the general population from pneumonia (RR=7.00, 95% CI: 6.79-7.23, n=3), any infectious diseases (RR=3.84, 95% CI: 2.10-7.01, n=10), any endocrine diseases (RR=3.80, 95% CI: 1.75-8.26, n=9), any respiratory diseases (RR=3.75, 95% CI: 2.99-

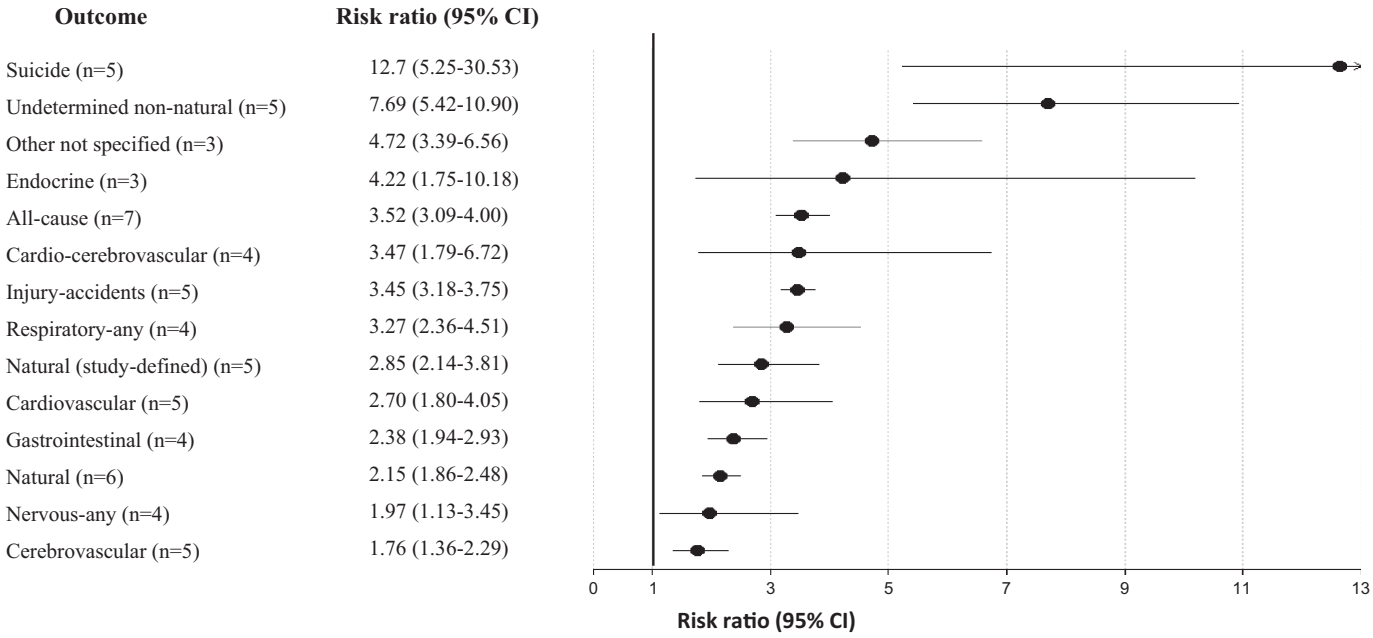

Figure 3 Significant findings for all-cause and cause-specific mortality risk in incident schizophrenia versus the general population

4.70, n=15), any urogenital diseases (RR=3.33, 95% CI: 2.06-5.37, n=9), diabetes mellitus (RR=3.16, 95% CI: 2.42-4.12, n=5), any gastrointestinal diseases (RR=2.86, 95% CI: 2.07-3.95, n=12), any neurological diseases (RR=2.35, 95% CI: 1.94-2.84, n=8), any liver diseases (RR=1.96, 95% CI: 1.90-2.03, n=2), and any cancer (RR=1.33, 95% CI: 1.19-1.48, n=25) (see Table 2 and Figure 2).

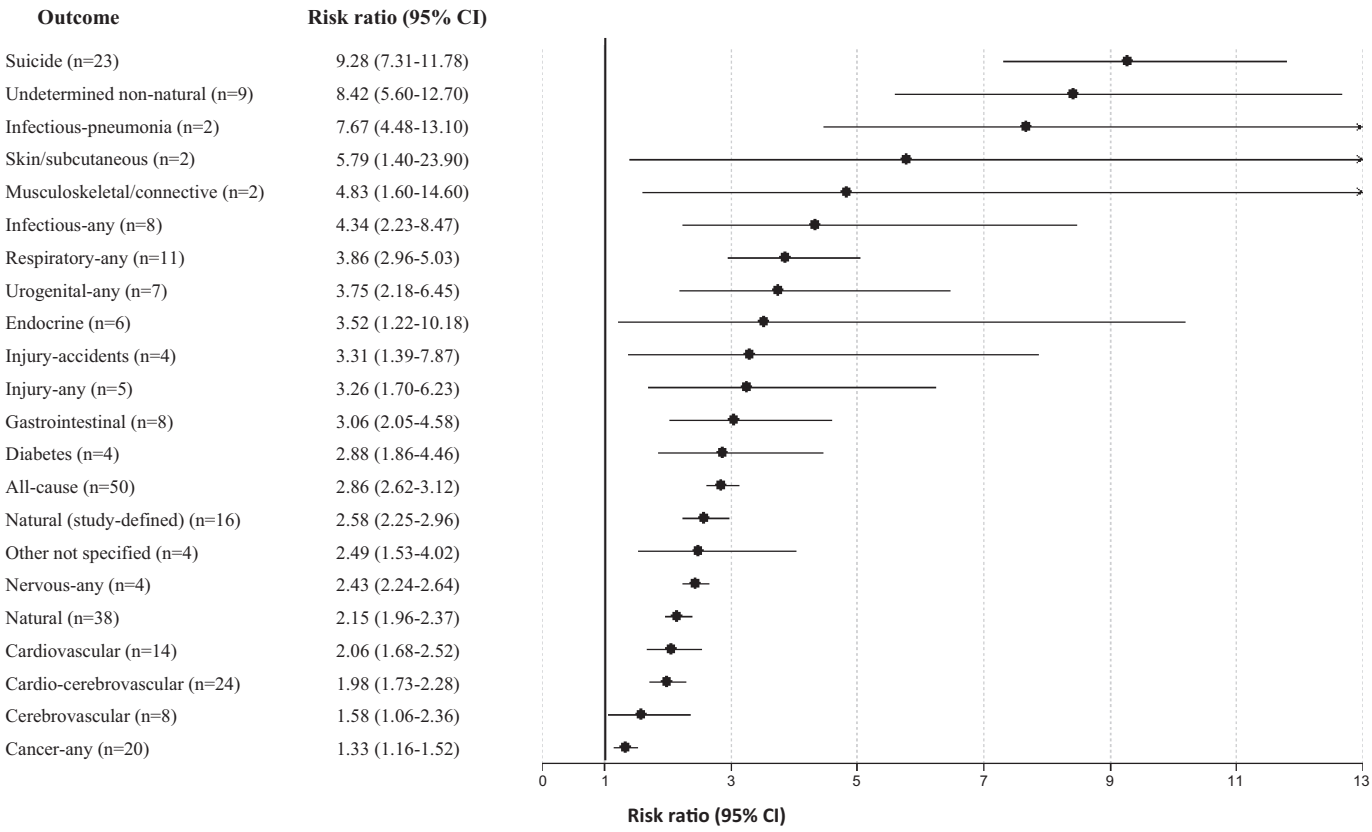

Figure 4 Significant findings for all-cause and cause-specific mortality risk in prevalent schizophrenia versus the general population

Among individuals with schizophrenia, mortality was significantly higher than the general population also from injury-poisoning (RR=9.06, 95% CI: 2.60-31.50, n=2) and undetermined non-natural causes (RR=8.42, 95% CI: 6.94-10.20, n=14) (see Figure 2 and supplementary information).

In incident schizophrenia, no significant association was found with death due to cancer (RR=1.31, 95% CI: 0.98-1.76, n=5), whereas the association was observed in prevalent schizophrenia (RR=1.33, 95% CI: 1.16-1.52, n=20) (see Table 2 and Figure 4). There was instead a significantly increased risk of mortality in both incident and prevalent schizophrenia cohorts due to endocrine diseases (incident: RR=4.22, 95% CI: 1.75-10.18, n=3; prevalent: RR=3.52, 95% CI: 1.22-10.18, n=6), gastrointestinal diseases (incident: RR=2.38, 95% CI: 1.94-2.93, n=4; prevalent: RR=3.06, 95% CI: 2.04-4.58, n=8), neurological diseases (incident: RR=1.97, 95% CI: 1.13-3.45, n=4; prevalent: RR=2.43, 95% CI: 2.24-2.64, n=4) and respiratory diseases (incident: RR=3.27, 95% CI: 2.36-4.51, n=4; prevalent: RR=3.86, 95% CI: 2.96-5.03, n=11) (see Table 2 and Figures 2-4).

Subgroup analyses and meta-regression

Use of any antipsychotic versus non-use was associated with a reduction of all-cause mortality in patients with incident plus prevalent schizophrenia (RR=0.71, 95% CI: 0.59-0.84, I^2=97.7%, n=11). Reduction of all-cause mortality risk versus no antipsychotic treatment differed significantly across antipsychotic subgroups (p=0.0001), in descending order as follows: any SGA LAI (RR=0.39, 95% CI: 0.27-0.56, I^2=81.0%, n=3), clozapine (RR=0.43, 95% CI: 0.34-0.55, I^2=77.9%, n=3), any LAI (RR=0.47, 95% CI: 0.39-0.58, I^2=91.8%, n=2), any oral SGA (RR=0.47, 95% CI: 0.45-0.50, I^2=18.9%, n=4), any first-generation antipsychotic (FGA) LAI (RR=0.50, 95% CI: 0.43-0.57, I^2=68.9%, n=3), any SGA (RR=0.53, 95% CI: 0.44-0.63, I^2=91.0%, n=4), any oral antipsychotic (RR=0.64, 95% CI: 0.51-0.80, I^2=95.9%, n=4), and any FGA (RR=0.73, 95% CI: 0.55-0.97, I^2=97.0%, n=5). There was a borderline significant all-cause mortality reduction among individuals with treatment-resistant schizophrenia who received clozapine compared with other medications (RR=0.70, 95% CI: 0.49-1.00, I^2=57.9%, n=5) (see Figure 5 and supplementary information).

In incident schizophrenia, the largest protective association emerged for SGA LAIs (RR=0.15, 95% CI: 0.04-0.55, n=1), whereas the protective effect was not significant for any oral antipsychotics, or FGA in any formulation (p=0.07 for comparison across antipsychotics). In prevalent schizophrenia, the largest association emerged for SGA LAIs again (RR=0.42, 95% CI: 0.29-0.59, n=2), and the smallest for any antipsychotic (RR=0.69, 95% CI: 0.57-0.84, n=7) (p=0.0001 for comparison across antipsychotics) (see supplementary information).

Use of any antipsychotic versus non-use was not associated with a reduction of suicide-related mortality in patients with incident plus prevalent schizophrenia (RR=0.73, 95% CI: 0.47-1.12, I^2=94.4%, n=4). Reduction of suicide-related mortality versus no antipsychotic treatment differed significantly across antipsychotic subgroups (p=0.0001), in descending order as follows: clozapine (RR=0.22, 95% CI: 0.16-0.30, I^2=0%, n=2), any SGA LAI (RR=0.43, 95% CI: 0.24-0.78, I^2 not available, n=1), any LAI (RR=0.60, 95% CI: 0.47-0.77, I^2 not available, n=1), any SGA oral (RR=0.64, 95% CI: 0.54-0.74, I^2=0, n=2), any FGA LAI (RR=0.64, 95% CI: 0.49-0.85, I^2 not available, n=1), and any SGA (RR=0.68, 95% CI: 0.56-0.82, I^2=44.2%, n=2). In contrast, compared to no antipsychotic, any FGA (RR=1.05, 95% CI: 0.37-2.99, I^2=97.2%, n=2) and oral FGAs (RR=1.13, 95% CI: 0.33-3.93, I^2=95.7%, n=2) did not protect individuals with schizophrenia against suicide-related mortality (see Figure 5 and supplementary information).

In incident schizophrenia, the largest protective association regarding suicide-related mortality emerged for clozapine (RR=0.29, 95% CI: 0.14-0.62, n=1), while, in contrast, oral FGAs were associated with increased mortality (RR=2.17, 95% CI: 1.36-3.48, n=1) (p=0.0001 for comparison across antipsychotics). In prevalent schizophrenia, the lowest risk of suicide-related mortality emerged for clozapine (RR=0.21, 95% CI: 0.15-0.29, n=1), and the closest to null effect emerged for any antipsychotic (RR=0.73, 95% CI: 0.36-1.49, n=2) (p=0.0001 for comparison across antipsychotics) (see supplementary information).

In incident plus prevalent schizophrenia, any antipsychotic versus no antipsychotic use was protective against natural causes of mortality (RR=0.76, 95% CI: 0.59-0.97, I^2=90.7%, n=3). Reduction of natural-cause mortality versus no antipsychotic treatment differed significantly across antipsychotic subgroups (p=0.04), in descending order as follows: clozapine (RR=0.50, 95% CI: 0.29-0.86, I^2=21.3%, n=2), any oral SGA (RR=0.57, 95% CI: 0.52-0.62, I^2=0%, n=2), any oral antipsychotic (RR=0.62, 95% CI: 0.59-0.66, I^2 not available, n=1), any SGA (RR=0.65, 95% CI: 0.48-0.89, I^2=71.4%, n=2), any SGA LAI (RR=0.66, 95% CI: 0.52-0.84, I^2 not available, n=1), any LAI (RR=0.69, 95% CI: 0.62-0.77, I^2 not available, n=1), any FGA LAI (RR=0.70, 95% CI: 0.62-0.78, I^2 not available, n=1). In contrast, any FGA or any oral FGA were not associated with lower natural-cause mortality (see Figure 5 and supplementary information).

In incident schizophrenia, no significant reduction of natural-cause mortality emerged for any antipsychotic subgroup versus no antipsychotic use. Oral FGAs were associated with increased natural-cause mortality (RR=2.20, 95% CI: 1.29-3.77, n=1) (p=0.0004 for comparison across antipsychotics). In prevalent schizophrenia, the largest protective effect emerged for clozapine (RR=0.55, 95% CI: 0.47-0.64, n=1), and the smallest for FGA LAIs (RR=0.70, 95% CI: 0.62-0.78, n=1) (p=0.0005 for comparison across antipsychotics) (see supplementary information).

In subgroup analyses of incident plus prevalent schizophrenia cohorts by age, the risk of all-cause mortality was significantly higher for patients aged <40 vs. ≥40 years (RR=3.93, 95% CI: 3.34-4.63 vs. RR=2.66, 95% CI: 2.18-3.26, p=0.003). A similar difference was observed for suicide-related mortality (RR=17.58, 95% CI: 12.36-24.99 vs. RR=4.69, 95% CI: 1.77-12.45, p=0.01). There was no significant difference between the two age groups for natural-cause mortality (see supplementary information).

No consistent and significant differences emerged from subgroup analyses considering nationwide versus other samples,

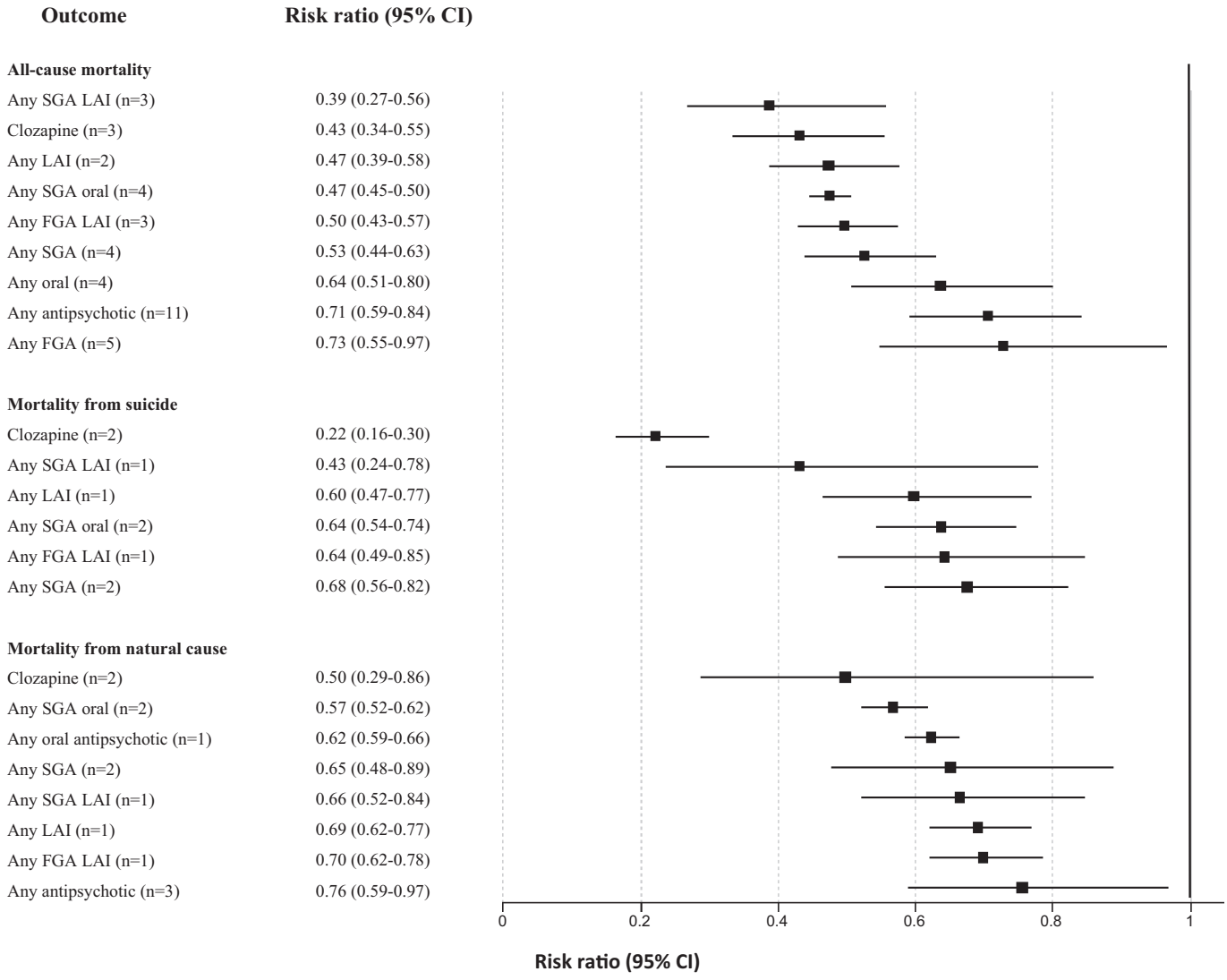

Figure 5 Findings in subgroup analyses of mortality risk due to any cause, suicide, and natural death by antipsychotic treatment within incident plus prevalent schizophrenia versus no antipsychotic. FGA – first-generation antipsychotic, SGA – second-generation antipsychotic, LAI – long-acting injectable antipsychotic

quality of studies, and adjustment of results, suggesting that findings concerning mortality are not systematically influenced by these moderators (see supplementary information).

In meta-regression analyses, we found in incident plus prevalent schizophrenia a significant increase of all-cause mortality (beta=0.0009, 95% CI: 0.001-0.02, p=0.02) and of natural-cause mortality (beta=0.01, 95% CI: 0.006-0.02, p=0.0002) with increasing median year of study publication, without a significant time trend for suicide-related mortality (beta=0.006, 95% CI: –0.01 to 0.03, p=0.56) (see supplementary information).

For all-cause mortality, in incident plus prevalent schizophrenia, more recent study year moderated a larger protective effect of any antipsychotic (beta=–0.11, 95% CI: –0.15 to –0.06) and of oral FGA versus no antipsychotic (beta=–0.11, 95% CI: –0.17 to –0.05). Similarly, for suicide-related mortality, more recent study year moderated a larger protective effect of any FGA versus no antipsychotic in incident plus prevalent schizophrenia (beta=–0.27, 95% CI: –0.36 to –0.18).

Longer duration of follow-up and more variables used to adjust the analyses increased the protective effect against suicide-related mortality of any antipsychotic in prevalent schizophrenia (beta=–0.14, 95% CI: –0.24 to –0.04, and beta =–0.23, 95% CI: –0.40 to –0.06, respectively). Higher percentage of females increased the risk of suicide-related mortality in incident schizophrenia (beta=0.36, 95% CI: 0.23-0.49, p<0.0001).

For natural-cause mortality, the protective effect of any FGA versus no antipsychotic in incident plus prevalent schizophrenia was increased by more recent study year (beta=–0.23, 95% CI: –0.33 to –0.13) and more variables used to adjust the analyses (beta=–0.12, 95% CI: –0.17 to –0.07). Natural-cause mortality versus any other population was greater in higher quality studies in incident plus prevalent schizophrenia (beta=0.11, 95% CI: 0.04-

0.18). Natural-cause mortality versus the general population was also greater in higher quality studies in incident plus prevalent schizophrenia (beta=0.13, 95% CI: 0.06-0.20), as well as in incident schizophrenia (beta=0.20, 95% CI: 0.08-0.31) and in prevalent schizophrenia (beta=0.11, 95% CI: 0.02-0.19). Natural-cause mortality was also larger, in incident schizophrenia, with higher number of variables that analyses were adjusted for (beta=0.12, 95% CI: 0.06-0.18).

DISCUSSION

Schizophrenia is one of the mental disorders with the highest mortality risk. This meta-analysis of 135 cohort studies comparing 4.5 million schizophrenia patients with about 1.11 billion people from the general population comprehensively quantified this increased risk. Specifically, we observed a 2.9-fold increased all-cause mortality in patients with schizophrenia versus the general population, and a somewhat lower but still significantly 1.6-fold increased risk versus physical disease-matched general population controls.

In addition, we identified significantly greater specific-cause mortality among individuals with schizophrenia versus the general population, which was particularly pronounced for suicide (9.7-fold); other non-natural causes, including poisoning (8- to 9-fold); and pneumonia (7-fold). The mortality risk remained greater for infectious, endocrine and respiratory diseases (3.7-3.8-fold); injury or accidents (3.3-fold); diabetes mellitus (3.2-fold); alcohol use and gastrointestinal diseases (2.9-fold); urogenital diseases (2.6-fold); neurological diseases (2.3-fold); cardiovascular diseases (2.2-fold); liver diseases (2-fold); and cerebrovascular diseases (1.6-fold); also extending to breast, colon, pancreas and any cancer (1.3- to 1.5-fold).

The relative increase in mortality compared to the general population was larger in incident (i.e., earlier-phase) than prevalent (i.e., more chronic) schizophrenia cohorts. Moreover, all-cause and suicide-related mortality were higher in patients <40 years old, whereas this was not the case for natural-cause mortality. Comorbid substance use disorder increased the all-cause mortality gap, while antipsychotic treatment versus no treatment decreased this gap. The largest protective effect was observed with SGA LAIs and clozapine. In contrast to this protective effect, FGAs increased suicide-related and natural-cause mortality in incident schizophrenia.

We found that first-episode schizophrenia was associated with a 7.4-fold higher all-cause mortality risk versus the general population, indicating the critical importance of providing a swift and accurate diagnosis followed by initiating effective treatment. The lifetime prevalence of completed suicide in patients with schizophrenia has been reported to be 5.6%, with the majority of these suicides occurring near illness onset[167]. Moreover, suicide attempts have been found to be predicted by greater severity of psychotic illness and of depressive symptoms[168], two factors that should prompt clinicians to screen for and guard against suicide attempts in the early phase of the illness. Furthermore, our finding that females with schizophrenia have a significantly higher risk increase than males for suicide-related mortality compared to the general population should prompt clinicians to extend the focus from males, who are still at the highest risk for completed suicide[169], to this additional high-risk group.

All-cause mortality was increased in persons with schizophrenia even when they were matched with general population controls for many relevant physical diseases. These included cardiovascular, cerebrovascular, endocrine, gastrointestinal, infectious, liver, neurological, respiratory and urogenital diseases, diabetes mellitus and cancer. Importantly, the relative mortality risk for cardio-cerebrovascular diseases was substantially greater in the incident (RR=3.47) versus prevalent (RR=1.98) cohorts, which is perhaps reflective of the lower overall frequency of these diseases in the younger general population and of their earlier onset in people with schizophrenia, likely due to poorer lifestyle behaviors[170-172] and to the effect of antipsychotic and other medications[21,173].

Disparities between individuals with schizophrenia and the general population with respect to the implementation of screening procedures (e.g., for cardiovascular risk factors and disorders, and for cancer) and the quality of medical care, including a lack of advice for lifestyle changes such as smoking cessation and physical activity, have been repeatedly reported[2,27,28,43,174,175]. Addressing smoking is of particular importance, given the 70-162% increased risk of asthma, chronic obstructive pulmonary disease and pneumonia in subjects with schizophrenia[176], and considering our finding that pneumonia confers the highest risk of death among natural causes. Thus, to close the mortality gap in individuals with schizophrenia, smoking cessation interventions, cardiovascular and cancer screening and monitoring, consistent healthy lifestyle instructions, as well as early interventions for detected physical diseases, should be regarded as imperative. Since individuals with schizophrenia may be less likely to receive or seek help from a medical health care provider than people from the general population, mental health care providers need to orchestrate physical care for these individuals as part of a comprehensive and collaborative care model[17].

Comorbid substance use disorders were found in our meta-analysis to be a significant risk factor for increased mortality in people with schizophrenia. This finding is likely due to the multiple adverse physical as well as intentional or accidental suicide-related effects of these disorders[177-181]. Additionally, comorbid substance use, and cannabis use in particular, can worsen adherence to antipsychotics[182-184]. All these factors point to the need to screen for and address substance use disorders as early as possible when treating patients with schizophrenia[185,186].

This meta-analysis found that, compared with no antipsychotic use, antipsychotic treatment was associated with reduced all-cause mortality in patients with schizophrenia. Specifically, factors associated with a reduction in all-cause mortality included the use of any LAI, any SGA and, especially, of clozapine. These findings support prior research which found that continuous clozapine use was associated with significantly lower long-term all-cause mortality compared with other antipsychotics in patients with schizophrenia, despite the adverse impact of clo-

zapine on cardiometabolic risk factors[187]. We also observed a borderline significant reduction in all-cause mortality among patients with treatment-resistant schizophrenia who were treated with clozapine compared with other antipsychotics, with lack of significance likely being due to low power of these analyses.

Recently, a Finnish national database study[20] indicated that patients with schizophrenia who were taking antipsychotics, especially LAIs and clozapine, were significantly less likely to interrupt ongoing treatment with statins, antidiabetic agents, anti-hypertensive medications, and beta-blockers. Such an association between the use of antipsychotics and better adherence to medical treatments – and potentially also closer and more regular medical monitoring as might be the case with clozapine and LAIs – is likely to be a mediator of the protective effect of antipsychotic use on mortality risk in people with schizophrenia. Studies that specifically test this hypothesis are warranted.

The use of any SGA or clozapine also had a significant protective effect against suicide-related mortality in prevalent schizophrenia, compared with no use of antipsychotics, which was not observed with FGAs. While the anti-suicidal efficacy of clozapine has been established[188], the differential finding favoring SGAs may be due to the fact that suicide in schizophrenia is often associated with the emergence of depression[168]. FGAs do not improve or even induce depressive symptoms, while many SGAs have been shown to be effective in treating these symptoms[189-191].

We found that, in incident schizophrenia, FGAs were even associated with an increased mortality risk due to suicide. This finding should caution against the use of these medications as first-line agents, in particular in earlier-phase patients. The fact that this increased mortality risk in incident schizophrenia was not found with FGA LAIs points to a potentially mediating effect of poorer adherence with oral FGAs or a protective effect of LAI use due to increased surveillance and, possibly, treatment of emergent depression.

Thus, in addition to underscoring the importance of comprehensive physical health monitoring and integrated or collaborative care to address and improve both physical and mental health problems in patients with schizophrenia, this meta-analysis points to the need for antipsychotic maintenance treatment, monitoring for and mitigating antipsychotic non-adherence, also through a broader and earlier consideration of SGA LAIs. Furthermore, our findings point to the need to screen for and treat substance use disorders as well as depression as important clinical strategies to reduce overall and specific-cause mortality in individuals with schizophrenia.

We found a slight but significant increase of the excess mortality in people with schizophrenia by median study year of investigation (ranging from 1957 to 2021). This finding further emphasizes the urgency with which the mortality gap in these people needs to be addressed.

Among the strengths of this meta-analysis are the large number of studies (n=135) that met the inclusion criteria, the substantial number of patients with schizophrenia (4,536,447) and general population controls (1,115,600,059); and the high quality of the studies included, with results being consistent and robust even after all trim and fill analyses. Moreover, directions for future research are provided, as analyses adjusted for more potentially relevant confounders and longer follow-up were associated with greater protective effects of antipsychotic medications against the increased mortality risk.

However, the results of this meta-analysis have to be interpreted within its limitations. First, meta-analyzed studies were observational cohort investigations. Their non-randomized nature cannot imply causality. However, since mortality is a relatively rare and late-onset/distal event, randomized controlled trials – that generally include relatively few individuals, have a modest follow-up duration and many dropouts, and that also exclude many patients that may be more severely mentally and physically ill[192] – are not the best or most feasible studies to quantify mortality risk and identify generalizable aggravating and protective factors. For the study of mortality risk, longitudinal cohort and, especially, nationwide database studies represent more appropriate study options. Furthermore, consistent with our meta-analysis, two smaller meta-analyses focusing on patients in randomized controlled trials reported similar results – i.e., an about 30-50% lower mortality among patients randomized to antipsychotics compared with patients randomized to placebo[193,194].

Second, although we were able to include as many as 135 individual studies, with a large number of individuals with schizophrenia and even more control subjects from the general population, some findings were based on five or fewer studies. The need for additional studies is particularly important with respect to the quantitative evaluation of specific factors that increase or decrease the existing mortality gap. Third, there was substantial inconsistency in the definitions of age groups across the included studies, which limited our ability to comprehensively analyze the effect of age on all-cause and specific-cause mortality risk. Future studies should report age both categorically across relevant age groups as well as continuously.

Fourth, few studies specifically evaluated mortality risk in patients with first-episode or treatment-resistant schizophrenia, two subgroups of considerable clinical interest. Fifth, some studies did not quantify the number of the general population control group, but used instead regional or nationwide control groups restricted to certain time periods and/or age groups. In such instances, we estimated the number of general population controls based on census-based (sub)population numbers at the time of data collection, which may have introduced some imprecision. Sixth, studies used different metrics to report mortality: in order to pool results, we combined risk estimates that have somewhat different characteristics, which could have led to some imprecision. However, since mortality is a relatively rare event and since all included studies used the same cohort design and evaluated the same population of interest, the degree of imprecision is likely low.

Finally, although we preferred the risk estimate that was adjusted for the most likely potential confounders, we also included unadjusted risk estimates, and adjustments may not have included all/the most relevant covariates that are associated with mortality risk. However, we were not interested in isolating the genetic or narrowly illness-related effect of schizophrenia on mortality

risk, but rather in estimating the differential risk of all-cause and specific-cause mortality in individuals with schizophrenia who differ in many psychological, behavioral, social and environmental respects from the general population and other control groups. The potential residual confounding from a statistical standpoint, therefore, represents the reality of individuals living with schizophrenia and ensures the desired generalizability of the findings.

CONCLUSIONS

This meta-analysis provides the largest and most comprehensive quantitative assessment of the all-cause and detailed specific-cause mortality risk of individuals with schizophrenia versus the general population and other control groups, additionally focusing on reported aggravating and protective factors. It confirms that the mortality gap between patients with and without schizophrenia is high, being highest for suicide-related mortality but extending to multiple other specific-cause mortality reasons. Results of this mortality gap in individuals with schizophrenia were based on high-quality data in >97% of the studies and were robust and confirmed in multiple subgroup and meta-regression analyses. Importantly, the increased mortality was associated with certain modifiable risk factors, which can inform clinical practice.

Consistent and long-term use of SGAs, SGA LAIs and, if indicated, clozapine in patients with schizophrenia across all stages of illness can reduce the mortality risk, as antipsychotics are protective compared to non-use of antipsychotics against many kinds of mortality, including that due to cardio-cerebrovascular disease. This finding indicates that even antipsychotics with elevated cardiometabolic adverse effects, such as clozapine, can reduce overall mortality, which is not counterbalanced by larger but supported by reduced cardiometabolic-related mortality. Results were confirmed or even stronger in more recent, higher quality, adjusted studies, and those with longer follow-up. Finally, despite heightened awareness of the mortality gap of people with severe mental illness and especially with schizophrenia, this gap seems to be increasing slightly with time, including data as recent as 2021.

These results underscore the urgency with which the mortality disparity in individuals with schizophrenia need to be addressed at multiple levels. Clinicians should routinely monitor patients with schizophrenia for cardiovascular risk and physical diseases and also screen for and address substance use disorders and depression. In addition, they should screen patients with first-episode schizophrenia, both males and females, for suicide risk and depression, and avoid FGAs.

Overall, integrated mental and physical health care of individuals with schizophrenia must be at the center of mental health research and policy making agendas. Data from this meta-analysis point to the responsibility of reducing mortality risk by screening for and optimizing the management of physical as well as psychiatric comorbidities, and by earlier use of LAIs and, if indicated, clozapine in individuals with schizophrenia. This information should be considered by treatment guidelines and incorporated into actionable policies by health care administrators.

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