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**Effects of antipsychotic treatment on cardio-cerebrovascular related mortality in schizophrenia: a subanalysis of a systematic review and meta-analysis with meta-regression of moderators**

Marco Solmi1-6\*, Giovanni Croatto7\*, Arnav Gupta8,9\*, Nicholas Fabiano1,6\*, Stanley Wong6,10, Michele Fornaro11, Lynne Kolton Schneider12, S. Christy Rohani-Montez12, Leanne Fairley12, Nathalie Smith12, István Bitter13, Philip Gorwood14,15, Heidi Taipale16-19, Jari Tiihonen16-18, Samuele Cortese20-24, Elena Dragioti25,26, Ebba Du Rietz27, Rene Ernst Nielsen28,29, Joseph Firth30, Paolo Fusar-Poli31-34, Catharina Hartman35, Richard I G Holt36, Anne Høye37, Ai Koyanagi38,39, Henrik Larsson40,41, Kelli Lehto42, Peter Lindgren43,44, Mirko Manchia45-47, Merete Nordentoft48, Karolina Skonieczna-Żydecka49, Brendon Stubbs50, Davy Vancampfort51,52, Michele De Prisco53, Laurent Boyer54, Eduard Vieta53, Christoph U. Correll5,55,56 for the ECNP Physical And meNtal Health Thematic Working Group (PAN-Health)

1. Department of Psychiatry, University of Ottawa, Ottawa, Canada

2. Department of Mental Health, The Ottawa Hospital, Ottawa, Canada

3. Ottawa Hospital Research Institute: Clinical Epidemiology Program, University of Ottawa, Ottawa, Canada

4. School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

5. Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany

6. SCIENCES Lab, Department of Psychiatry, University of Ottawa, Ottawa, Canada

7. Mental Health Department, AULSS 3 Serenissima, Mestre, Venice, Italy

8. Department of Medicine, University of Calgary, Calgary, Canada

9. College of Public Health, Kent State University, Kent, United States

10. Department of Psychiatry, University of Toronto, Toronto, Canada

11. Section of Psychiatry, Department of Neuroscience, Reproductive Science, and Dentistry, Federico II University of Naples, Naples, Italy

12. WebMD Global LLC, London, UK

13. Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

14. Université Paris Cité, INSERM U1266, Institute of Psychiatry and Neurosciences of Paris (IPNP), Paris, France

15. GHU Paris Psychiatrie et Neurosciences (CMME, Sainte-Anne Hospital), Paris, France

16. Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden;

17. Center for Psychiatry Research, Stockholm City Council, Stockholm, Sweden;

18. Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland

19. School of Pharmacy, University of Eastern Finland, Kuopio, Finland

20. Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK.

21. Solent NHS Trust, Southampton, UK

22. Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK.

23. Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, NY, USA.

24. DiMePRe-J-Department of Precision and Regenerative Medicine-Jonic Area, University of Bari "Aldo Moro", Bari, Italy

25. Pain and Rehabilitation Centre, Department of Medical and Health Sciences, Linköping University, Linköping, Sweden.

26. Research Laboratory Psychology of Patients, Families, and Health Professionals, Department of Nursing, School of Health Sciences, University of Ioannina, Ioannina, Greece

27. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

28. Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

29. Department of Psychiatry, Aalborg University Hospital, Aalborg, Denmark.

30. Division of Psychology and Mental Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom

31. Early Psychosis: Interventions and Clinical-Detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

32. Outreach and Support in South-London (OASIS) service, South London and Maudlsey (SLaM) NHS Foundation Trust, UK

33. Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

34. Department of Psychiatry and Psychotherapy, University Hospital, Ludwig-Maximilian-University (LMU), Munich, Germany

35. Interdisciplinary Center Psychopathology and Emotion regulation (ICPE), Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

36. Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK

37. Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

38. Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, ISCIII, Dr. Antoni Pujadas, 42, Sant Boi de Llobregat, 08830, Barcelona, Spain

39. ICREA, Pg. Lluis Companys 23, 08010 Barcelona, Spain

40. School of Medical Sciences, Örebro University, Örebro, Sweden

41. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

42. Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia

43. Department of Learning, Informatics, Management and Ethics, Karolinska Institutet, Stockholm, Sweden.

44. The Swedish Institute for Health Economics, Lund, Sweden

45. Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

46. Unit of Clinical Psychiatry, University Hospital Agency of Cagliari, Cagliari, Italy

47. Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada.

48. Mental Health Centre Copenhagen, Department of Clinical Medicine, Copenhagen University Hospital, Denmark

49. Department of Biochemical Science, Pomeranian Medical University in Szczecin, 71-460 Szczecin, Poland

50. Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK

51. Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium

52. University Psychiatric Centre KU Leuven,

Kortenberg, Leuven, Belgium.

53. Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

54. AP-HM, Aix-Marseille University, School of medicine - La Timone Medical Campus, UR3279: Health Service Research and Quality of Life Center (CEReSS), Marseille, France

55. Department of Psychiatry, Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA;

56. Department of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

\* Marco, Giovanni, Arnav and Nicholas contributed equally as first authors for this manuscript.

Corresponding author

Marco Solmi

[msolmi@toh.ca](mailto:msolmi@toh.ca)

Psychiatry Department, University of Ottawa,

501 Smyth Road, Ottawa, ON, Canada

**Abstract (239/250 words)**

To further explore the role of different antipsychotic treatments for cardio-cerebrovascular mortality, we performed several subgroup, sensitivity and meta-regression analyses based on a large previous meta-analysis focusing on cohort studies assessing mortality relative risk (RR) for cardio-cerebrovascular disorders in people with schizophrenia, comparing antipsychotic treatment versus no antipsychotic. Quality assessment through the Newcastle-Ottawa Scale (NOS) and publication bias was measured. We meta-analyzed 53 different studies (schizophrenia patients: n=2,513,359; controls: n=360,504,484) to highlight the differential effects of antipsychotic treatment regimens on cardio-cerebrovascular-related mortality in incident and prevalent samples of patients with schizophrenia. We found first generation antipsychotics (FGA) to be associated with higher mortality in incident samples of schizophrenia (oral FGA [RR=2.20, 95%CI=1.29-3.77, k=1] and any FGA [RR=1.70, 95%CI=1.20-2.41, k=1]). Conversely, second generation antipsychotics (SGAs) and clozapine were associated with reduced cardio-cerebrovascular-related mortality, in prevalent samples of schizophrenia. Subgroup analyses with NOS score ≥7 (higher quality) demonstrated a significantly increased cardio-cerebrovascular disorder-related mortality, among those exposed to FGAs vs SGAs. Meta-regression analyses demonstrated a larger association between antipsychotics and decreased risk of mortality with longer follow-up, recent study year, and higher number of adjustment variables. Overall, this subanalysis of a systematic review contributes to the evolving understanding of the complex role of antipsychotic treatment for cardio-cerebrovascular mortality in schizophrenia, paving the way for more targeted interventions and improved patient outcomes.

**Keywords**

Schizophrenia; mortality; cardiovascular; cerebrovascular; antipsychotic; systematic review; meta-analysis.

**Introduction**

Schizophrenia is known to bear a very high burden on individuals worldwide, due to its high impact on the lives of individuals, premature mortality, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs) [1,2](https://www.zotero.org/google-docs/?MmFgKy). This high burden has not changed substantially in the last decade.[3,4](https://www.zotero.org/google-docs/?mSSibd) Also, partially due to its relatively low prevalence, the epidemiological and burden estimates associated with schizophrenia are underestimated compared to other mental disorders.[5](https://www.zotero.org/google-docs/?abSq0e)

Compared to the general population, people with schizophrenia have, on average, a shortened life expectancy by approximately 20 years, with the mortality gap potentially increasing over time .[6,7](https://www.zotero.org/google-docs/?nFmPZL) A recent large-scale systematic review and meta-analysis of prospective, retrospective nationwide, and targeted cohort studies found a 152% increased risk in all-cause mortality in people with schizophrenia vs. any control group based on 135 records published between the years 1957-2021, with regional differences in mortality risk.[8,9](https://www.zotero.org/google-docs/?BVKh0I)

The same meta-analysis also reported cause-specific mortality risk estimates, showing a risk increase of 876% for suicide/injury-poisoning/undetermined non-natural cause risk, 600% for pneumonia, 200-300% for infectious or endocrine or respiratory or urogenital or diabetes causes, 100-200% for alcohol, gastrointestinal or renal or nervous system or cardio-cerebrovascular or any natural causes, and 33-96% increase for liver or cerebrovascular, or breast or colon or pancreas or any cancer causes compared to the general population.[8](https://www.zotero.org/google-docs/?8KeC9F) In addition, incident schizophrenia was associated with higher all-cause and suicide mortality risks than prevalent schizophrenia. Antipsychotics were associated with lower mortality relative risk and comorbid substance use disorder with higher mortality relative risk.[8](https://www.zotero.org/google-docs/?nIayDT)

Also, the previous meta-analysis showed that the mortality gap between people with schizophrenia and the general population increased despite the development and implementation of new methods for reducing cardiovascular mortality in the general population over time.[8](https://www.zotero.org/google-docs/?1rbnkb) While the general population may have benefitted from such novel interventions, it appears that people with schizophrenia have benefitted to a lesser degree, thus increasing the mortality gap.[10](https://www.zotero.org/google-docs/?JdnY8z) Despite these advances, some gaps exist. For instance, no meta-analysis so far has explored specific moderators, with a special emphasis towards modifiable factors, of this higher cardiovascular and cerebrovascular-related mortality, which could help in suggesting differential interpretations of the phenomenon. This applies equally to characteristics of the included sample, methods used for the analyses, and different treatments offered to patients.

Therefore, the present subanalysis of a previous systematic review and meta-analysis aims at exploring the differential influence on cardio-cerebrovascular mortality of different antipsychotic treatments in people with schizophrenia, conducting subgroup and meta-regression analyses.

**Methods**

*Search*

We used data from the recently published[8](https://www.zotero.org/google-docs/?rrL6Oe) PRISMA 2020-compliant systematic review[11](https://www.zotero.org/google-docs/?odljOg), which searched Medline, PubMed, and PsycINFO for relevant records indexed up to 09/09/2021. The previous systematic review used the key (schizophrenia AND (mortal\* OR death\* OR fatal\*)) NOT (animals [mesh] NOT humans [mesh]), plus manual search. The PRISMA 2020 checklist is available in the supplementary material 1 (eTable 1).

*Inclusion and exclusion criteria*

The previous systematic review included: i) peer-reviewed publications of a cohort study (prospective, retrospective or bidirectional; nationwide or not); ii) including >70% of participants with schizophrenia and in a minimum of 100 patients; and iii) reporting quantitative information 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. The previous systematic review excluded: i) non-cohort studies such as case-control studies, reviews, meta-analyses, and systematic reviews; ii) studies that did not provide quantitative data on mortality; iii) publications that contained non-peer-reviewed data (such as proceedings, poster abstracts, or posters). No language or time restrictions were applied.

*Screening, data extraction, and quality assessment*

In the previous systematic review, title, abstract and full-text screening were conducted in duplicate (GC, LKS, MS, NS) with conflicts resolved by a third reviewer (CUC).

Details on the overall data extraction procedure are available in the previous systematic review[8](https://www.zotero.org/google-docs/?DwrDIS) and the Newcastle-Ottawa Scale[12](https://www.zotero.org/google-docs/?mE6YyJ) was used to measure the quality of the studies. Authors were contacted to provide missing data for the relevant original studies.

*Outcomes*

For the present paper, we focused only on the studies assessing cardio-cerebrovascular-related mortality in people with schizophrenia. Our primary outcome was the comparison between treatment with any antipsychotic, also differentiating among different classes and regimens whenever available, versus no antipsychotic.

As reported in the reference paper, people with schizophrenia suffer a 2-3 fold higher mortality from cardio-cerebrovascular disorders compared to the different control groups.[8](https://www.zotero.org/google-docs/?pCptNC) In this paper we sought to deepen those analyses through subgroup analyses (grouping for nation-wide sample, Newcastle-Ottawa (NOS) score, adjustment of results, mean age, incident vs prevalent sample) and meta-regression analyses (considering as moderators: follow up time, median study year, NOS score, number of variables adjusted for, mean age, sample size, proportion of females).

*Data analysis*

Main analyses examined incident plus prevalent cohorts together, comparing cardio-cerebrovascular mortality risk between the schizophrenia and control groups by antipsychotic class. We conducted a random-effects meta-analysis[13](https://www.zotero.org/google-docs/?RQYU2S) 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. I2 was used to measure the proportion of variability[14](https://www.zotero.org/google-docs/?VIfYEd) calculating the pooled RR.

Sources of heterogeneity were explored with meta-regression, sensitivity and subgroup analyses. Random-effects meta-regression analyses were conducted using follow-up time, median study year, number of variables adjusted for, mean age, sex, NOS score and sample size as moderator variables. We conducted meta-regression even if less than 10 studies provided the needed information, and we interpreted findings as exploratory. 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, NOS score ≥7 (indicating higher quality), 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.[15](https://www.zotero.org/google-docs/?M9KHFI)

**Results**

Search results

The literature search of the previous systematic review considered 8,345 abstracts that were reduced to 6,390 after the removal of duplicates and ultimately included 135 studies. After further removal of studies which did not focus on cardio-cerebrovascular related mortality in schizophrenia, 53 studies were included in this current review (Figure 1), reporting on 2,513,359 people with schizophrenia. The list of studies and reasons for exclusion of the studies evaluated at full text are reported fully elsewhere[8](https://www.zotero.org/google-docs/?0JiwQA), with additional excluded studies reported in the supplementary material 2 (eTable 2).

Thirty studies were released in Europe, 12 in North America, 10 in Asia and one included multiple countries. Overall 44 studies included only prevalent schizophrenia, eight only incident schizophrenia, and one both. For antipsychotic treatment, since only one study[16](https://www.zotero.org/google-docs/?kbYRaE) specifically reported individual data for strict cardiovascular and cerebrovascular disorders, we performed the analyses on all the studies providing data for any cardio-cerebrovascular disorder.

*Cardio-cerebrovascular mortality risk among people with schizophrenia by antipsychotic treatment regimen*

Incident plus prevalent, incident, and prevalent risks for cardio-cerebrovascular mortality in schizophrenia by antipsychotic treatment are reported in Table 2.

In incident plus prevalent schizophrenia, there was no statistically significant difference between antipsychotic treatment subgroups. Nevertheless, considering single classes, the highest protective effect emerged for clozapine (RR=0.50, 95%CI=0.29-0.86, k=2, I2=21.3), followed by any oral second-generation antipsychotic (SGA) (RR=0.57, 95%CI=0.52-0.62, k=2, I2=0), any SGA (RR=0.65, 95%CI=0.48-0.89, k=2, I2=71.4), any long-acting injectable (LAI) SGA (RR=0.66, 95%CI=0.52-0.84, k=1) and any LAI first-generation antipsychotics (FGA) (RR=0.70, 95%CI=0.62-0.78, k=1). A neutral effect emerged for any oral FGA and any antipsychotic.

In incident schizophrenia, a statistically significant difference emerged among antipsychotic treatment subgroups (p=0.001). No antipsychotic regimen ensured a protective effect; instead, while treatment with any SGA, any oral SGA, and clozapine proved to be neutral, a harming effect emerged for any oral FGA (RR=2.20, 95%CI=1.29-3.77, k=1) and any FGA (RR=1.70, 95%CI=1.20-2.41, k=1).

In prevalent schizophrenia, a statistically significant difference emerged among subgroups (p=0.001). A protective effect was shown by any regimen, with effect size highest for clozapine (RR=0.55, 95%CI=0.47-0.64, k=1) and lowest for any LAI FGA (RR=0.70, 95%CI=0.62-0.78, k=1).

*Subgroup analyses*

Subgroup analyses are available in Table 3 by nation-wide sample, NOS score, adjustment of results, mean age, and incident versus prevalent for any cardio-cerebrovascular, cardiovascular, cerebrovascular mortality in people with schizophrenia versus control groups. For any cardio-cerebrovascular disorder-related death: i) comparing people with schizophrenia with any control group, a significantly higher cardio-cerebrovascular mortality rate was observed with NOS score ≥7; ii) compared to the general population, a significantly higher cardio-cerebrovascular mortality rate was observed with use of nation-wide sample and NOS score ≥7; and iii) compared to people matched for comorbid condition, a significant higher cardio-cerebrovascular mortality risk emerged when results were not adjusted. Finally, the protective effect of antipsychotics was not different in the incident compared to the prevalent sample.

For cardiovascular disorders-related death: comparing people with schizophrenia both with any control group and with the general population, a significantly higher cardio-cerebrovascular mortality rate was observed with NOS score ≥7 and mean age ≥40 years; ii) compared to people matched for comorbid condition a significantly higher cardio-cerebrovascular mortality rate was observed when results were not adjusted.

For cerebrovascular disorders-related death, comparing people with schizophrenia with the general population, a significantly higher cardio-cerebrovascular mortality rate was observed with NOS score ≥7 and without adjustment of results for covariates.

*Meta-regression analyses*

Meta-regression analyses are available in Table 4. For any cardio-cerebrovascular disorder, when comparing people with schizophrenia with any control group, a higher mortality rate was significantly moderated by more recent median study year (beta=0.02) and lower number of variables used for adjusting (beta=-0.02); when compared to the general population by more recent median study year (beta=0.02) and higher NOS score (beta=0.22). Regarding effect of antipsychotic treatment, a significantly enhanced protective effect for treatment with any antipsychotic was moderated by longer follow-up time (beta=-0.04), more recent median study year (beta=-0.09), higher number of variables adjusted for (beta=-0.06), and higher sample size (beta<-0.001). The same was observed for treatment with any FGA, except for sample size (beta respectively -0.07, -0.23, -0.12).

For cardiovascular disorders, when comparing people with schizophrenia with any control group, a higher cardio-cerebrovascular mortality rate was significantly moderated by lower follow-up time (beta=-0.01) and higher sample size (beta<0.001).

For cerebrovascular disorders, when comparing people with schizophrenia with any control group, a higher cardio-cerebrovascular mortality rate was significantly moderated by higher NOS score (beta=0.18) and lower number of variables used for adjusting results (beta=-0.08); when compared to the general population, by more recent median study year (beta=0.02) and higher NOS score (beta=0.23).

**Discussion**

Overall, we meta-analyzed 53 different studies including 2,513,359 patients with schizophrenia and 360,504,484 control subjects to highlight the differential effects of antipsychotic treatment regimens on cardio-cerebrovascular-related mortality in incident and prevalent samples of people with schizophrenia. We most notably found FGAs to be significantly harmful, compared to other antipsychotics, in incident samples of schizophrenia, i.e., earlier in the illness course. Conversely, the available data indicated that SGAs and clozapine were protective, as compared to FGAs, in prevalent samples of schizophrenia. Meta-regression analyses demonstrated reduced cardio-cerebrovascular mortality from SGA usage was associated with longer follow-up periods, more recent median study year, and higher number of adjustment variables in statistical models as well as higher study quality.

In incident schizophrenia samples, FGAs were associated with increased cardio-cerebrovascular mortality as compared to SGAs. These results correspond with previous registry data demonstrating higher sudden cardiac death among patients with schizophrenia, especially those treated with FGAs.[17](https://www.zotero.org/google-docs/?wIZIXb) In particular, due to autonomic system dysfunction at baseline, patients with schizophrenia generally have lower heart rate variability and prolonged QT intervals, which when augmented by FGA use may increase their risk of sudden cardiac death.[18](https://www.zotero.org/google-docs/?QerWeB) In incident cases with little previous follow-up, baseline comorbidities (i.e., diabetes, obesity) also put people with schizophrenia at higher risk of antipsychotic-induced acceleration of metabolic syndrome, which mediates both mortality related to ischemic heart disease and intracranial atherosclerosis.[19](https://www.zotero.org/google-docs/?1Gom3Z) However, due to the relatively shorter treatment period, increased cardio-cerebral mortality among incident samples may be more attributable to patient-specific factors limiting the ability to provide effective schizophrenia-pertinent care. Viron and colleagues (2013) have previously emphasized how paranoia and other symptoms of illness may influence engagement and therapeutic alliance-building with healthcare providers.[20](https://www.zotero.org/google-docs/?ZXSZU0) Hence, while prevalent samples may have established care plans or relationships, incident cases may not have had sufficient time to achieve those necessary components to effective care, leading to higher rates of antipsychotic treatment discontinuation[21](https://www.zotero.org/google-docs/?yyTOEa) and cardio-cerebrovascular mortality.[20](https://www.zotero.org/google-docs/?kJOkMU) Of note, Ray and colleagues (2001) postulated the most dramatic increase in antipsychotic-associated cardio-cerebrovascular mortality occurs at younger ages among FGA-treated patients as compared to SGA-treated counterparts,[19](https://www.zotero.org/google-docs/?4I6vk3) which may be due to autonomic system dysfunction, direct cardiac repolarization effects or, even depressogenic effects of FGAs.[22](https://www.zotero.org/google-docs/?u4OS3M). As incident samples in this meta-analysis were younger, this is an important effect modifier, which may have influenced our findings.

Meanwhile, in prevalent samples, SGAs and clozapine were considered protective with respect to cardio-cerebrovascular mortality. Cardio-metabolic adverse effects are known to emerge commonly during treatment with antipsychotics, especially clozapine and SGAs; nevertheless, in our meta-analysis they proved to be protective in the overall and prevalent sample, and not increasing cardio-cerebrovascular mortality risk in the incident sample. This seeming discordance might be due to a parallel enhancement of patients’ adherence towards comorbid medical disease monitoring and treatment.[23](https://www.zotero.org/google-docs/?jEq7Ba) Previous consensus guidelines for diabetes-monitoring among patients with schizophrenia recommended more frequent testing and monitoring as compared to the general population.[24](https://www.zotero.org/google-docs/?cAWHnh) People with prevalent schizophrenia may more often have multidisciplinary teams led by both primary care physicians and psychiatrists who may provide more intensive screening as compared to the general population.[20](https://www.zotero.org/google-docs/?6M4pBV) Likewise, in cases of clozapine titration, patients have received as frequent as daily or weekly follow-up, which may better facilitate comorbidity treatment.[8,25](https://www.zotero.org/google-docs/?uuWJnw) Furthermore, a Finnish national database within-subject analysis study indicated that patients with schizophrenia who were taking antipsychotics were significantly less likely to interrupt ongoing treatment with statins, antidiabetic agents, anti-hypertensive medications, and beta-blockers than when they were not taking these medications.[26](https://www.zotero.org/google-docs/?IGYIIL) In another Finnish nation-wide cohort, clozapine was associated with the lowest risk of developing a substance use disorder among patients with schizophrenia.[27](https://www.zotero.org/google-docs/?kLdYVe) Such association between the use of antipsychotics and better adherence to medical treatments is likely to be another mediator of the protective effect of antipsychotic use on cardio-cerebrovascular mortality risk in people with schizophrenia, even among those using FGA. However, documentation of the number of follow-up visits and compliance metrics are necessary to validate this hypothesis.

Notably, from meta-regression analyses, reduced cardio-cerebrovascular mortality was associated with recent median study year, higher study quality, and higher number of variables used for adjusting results. In keeping with intensive comorbidity monitoring and higher treatment adherence, more recent studies may include samples who could have benefited from updated guidelines. The majority of schizophrenia-related comorbidity management guidelines have been issued in more recent years since 2010, with recent guidelines newly emphasizing monitoring for metabolic syndrome and pursuing interdisciplinary collaborations with primary care providers for holistic care.[28](https://www.zotero.org/google-docs/?c2PvyV) As guidelines are further consolidated into clinical practice, mortality risk is expected to reduce further; although, this possibility warrants further investigation with studies adjusting for year of presentation (e.g., pre- versus post-implementation of comorbidity management models or guidelines). While lower study quality and lower number of adjustment variables as predictors of higher mortality may lead to confounding, the insufficiently adjusted statistical models did not overestimate, but rather seemed to underestimate the effect size of the protective antipsychotic effect. This seeming discordance is likely due to the fact that the studies with higher quality and a higher number of adjustment variables, as well as longer follow-up, were nationwide or other large database studies that are expected to most accurately reflect the interaction between antipsychotic treatment and mortality risk.

The strengths of this study include its inclusion of comparative studies from multiple databases, and a broad search strategy. The a priori protocol minimizes reporting bias, and the screening, extraction and quality assessment in duplicate reduced errors. Furthermore, the included studies were mainly of fair or higher quality, which allowed for synthesis of generally reliable evidence. Finally, in studying mortality risk, randomized controlled trials, with their limited sample size, modest follow-up duration, high dropout rates, and exclusion of severely ill patients, may not be the most effective or feasible approach. Instead, longitudinal cohort studies and nationwide database analyses offer more suitable options for quantifying mortality risk and identifying generalizable aggravating and protective factors.

Nevertheless, it is crucial to approach the findings of this meta-analysis with caution, bearing also its limitations in mind. First, while the selected methods are appropriate for estimating cardio-cerebrovascular mortality risk, the absence of randomization limits our ability to control for unmeasured confounders, such as the severity of schizophrenia.[29](https://www.zotero.org/google-docs/?6Vz0Wq) Despite our efforts to enhance the analysis by including unadjusted risk estimates, there is a possibility that we missed some of the most relevant covariates associated with cardio-cerebrovascular mortality risk. The potential residual confounding, encompassing differences in psychological, behavioral, social, and environmental factors, represents the complex reality of individuals living with schizophrenia. Second, although we included 53 studies, certain conclusions were drawn from syntheses with few included studies. Thus, further research is warranted, particularly for a quantitative evaluation of factors influencing cardio-cerebrovascular mortality. Third, uncertainties may have been introduced by issues, such as inconsistencies in age group definitions and imprecision in control numbers, despite our efforts to estimate them based on census-based subpopulation numbers during data collection. Fourth, the included studies are mainly Scandinavian, which limits the generalizability to other geographical regions. Fifth, the classification of antipsychotics, other than clozapine, based on an arbitrary dichotomy (FGA or SGA) limits the applicability of our findings, whereby understanding the relative risk associated with individual drugs would be of clinical benefit. Sixth, as our study focused on mortality, we did not consider the effect of antipsychotics on symptom reduction of the disease itself. SGAs have a broader efficacy profile, also improving negative and depressive symptoms, and ultimately having better acceptability, which may lead to better treatment of other medical conditions.[30](https://www.zotero.org/google-docs/?IYC4A2) Finally, the varied metrics used by the meta-analyzed studies to report cardio-cerebrovascular mortality required combining risk estimates with slightly different characteristics, potentially introducing some imprecision. However, given the rarity of cardio-cerebrovascular mortality events in the studies with limited follow-up time, the uniform cohort design and population evaluation across all included studies, the overall level of imprecision is likely to be low. Nevertheless, based on these considerations, future studies should include large sample sizes[31](https://www.zotero.org/google-docs/?UI7Zla), longitudinal follow-up, standardized outcomes documentation, comprehensive covariate data collection, and robust methods to minimize the impact of reporting or selection bias.

**Conclusion**

This meta-analysis synthesized the complex relationship between antipsychotic treatment regimens and cardiovascular- and cerebrovascular-related mortality in patients with schizophrenia. Findings demonstrate increased cardio-cerebrovascular mortality risk with FGA treatment in incident cases with schizophrenia, likely linked to autonomic system dysfunction, direct cardiac repolarization effects, exacerbation of baseline comorbidities, and/or challenges to effective schizophrenia care. In contrast, SGAs and clozapine appeared to be protective in prevalent cases with schizophrenia, potentially resulting from improved adherence, improved follow-up and related monitoring, and multidisciplinary care. The differential effects observed in incident and prevalent samples highlight the importance of considering the stage of illness and the duration of antipsychotic use. Future research should focus on large sample sizes, longitudinal follow-up, standardized outcomes, and robust methods to further elucidate the factors influencing cardio-cerebrovascular and other types of mortality in this population. Overall, this systematic review and meta-analysis contributes to the evolving understanding of the differentiated role of antipsychotic treatment regarding mortality in schizophrenia, paving the way for more targeted interventions and improved patient outcomes.

**Disclosures**

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

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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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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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**References**

[1 GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Lond Engl* 2020; **396**: 1204–22.](https://www.zotero.org/google-docs/?nL4bjH)

[2 Fusar-Poli P, Estradé A, Stanghellini G, *et al.* The lived experience of psychosis: a bottom-up review co-written by experts by experience and academics. *World Psychiatry Off J World Psychiatr Assoc WPA* 2022; **21**: 168–88.](https://www.zotero.org/google-docs/?nL4bjH)

[3 Charlson FJ, Ferrari AJ, Santomauro DF, *et al.* Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophr Bull* 2018; **44**: 1195–203.](https://www.zotero.org/google-docs/?nL4bjH)

[4 Whiteford HA, Degenhardt L, Rehm J, *et al.* Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet Lond Engl* 2013; **382**: 1575–86.](https://www.zotero.org/google-docs/?nL4bjH)

[5 GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* 2022; **9**: 137–50.](https://www.zotero.org/google-docs/?nL4bjH)

[6 Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. *Am J Psychiatry* 2013; **170**: 324–33.](https://www.zotero.org/google-docs/?nL4bjH)

[7 Tanskanen A, Tiihonen J, Taipale H. Mortality in schizophrenia: 30-year nationwide follow-up study. *Acta Psychiatr Scand* 2018; **138**: 492–9.](https://www.zotero.org/google-docs/?nL4bjH)

[8 Correll CU, Solmi M, Croatto G, *et al.* Mortality in people with schizophrenia: a systematic review and meta‐analysis of relative risk and aggravating or attenuating factors. *World Psychiatry* 2022; **21**: 248–71.](https://www.zotero.org/google-docs/?nL4bjH)

[9 Solmi M, Croatto G, Fornaro M, *et al.* Regional differences in mortality risk and in attenuating or aggravating factors in schizophrenia: A systematic review and meta-analysis. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol* 2024; **80**: 55–69.](https://www.zotero.org/google-docs/?nL4bjH)

[10 Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007; **64**: 1123–31.](https://www.zotero.org/google-docs/?nL4bjH)

[11 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; : n71.](https://www.zotero.org/google-docs/?nL4bjH)

[12 Wells G, Shea B, O’Connell J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical\_epidemiology/oxford.asp.](https://www.zotero.org/google-docs/?nL4bjH)

[13 Serghiou S, Goodman SN. Random-Effects Meta-analysis: Summarizing Evidence With Caveats. *JAMA* 2019; **321**: 301–2.](https://www.zotero.org/google-docs/?nL4bjH)

[14 Seagroatt V, Stratton I. Bias in meta-analysis detected by a simple, graphical test. Test had 10% false positive rate. *BMJ* 1998; **316**: 470; author reply 470-471.](https://www.zotero.org/google-docs/?nL4bjH)

[15 Pierce CA. Software Review: Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2006). Comprehensive Meta-Analysis (Version 2.2.027) [Computer software]. Englewood, NJ: Biostat. *Organ Res Methods* 2008; **11**: 188–91.](https://www.zotero.org/google-docs/?nL4bjH)

[16 Oh J, Nam H, Park S, Chae J-H, Kim T-S. Decreased cardiovascular death in schizophrenia patients treated with antipsychotics: A Korean national cohort study. *Schizophr Res* 2021; **228**: 417–24.](https://www.zotero.org/google-docs/?nL4bjH)

[17 Kiviniemi M, Suvisaari J, Koivumaa-Honkanen H, Häkkinen U, Isohanni M, Hakko H. Antipsychotics and mortality in first-onset schizophrenia: Prospective Finnish register study with 5-year follow-up. *Schizophr Res* 2013; **150**: 274–80.](https://www.zotero.org/google-docs/?nL4bjH)

[18 Koponen H, Alaräisänen A, Saari K, *et al.* Schizophrenia and sudden cardiac death—A review. *Nord J Psychiatry* 2008; **62**: 342–5.](https://www.zotero.org/google-docs/?nL4bjH)

[19 Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the Risk of Sudden Cardiac Death. *Arch Gen Psychiatry* 2001; **58**: 1161.](https://www.zotero.org/google-docs/?nL4bjH)

[20 Viron M, Baggett T, Hill M, Freudenreich O. Schizophrenia for Primary Care Providers: How to Contribute to the Care of a Vulnerable Patient Population. *Am J Med* 2012; **125**: 223–30.](https://www.zotero.org/google-docs/?nL4bjH)

[21 Rubio JM, Taipale H, Tanskanen A, Correll CU, Kane JM, Tiihonen J. Long-term Continuity of Antipsychotic Treatment for Schizophrenia: A Nationwide Study. *Schizophr Bull* 2021; **47**: 1611–20.](https://www.zotero.org/google-docs/?nL4bjH)

[22 Voruganti L, Awad AG. Neuroleptic dysphoria: towards a new synthesis. *Psychopharmacology (Berl)* 2004; **171**: 121–32.](https://www.zotero.org/google-docs/?nL4bjH)

[23 Solmi M, Correll CU. The antipsychotic paradox: Lessons regarding determinants of premature mortality. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol* 2022; **62**: 1–3.](https://www.zotero.org/google-docs/?nL4bjH)

[24 Suvisaari J, Keinänen J, Eskelinen S, Mantere O. Diabetes and Schizophrenia. *Curr Diab Rep* 2016; **16**: 16.](https://www.zotero.org/google-docs/?nL4bjH)

[25 Bhamidipati T, Divadeenam K. Management of Clozapine Titration in the Setting of Cardiac Comorbidities. *Cureus* 2021; published online Nov 4. DOI:10.7759/cureus.19257.](https://www.zotero.org/google-docs/?nL4bjH)

[26 Taipale H, Tanskanen A, Mehtälä J, Vattulainen P, Correll CU, Tiihonen J. 20‐year follow‐up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry* 2020; **19**: 61–8.](https://www.zotero.org/google-docs/?nL4bjH)

[27 Lähteenvuo M, Luykx JJ, Taipale H, *et al.* Associations between antipsychotic use, substance use and relapse risk in patients with schizophrenia: real-world evidence from two national cohorts. *Br J Psychiatry J Ment Sci* 2022; **221**: 758–65.](https://www.zotero.org/google-docs/?nL4bjH)

[28 Kuipers E, Yesufu-Udechuku A, Taylor C, Kendall T. Management of psychosis and schizophrenia in adults: summary of updated NICE guidance. *BMJ* 2014; **348**: g1173–g1173.](https://www.zotero.org/google-docs/?nL4bjH)

[29 Ilzarbe L, Vieta E. The elephant in the room: Medication as confounder. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol* 2023; **71**: 6–8.](https://www.zotero.org/google-docs/?nL4bjH)

[30 Zhang J-P, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *Int J Neuropsychopharmacol* 2013; **16**: 1205–18.](https://www.zotero.org/google-docs/?nL4bjH)

[31 De Prisco M, Vieta E. The never-ending problem: Sample size matters. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol* 2024; **79**: 17–8.](https://www.zotero.org/google-docs/?nL4bjH)

[32 Allebeck P, Wistedt B. Mortality in schizophrenia. A ten-year follow-up based on the Stockholm County inpatient register. *Arch Gen Psychiatry* 1986; **43**: 650–3.](https://www.zotero.org/google-docs/?nL4bjH)

[33 Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry J Ment Sci* 2010; **196**: 116–21.](https://www.zotero.org/google-docs/?nL4bjH)

[34 Buda M, Tsuang MT, Fleming JA. Causes of death in DSM-III schizophrenics and other psychotics (atypical group). A comparison with the general population. *Arch Gen Psychiatry* 1988; **45**: 283–5.](https://www.zotero.org/google-docs/?nL4bjH)

[35 Cheng K-Y, Lin C-Y, Chang T-K, Lin CCH, Lu T-H, Chen S-Y. Mortality among long-stay patients with schizophrenia during the setting-up of community facilities under the Yuli model. *Health Psychol Behav Med* 2014; **2**: 602–12.](https://www.zotero.org/google-docs/?nL4bjH)

[36 Fors BM, Isacson D, Bingefors K, Widerlöv B. Mortality among persons with schizophrenia in Sweden: an epidemiological study. *Nord J Psychiatry* 2007; **61**: 252–9.](https://www.zotero.org/google-docs/?nL4bjH)

[37 Hayes JF, Marston L, Walters K, King MB, Osborn DPJ. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. *Br J Psychiatry J Ment Sci* 2017; **211**: 175–81.](https://www.zotero.org/google-docs/?nL4bjH)

[38 Kredentser MS, Martens PJ, Chochinov HM, Prior HJ. Cause and rate of death in people with schizophrenia across the lifespan: a population-based study in Manitoba, Canada. *J Clin Psychiatry* 2014; **75**: 154–61.](https://www.zotero.org/google-docs/?nL4bjH)

[39 Kugathasan P, Stubbs B, Aagaard J, Jensen SE, Munk Laursen T, Nielsen RE. Increased mortality from somatic multimorbidity in patients with schizophrenia: a Danish nationwide cohort study. *Acta Psychiatr Scand* 2019; **140**: 340–8.](https://www.zotero.org/google-docs/?nL4bjH)

[40 Lahti M, Tiihonen J, Wildgust H, *et al.* Cardiovascular morbidity, mortality and pharmacotherapy in patients with schizophrenia. *Psychol Med* 2012; **42**: 2275–85.](https://www.zotero.org/google-docs/?nL4bjH)

[41 Laursen TM, Wahlbeck K, Hällgren J, *et al.* Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. *PloS One* 2013; **8**: e67133.](https://www.zotero.org/google-docs/?nL4bjH)

[42 Mortensen PB, Juel K. Mortality and causes of death in schizophrenic patients in Denmark. *Acta Psychiatr Scand* 1990; **81**: 372–7.](https://www.zotero.org/google-docs/?nL4bjH)

[43 Mortensen PB, Juel K. Mortality and causes of death in first admitted schizophrenic patients. *Br J Psychiatry J Ment Sci* 1993; **163**: 183–9.](https://www.zotero.org/google-docs/?nL4bjH)

[44 Newman SC, Bland RC. Mortality in a cohort of patients with schizophrenia: a record linkage study. *Can J Psychiatry Rev Can Psychiatr* 1991; **36**: 239–45.](https://www.zotero.org/google-docs/?nL4bjH)

[45 Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature Mortality Among Adults With Schizophrenia in the United States. *JAMA Psychiatry* 2015; **72**: 1172–81.](https://www.zotero.org/google-docs/?nL4bjH)

[46 Talaslahti T, Alanen H-M, Hakko H, Isohanni M, Häkkinen U, Leinonen E. Mortality and causes of death in older patients with schizophrenia. *Int J Geriatr Psychiatry* 2012; **27**: 1131–7.](https://www.zotero.org/google-docs/?nL4bjH)

[47 Westman J, Eriksson SV, Gissler M, *et al.* Increased cardiovascular mortality in people with schizophrenia: a 24-year national register study. *Epidemiol Psychiatr Sci* 2018; **27**: 519–27.](https://www.zotero.org/google-docs/?nL4bjH)

[48 Zilber N, Schufman N, Lerner Y. Mortality among psychiatric patients--the groups at risk. *Acta Psychiatr Scand* 1989; **79**: 248–56.](https://www.zotero.org/google-docs/?nL4bjH)

[49 Torniainen M, Mittendorfer-Rutz E, Tanskanen A, *et al.* Antipsychotic treatment and mortality in schizophrenia. *Schizophr Bull* 2015; **41**: 656–63.](https://www.zotero.org/google-docs/?nL4bjH)

[50 Berardi D, Stivanello E, Chierzi F, *et al.* Mortality in mental health patients of the Emilia-Romagna region of Italy: A registry-based study. *Psychiatry Res* 2021; **296**: 113702.](https://www.zotero.org/google-docs/?nL4bjH)

[51 Pan Y-J, Yeh L-L, Chan H-Y, Chang C-K. Excess mortality and shortened life expectancy in people with major mental illnesses in Taiwan. *Epidemiol Psychiatr Sci* 2020; **29**: e156.](https://www.zotero.org/google-docs/?nL4bjH)

[52 Yung NCL, Wong CSM, Chan JKN, Or PCF, Chen EYH, Chang WC. Mortality in patients with schizophrenia admitted for incident ischemic stroke: A population-based cohort study. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol* 2020; **31**: 152–7.](https://www.zotero.org/google-docs/?nL4bjH)

[53 Curkendall SM, Mo J, Glasser DB, Rose Stang M, Jones JK. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. *J Clin Psychiatry* 2004; **65**: 715–20.](https://www.zotero.org/google-docs/?nL4bjH)

[54 Kiviniemi M, Suvisaari J, Pirkola S, Häkkinen U, Isohanni M, Hakko H. Regional differences in five-year mortality after a first episode of schizophrenia in Finland. *Psychiatr Serv Wash DC* 2010; **61**: 272–9.](https://www.zotero.org/google-docs/?nL4bjH)

[55 Girardi P, Schievano E, Fedeli U, Braggion M, Nuti M, Amaddeo F. Causes of mortality in a large population-based cohort of psychiatric patients in Southern Europe. *J Psychiatr Res* 2021; **136**: 167–72.](https://www.zotero.org/google-docs/?nL4bjH)

[56 Enger C, Weatherby L, Reynolds RF, Glasser DB, Walker AM. Serious cardiovascular events and mortality among patients with schizophrenia. *J Nerv Ment Dis* 2004; **192**: 19–27.](https://www.zotero.org/google-docs/?nL4bjH)

[57 Kilbourne AM, Morden NE, Austin K, *et al.* Excess heart-disease-related mortality in a national study of patients with mental disorders: identifying modifiable risk factors. *Gen Hosp Psychiatry* 2009; **31**: 555–63.](https://www.zotero.org/google-docs/?nL4bjH)

[58 Laursen TM, Nordentoft M. Heart disease treatment and mortality in schizophrenia and bipolar disorder - changes in the Danish population between 1994 and 2006. *J Psychiatr Res* 2011; **45**: 29–35.](https://www.zotero.org/google-docs/?nL4bjH)

[59 Bodén R, Molin E, Jernberg T, Kieler H, Lindahl B, Sundström J. Higher mortality after myocardial infarction in patients with severe mental illness: a nationwide cohort study. *J Intern Med* 2015; **277**: 727–36.](https://www.zotero.org/google-docs/?nL4bjH)

[60 Chen P-H, Tsai S-Y, Pan C-H, *et al.* Age Effect on Incidence, Physical, and Psychiatric Comorbidity for Sudden Cardiac Death in Schizophrenia: Effet de l’âge sur l’incidence, la comorbidité physique et psychiatrique de la mort cardiaque subite dans la schizophrénie. *Can J Psychiatry Rev Can Psychiatr* 2021; **66**: 367–75.](https://www.zotero.org/google-docs/?nL4bjH)

[61 Wellejus Albertsen L, Heide-Jørgensen U, Schmidt SAJ, *et al.* The DANish Comorbidity Index for Acute Myocardial Infarction (DANCAMI): Development, Validation and Comparison with Existing Comorbidity Indices. *Clin Epidemiol* 2020; **12**: 1299–311.](https://www.zotero.org/google-docs/?nL4bjH)

[62 Castagnini A, Foldager L, Bertelsen A. Excess mortality of acute and transient psychotic disorders: comparison with bipolar affective disorder and schizophrenia. *Acta Psychiatr Scand* 2013; **128**: 370–5.](https://www.zotero.org/google-docs/?nL4bjH)

[63 Daumit GL, Anthony CB, Ford DE, *et al.* Pattern of mortality in a sample of Maryland residents with severe mental illness. *Psychiatry Res* 2010; **176**: 242–5.](https://www.zotero.org/google-docs/?nL4bjH)

[64 Osby U, Correia N, Brandt L, Ekbom A, Sparén P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res* 2000; **45**: 21–8.](https://www.zotero.org/google-docs/?nL4bjH)

[65 Hennessy S, Bilker WB, Knauss JS, *et al.* Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *BMJ* 2002; **325**: 1070.](https://www.zotero.org/google-docs/?nL4bjH)

[66 Attar R, Valentin JB, Freeman P, Andell P, Aagaard J, Jensen SE. The effect of schizophrenia on major adverse cardiac events, length of hospital stay, and prevalence of somatic comorbidities following acute coronary syndrome. *Eur Heart J Qual Care Clin Outcomes* 2019; **5**: 121–6.](https://www.zotero.org/google-docs/?nL4bjH)

[67 Fleetwood K, Wild SH, Smith DJ, *et al.* Severe mental illness and mortality and coronary revascularisation following a myocardial infarction: a retrospective cohort study. *BMC Med* 2021; **19**: 67.](https://www.zotero.org/google-docs/?nL4bjH)

[68 Kang J-H, Xirasagar S, Lin H-C. Lower mortality among stroke patients with schizophrenia: a nationwide population-based study. *Psychosom Med* 2011; **73**: 106–11.](https://www.zotero.org/google-docs/?nL4bjH)

[69 Kapral MK, Kurdyak P, Casaubon LK, Fang J, Porter J, Sheehan KA. Stroke care and case fatality in people with and without schizophrenia: a retrospective cohort study. *BMJ Open* 2021; **11**: e044766.](https://www.zotero.org/google-docs/?nL4bjH)

[70 Kurdyak P, Vigod S, Calzavara A, Wodchis WP. High mortality and low access to care following incident acute myocardial infarction in individuals with schizophrenia. *Schizophr Res* 2012; **142**: 52–7.](https://www.zotero.org/google-docs/?nL4bjH)

[71 Mohamed MO, Rashid M, Farooq S, *et al.* Acute Myocardial Infarction in Severe Mental Illness: Prevalence, Clinical Outcomes, and Process of Care in U.S. Hospitalizations. *Can J Cardiol* 2019; **35**: 821–30.](https://www.zotero.org/google-docs/?nL4bjH)

[72 Søgaard M, Skjøth F, Kjældgaard JN, Larsen TB, Hjortshøj SP, Riahi S. Atrial fibrillation in patients with severe mental disorders and the risk of stroke, fatal thromboembolic events and bleeding: a nationwide cohort study. *BMJ Open* 2017; **7**: e018209.](https://www.zotero.org/google-docs/?nL4bjH)

[73 Strom BL, Eng SM, Faich G, *et al.* Comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). *Am J Psychiatry* 2011; **168**: 193–201.](https://www.zotero.org/google-docs/?nL4bjH)

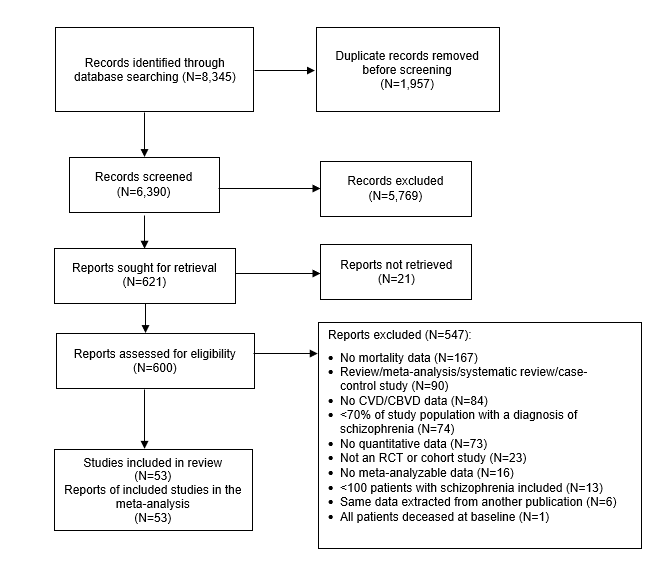
[74 Tang C-H, Ramcharran D, Yang C-WW, *et al.* A nationwide study of the risk of all-cause, sudden death, and cardiovascular mortality among antipsychotic-treated patients with schizophrenia in Taiwan. *Schizophr Res* 2021; **237**: 9–19.](https://www.zotero.org/google-docs/?nL4bjH)

[75 Chan JKN, Wong CSM, Yung NCL, Chen EYH, Chang WC. Pre-existing chronic physical morbidity and excess mortality in people with schizophrenia: a population-based cohort study. *Soc Psychiatry Psychiatr Epidemiol* 2022; **57**: 485–93.](https://www.zotero.org/google-docs/?nL4bjH)

[76 Kugathasan P, Wu H, Gaughran F, *et al.* Association of physical health multimorbidity with mortality in people with schizophrenia spectrum disorders: Using a novel semantic search system that captures physical diseases in electronic patient records. *Schizophr Res* 2020; **216**: 408–15.](https://www.zotero.org/google-docs/?nL4bjH)

[77 Hjorthøj C, Østergaard MLD, Benros ME, *et al.* Association between alcohol and substance use disorders and all-cause and cause-specific mortality in schizophrenia, bipolar disorder, and unipolar depression: a nationwide, prospective, register-based study. *Lancet Psychiatry* 2015; **2**: 801–8.](https://www.zotero.org/google-docs/?nL4bjH)

[78 Chong S-A, Tay JAM, Subramaniam M, Pek E, Machin D. Mortality rates among patients with schizophrenia and tardive dyskinesia. *J Clin Psychopharmacol* 2009; **29**: 5–8.](https://www.zotero.org/google-docs/?nL4bjH)



**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** |
| Allebeck 1986[32](https://www.zotero.org/google-docs/?Y1f5BG) | Sweden | 1971-1981 | Schizophrenia vs general population | P | 1,190 | 16,902 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 9 |
| Brown 2010[33](https://www.zotero.org/google-docs/?g21CbV) | UK | 1981-2006 | Schizophrenia vs general population | P | 370 | 24,328,853 | Any cardio-cerebrovascular, cardiovascular | 9 |
| Buda 1988[34](https://www.zotero.org/google-docs/?xBeUCb) | US | 1934-1974 | Schizophrenia vs general population | P | 332 | na | Any cardio-cerebrovascular | 9 |
| Cheng 2014[35](https://www.zotero.org/google-docs/?5llwUO) | Taiwan | 1998-2008 | Schizophrenia vs general population | P | 2,457 | 22,561,450 | Any cardio-cerebrovascular | 9 |
| Crump 2013[6](https://www.zotero.org/google-docs/?6U10Sp) | Sweden | 2003-2009 | Schizophrenia vs general population | P | 8,277 | 6,097,834 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 9 |
| Fors 2007[36](https://www.zotero.org/google-docs/?iMwkkr) | Sweden | 1991-2000 | Schizophrenia vs general population | P | 255 | 1,530 | Any cardio-cerebrovascular | 9 |
| Hayes 2017[37](https://www.zotero.org/google-docs/?Hoc7vS) | UK | 2000-2014 | Schizophrenia vs general population | P | 22,497 | 241,884 | Any cardio-cerebrovascular | 9 |
| Kredentser 2014[38](https://www.zotero.org/google-docs/?LEzWmw) | Canada | 1999-2008 | Schizophrenia vs general population | P | 9,038 | 978,128 | Any cardio-cerebrovascular | 9 |
| Kugathasan 2019[39](https://www.zotero.org/google-docs/?UNt3Zh) | Denmark | 1995-2015 | Schizophrenia vs general population | P | 30,210 | 5,432,821 | Any cardio-cerebrovascular | 9 |
| Lahti 2012[40](https://www.zotero.org/google-docs/?cP0Xtz) | Finland | 1969-2004 | Schizophrenia vs general population | I | 204 | 12,735 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 9 |
| Laursen 2013[41](https://www.zotero.org/google-docs/?LLsXbB) | Denmark, Finland, Sweden | 2000-2007 | Schizophrenia vs general population | P | 66,088 | 4,490,039 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 9 |
| Mortensen 1990[42](https://www.zotero.org/google-docs/?vcuP2Z) | Denmark | 1957-1986 | Schizophrenia vs general population | P | 6,178 | 2,494,178 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 6 |
| Mortensen 1993[43](https://www.zotero.org/google-docs/?ksRcib) | Denmark | 1970-1987 | Schizophrenia vs general population | I | 9,156 | 2,561,000 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 6 |
| Newman 1991[44](https://www.zotero.org/google-docs/?hRECPL) | Canada | 1976-1985 | Schizophrenia vs general population | P | 3,623 | 2,238,000 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 6 |
| Olfson 2015[45](https://www.zotero.org/google-docs/?T4Hwk4) | US | 2001-2007 | Schizophrenia vs general population | I | 1,138,853 | 173,699,853 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 9 |
| Talaslahti 2012[46](https://www.zotero.org/google-docs/?DfUsBp) | Finland | 1992-2008 | Schizophrenia vs general population | P | 9,461 | 941,041 | Any cardio-cerebrovascular | 9 |
| Tanskanen 2018[7](https://www.zotero.org/google-docs/?RLJ6Mn) | Finland | 1984-2014 | Schizophrenia vs general population | P | 42,343 | 4,515,838 | Any cardio-cerebrovascular | 9 |
| Westman 2017[47](https://www.zotero.org/google-docs/?4T9UwX) | Sweden | 1987-2010 | Schizophrenia vs general population | P | 46,911 | 10,678,728 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 9 |
| Zilber 1989[48](https://www.zotero.org/google-docs/?wWtjXp) | Israel | 1978-1983 | Schizophrenia vs general population | P | 9,282 | na | Any cardio-cerebrovascular | 9 |
| Torniainen 2015[49](https://www.zotero.org/google-docs/?7jFuel) | Sweden | 2006-2010 | Schizophrenia vs general population | P | 20,262 | 214,670 | Any cardio-cerebrovascular | 9 |
| Berardi 2021[50](https://www.zotero.org/google-docs/?iZvLcZ) | Italy | 2008-2017 | Schizophrenia vs general population | P | 7,940 | 4,250,075 | Any cardio-cerebrovascular | 9 |
| Pan 2020[51](https://www.zotero.org/google-docs/?qj5a9T) | Taiwan | 2005-2013 | Schizophrenia vs general population | P | 200,193 | 2,521,200 | Any cardio-cerebrovascular | 9 |
| Yung 2020[52](https://www.zotero.org/google-docs/?MHyTex) | Hong Kong | 2006-2016 | Schizophrenia vs general population | P | 46,896 | 7,500,000 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 9 |
| Curkendall 2004[53](https://www.zotero.org/google-docs/?ixZbWR) | Canada | 1994-1998 | Schizophrenia vs general population | P | 3,022 | 13,110 | Any cardio-cerebrovascular | 8 |
| Kiviniemi 2010[54](https://www.zotero.org/google-docs/?2gzukG) | Finland | 1995-2001 | Schizophrenia vs general population | I | 7,591 | 5,120,000 | Any cardio-cerebrovascular | 9 |
| Girardi 2021[55](https://www.zotero.org/google-docs/?nx65Tt) | Italy | 2008-2018 | Schizophrenia vs general population | P | 12,196 | 4,887,004 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 9 |
| Enger 2004[56](https://www.zotero.org/google-docs/?qAQ13R) | US | 1995-1999 | Schizophrenia vs general population | P | 1,920 | 11,520 | Cardiovascular | 9 |
| Kilbourne 2009[57](https://www.zotero.org/google-docs/?GWXZTp) | US | 1999-2006 | Schizophrenia vs general population | P | 22,817 | 38,859 | Cardiovascular | 9 |
| Laursen 2011[58](https://www.zotero.org/google-docs/?KtlneS) | Denmark | 1992-2006 | Schizophrenia vs general population | P | 30,614 | 8,999,225 | Cardiovascular | 9 |
| Boden 2015[59](https://www.zotero.org/google-docs/?2430MY) | Sweden | 1997-2010 | Schizophrenia vs without schizophrenia matched for comorbid condition | P | 541 | 209,592 | Cardiovascular | 9 |
| Chen 2020[60](https://www.zotero.org/google-docs/?NUIoOz) | Taiwan | 2000-2016 | Schizophrenia vs general population | P | 170,322 | 22,710,322 | Cardiovascular | 9 |
| Wellejus Albertsen 2020[61](https://www.zotero.org/google-docs/?OMzR3v) | Denmark | 2000-2013 | Schizophrenia vs without schizophrenia matched for comorbid condition | P | 1,160 | 36,685 | Cardiovascular | 9 |
| Castagnini 2013[62](https://www.zotero.org/google-docs/?N4n26e) | Denmark | 1995-2008 | Schizophrenia vs general population | I | 4,576 | 3,565,833 | Cardiovascular, cerebrovascular | 9 |
| Daumit 2010[63](https://www.zotero.org/google-docs/?FqE1vq) | US | 1992-2001 | Schizophrenia vs general population | P | 2,303 | 5,171,640 | Cardiovascular | 8 |
| Osby 2000[64](https://www.zotero.org/google-docs/?PQUe5U) | Sweden | 1973-1995 | Schizophrenia vs general population | I | 7,784 | 1,792,216 | Cardiovascular, cerebrovascular | 9 |
| Chen 2021[60](https://www.zotero.org/google-docs/?zOWyxU) | Taiwan | 2001-2016 | Schizophrenia vs general population | P | 170,322 | 22,829,678 | Cardiovascular | 9 |
| Hennessy 2002[65](https://www.zotero.org/google-docs/?14a5aB) | US | 1993-1996 | Schizophrenia vs general population; Schizophrenia with different antipsychotic regimens | P | 136,927 | 29,086 | Cardiovascular | 7 |
| Attar 2018[66](https://www.zotero.org/google-docs/?x9bj9a) | Denmark | 1995-2013 | Schizophrenia vs without schizophrenia matched for comorbid condition | P | 726 | 2,178 | Any cardio-cerebrovascular, cardiovascular | 9 |
| Fleetwood 2021[67](https://www.zotero.org/google-docs/?HmuAiN) | UK | 1991-2014 | Schizophrenia vs without schizophrenia matched for comorbid condition | P | 923 | 235,310 | Cardiovascular | 9 |
| Kang 2011[68](https://www.zotero.org/google-docs/?e6LpF8) | Taiwan | 2002-2004 | Schizophrenia vs without schizophrenia matched for comorbid condition | P | 485 | 2,910 | Cerebrovascular | 9 |
| Kapral 2021[69](https://www.zotero.org/google-docs/?8Eu7Y4) | Canada | 2002-2012 | Schizophrenia vs without schizophrenia matched for comorbid condition | P | 612 | 52,473 | Cerebrovascular | 9 |
| Kurdyak 2012[70](https://www.zotero.org/google-docs/?SgcQx7) | Canada | 2002-2006 | Schizophrenia vs without schizophrenia matched for comorbid condition | P | 842 | 70,826 | Cardiovascular | 9 |
| Mohamed 2019[71](https://www.zotero.org/google-docs/?icifP1) | US | 2004-2014 | Schizophrenia vs without schizophrenia matched for comorbid condition | P | 23,582 | 6,322,796 | Any cardio-cerebrovascular, cardiovascular | 9 |
| Sogaard 2017[72](https://www.zotero.org/google-docs/?iAiyJZ) | Denmark | 2000-2015 | Schizophrenia vs without schizophrenia matched for comorbid condition | P | 534 | 2,552,772 | Cardiovascular | 9 |
| Kiviniemi 2013[17](https://www.zotero.org/google-docs/?JKnU5X) | Finland | 1998-2003 | Schizophrenia treated with antipsychotics vs not treated | I | 5,266 | 6,713 | Any cardio-cerebrovascular | 9 |
| Oh 2021[16](https://www.zotero.org/google-docs/?0ctYGr) | Korea | 2003-2017 | Schizophrenia treated with antipsychotics vs not treated | P | 77,139 | 9,784 | Any cardio-cerebrovascular, cardiovascular, cerebrovascular | 9 |
| Taipale 2020[26](https://www.zotero.org/google-docs/?JbxY4Y) | Finland | 1996-2015 | Schizophrenia treated with antipsychotics vs not treated | I , P | 62,250 | na | Any cardio-cerebrovascular | 9 |
| Strom 2011[73](https://www.zotero.org/google-docs/?tMb035) | Multi-nation | 2002-2006 | Schizophrenia with different antipsychotic regimens | P | 9,077 | 9,077 | Cardiovascular | 9 |
| Tang 2021[74](https://www.zotero.org/google-docs/?O6rzkm) | Taiwan | 2001-2015 | Schizophrenia with different antipsychotic regimens | P | 58,615 | 9,544 | Any cardio-cerebrovascular | 9 |
| Chan 2021[75](https://www.zotero.org/google-docs/?i8POyL) | Hong Kong | 2006-2016 | Schizophrenia with versus without multiple physical comorbidities | I | 395 | 13,545 | Any cardio-cerebrovascular | 9 |
| Kugathasan 2019[76](https://www.zotero.org/google-docs/?N3uI1M) | UK | 2013-2017 | Schizophrenia with vs without cardiovascular disease | P | na | 1,798 | Any cardio-cerebrovascular | 9 |
| Hjorthoj 2015[77](https://www.zotero.org/google-docs/?Z8KiM4) | Denmark | 1969-2013 | Schizophrenia with vs without substance use disorder | P | 18,561 | 22,909 | Any cardio-cerebrovascular | 9 |
| Chong 2009[78](https://www.zotero.org/google-docs/?e3Wvgj) | Singapore | 2000-2006 | Schizophrenia with vs without tardive dyskinesia | P | 241 | 320 | Any cardio-cerebrovascular | 9 |

Legend. FGA, first generation antipsychotic; I, incident; LAI, long-acting injectable antipsychotic; NOS, Newcastle-Ottawa scale; P, prevalent; SGA, second generation antipsychotic.

Table 2. Effect of antipsychotics on any cardio-cerebrovascular disease-related mortality in people with schizophrenia.

| Comparison | k | ES | 95%CI | p | I2 | Between groups p |
| --- | --- | --- | --- | --- | --- | --- |
| ***Incident + prevalent*** | | | | | | |
| Any AP | 3 | 0.719 | 0.495-1.043 | 0.082 | 92.813 | 0.085 |
| Any FGA | 2 | 1.061 | 0.433-2.597 | 0.897 | 96.076 |  |
| **Any FGA LAI** | **1** | **0.698** | **0.621-0.784** | **0.0001** | **0** |  |
| Any FGA oral | 2 | 1.180 | 0.370-3.760 | 0.779 | 94.477 |  |
| **Any SGA** | **2** | **0.651** | **0.477-0.887** | **0.007** | **71.367** |  |
| **Any SGA LAI** | **1** | **0.664** | **0.522-0.844** | **0.001** | **0** |  |
| **Any SGA oral** | **2** | **0.567** | **0.522-0.617** | **0.0001** | **0** |  |
| **Clozapine** | **2** | **0.498** | **0.289-0.858** | **0.012** | **21.326** |  |
| ***Incident*** | | | | | | |
| Any AP | 2 | 0.964 | 0.7401.257 | 0.789 | 57.480 | **0.001** |
| **Any FGA** | **1** | **1.703** | **1.203-2.412** | **0.003** | **0** |  |
| **Any FGA oral** | **1** | **2.200** | **1.285-3.767** | **0.004** | **0** |  |
| Any SGA | 1 | 0.799 | 0.5721.116 | 0.188 | 0 |  |
| Any SGA oral | 1 | 0.720 | 0.300-1.729 | 0.462 | 0 |  |
| Clozapine | 1 | 0.230 | 0.051-1.039 | 0.056 | 0 |  |
| ***Prevalent*** | | | | | | |
| **Any AP** | **2** | **0.606** | **0.583-0.629** | **0.0001** | **0** | **0.001** |
| **Any FGA** | **1** | **0.683** | **0.635-0.734** | **0.0001** | **0** |  |
| **Any FGA LAI** | **1** | **0.698** | **0.621-0.784** | **0.0001** | **0** |  |
| **Any FGA oral** | **1** | **0.673** | **0.614-0.738** | **0.0001** | **0** |  |
| **Any SGA** | **1** | **0.576** | **0.532-0.623** | **0.0001** | **0** |  |
| **Any SGA LAI** | **1** | **0.664** | **0.522-0.844** | **0.001** | **0** |  |
| **Any SGA oral** | **1** | **0.566** | **0.521-0.615** | **0.0001** | **0** |  |
| **Clozapine** | **1** | **0.550** | **0.471-0.642** | **0.0001** | **0** |  |

Legend. AP, antipsychotic; FGA, first generation antipsychotic; LAI, long acting injectable; SGA, second generation antipsychotic; k, number of primary studies in meta-analysis; ES, effect size; 95%CI, 95% confidence interval; p, p-value; I2, heterogeneity measure.

Table 3. Subgroup analyses by nation-wide sample, NOS score, adjustment of results, mean age, and incident versus prevalent for any cardio-cerebrovascular, cardiovascular, cerebrovascular mortality in people with schizophrenia versus control groups.

| **Comparison** | **I/P** | **Group** | **k** | **RR** | **95%CI** | **p** | **I2** | **Between groups p** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **NATION-WIDE SAMPLE** | | | | | | | | |
| **Any cardio-cerebrovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | **N** | **9** | **1.690** | **1.455-1.964** | **0.0001** | **62.296** | 0.063 |
| **Y** | **21** | **2.184** | **1.744-2.734** | **0.0001** | **99.620** |
| P | **N** | **9** | **1.690** | **1.455-1.964** | **0.0001** | **62.296** | 0.201 |
| **Y** | **17** | **1.789** | **1.583-2.022** | **0.0001** | **99.272** |
| SCZ-GP | I + P | **N** | **9** | **1.690** | **1.455-1.964** | **0.0001** | **62.296** | **0.01** |
| **Y** | **19** | **2.304** | **1.924-2.759** | **0.0001** | **99.262** |
| P | **N** | **9** | **1.690** | **1.455-1.964** | **0.0001** | **62.296** | **0.035** |
| **Y** | **15** | **1.884** | **1.685-2.105** | **0.0001** | **98.434** |
| **Cardiovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | **N** | **9** | **1.925** | **1.431-2.590** | **0.0001** | **98.300** | 0.490 |
| **Y** | **16** | **2.173** | **1.826-2.585** | **0.0001** | **99.148** |
| P | **N** | **8** | **1.889** | **1.336-2.670** | **0.0001** | **98.350** | 0.767 |
| **Y** | **12** | **2.003** | **1.684-2.381** | **0.0001** | **98.475** |
| SCZ-GP | I + P | **N** | **7** | **1.978** | **1.392-2.810** | **0.0001** | **98.716** | 0.418 |
|  |  | **Y** | **12** | **2.330** | **1.937-2.804** | **0.0001** | **99.221** |  |
|  | I | **N** | **1** | **2.166** | **1.997-2.349** | **0.0001** | **0** | 0.333 |
|  |  | **Y** | **4** | **2.892** | **1.620-5.161** | **0.0001** | **97.004** |  |
|  | P | **N** | **6** | **1.937** | **1.266-2,964** | **0.0020** | **98.805** | 0.667 |
|  |  | **Y** | **8** | **2.146** | **1.780-2.586** | **0.0001** | **98.639** |  |
| SCZ-noSCZ | P | **N** | **2** | **1.852** | **1.540-2.227** | **0.0001** | **16.343** | 0.875 |
|  |  | **Y** | **5** | **1.921** | **1.264-2.920** | **0.002** | **94.052** |  |
| **Cerebrovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | **N** | 5 | 1.540 | 0.909-2.610 | 0.108 | 96.202 | 0.974 |
| **Y** | **11** | **1.526** | **1.278-1.823** | **0.0001** | **94.203** |
| P | **N** | 4 | 1.504 | 0.809-2.796 | 0.197 | 95.649 | 0.809 |
| **Y** | **7** | **1.383** | **1.037-1.844** | **0.027** | **96.247** |
| SCZ-GP | I + P | **N** | 4 | 1.579 | 0.796-3.130 | 0.191 | 96.528 | 0.811 |
| **Y** | **9** | **1.721** | **1.450-2.042** | **0.0001** | **93.512** |
| I | **N** | **1** | **1.705** | **1.396-2.082** | **0.0001** | **0** | 1 |
| **Y** | **4** | **1.705** | **1.116-2.604** | **0.014** | **63.090** |
| P | **N** | 3 | 1.566 | 0.574-4.721 | 0.381 | 94.403 | 0.920 |
| **Y** | **5** | **1.653** | **1.232-2.217** | **0.001** | **96.468** |
| SCZ-noSCZ | P | **N** | **1** | **1.470** | **1.2001.800** | **0.0001** | **0** | 0.354 |
| **Y** | 2 | 0.731 | 0.170-3.151 | 0.675 | 95.473 |
| **NOS SCORE** | | | | | | | | |
| **Any cardio-cerebrovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | **< 7** | **3** | **1.321** | **1.002-1.741** | **0.048** | **61.813** | **0.006** |
| **≥ 7** | **27** | **2.133** | **1.748-2.603** | **0.0001** | **99.515** |
| P | < 7 | 2 | 1.180 | 0.671-2.075 | 0.565 | 76.781 | 0.091 |
| **≥ 7** | **24** | **1.965** | **1.646-2.346** | **0.0001** | **98.967** |
| SCZ-GP | I + P | **< 7** | **3** | **1.321** | **1.002-1.741** | **0.048** | **61.813** | **0.001** |
| **≥ 7** | **25** | **2.221** | **1.891-2.609** | **0.0001** | **99.069** |
| I | **< 7** | **1** | **1.466** | **1.246-1.726** | **0.0001** | **0** | **0.0001** |
| **≥ 7** | **3** | **4.151** | **3.498-4.925** | **0.0001** | **20.726** |
| P | < 7 | 2 | 1.180 | 0.671-2.075 | 0.565 | 76.781 | 0.06 |
| **≥ 7** | **22** | **2.062** | **1.791-2.375** | **0.0001** | **97.831** |
| **Cardiovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | < 7 | **3** | **1.304** | **1.010-1.683** | **0.041** | **82.874** | **0.0001** |
| ≥ 7 | **22** | **2.224** | **1.908-2.593** | **0.0001** | **99.033** |
| P | < 7 | **2** | **1.125** | **1.011-1.253** | **0.031** | **8.843** | **0.0001** |
| ≥ 7 | **18** | **2.069** | **1.786-2.396** | **0.0001** | **98.166** |
| SCZ-GP | I + P | < 7 | **3** | **1.034** | **1.010-1.683** | **0.041** | **82.874** | **0.0001** |
| ≥ 7 | **16** | **2.430** | **2.051-2.880** | **0.0001** | **99.172** |
| I | < 7 | **1** | **1.521** | **1.272-1.820** | **0.0001** | **0** | **0.001** |
| ≥ 7 | **4** | **3.153** | **2.095-4.746** | **0.0001** | **98.294** |
| P | < 7 | **2** | **1.125** | **1.011-1.253** | **0.031** | **8.843** | **0.0001** |
| ≥ 7 | **12** | **2.248** | **1.903-2.655** | **0.0001** | **98.475** |
| **Cerebrovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | < 7 | 3 | 1.008 | 0.617-1.647 | 0.975 | 86.592 | 0.062 |
| **≥ 7** | **13** | **1.648** | **1.405-1.934** | **0.0001** | **93.359** |
| P | < 7 | 2 | 0.917 | 0.494-1.700 | 0.782 | 88.162 | 0.127 |
| **≥ 7** | **9** | **1.540** | **1.197-1.983** | **0.001** | **95.226** |
| SCZ-GP | I + P | < 7 | 3 | 1.008 | 0.617-1.647 | 0.975 | 86.592 | **0.019** |
| **≥ 7** | **10** | **1.871** | **1.598-2.191** | **0.0001** | **92.357** |
| I | **< 7** | 1 | 1.258 | 0.828-1.912 | 0.282 | 0 | 0.069 |
| **≥ 7** | **4** | **1.956** | **1.559-2.454** | **0.0001** | **61.056** |
| P | < 7 | 2 | 0.917 | 0.494-1.700 | 0.782 | 88.162 | **0.04** |
| **≥ 7** | **6** | **1.864** | **1.415-2.455** | **0.0001** | **95.416** |
| **ADJUSTMENT OF RESULTS** | | | | | | | | |
| **Any cardio-cerebrovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | N | **15** | **2.248** | **1.756-2.878** | **0.0001** | **97.975** | 0.285 |
| Y | **15** | **1.836** | **1.392-2.422** | **0.0001** | **99.690** |
| P | N | **12** | **2.093** | **1.596-2.745** | **0.0001** | **98.289** | 0.320 |
| Y | **14** | **1.745** | **1.380-2.206** | **0.0001** | **99.155** |
| SCZ-GP | I + P | N | **14** | **2.308** | **1.774-3.003** | **0.0001** | **98.005** | 0.297 |
| Y | **14** | **1.935** | **1.583-2.365** | **0.0001** | **99.224** |
| I | N | **3** | **3.405** | **1.216-9.535** | **0.02** | **94.841** | 0.784 |
| Y | **1** | **3.932** | **3.872-3.992** | **0.0001** | **0** |
| P | N | **11** | **2.144** | **1.602-2.869** | **0.0001** | **98.334** | 0.404 |
| Y | **13** | **1.864** | **1.601-2.169** | **0.0001** | **96.965** |
| SCZ-noSCZ | P | N | **1** | **1.620** | **1.450-1.810** | **0.0001** | **0** | **0.0001** |
| Y | **1** | **1.097** | **1.055-1.141** | **0.0001** | **0** |
| **Cardiovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | N | **8** | **1.751** | **1.377-2.226** | **0.0001** | **97.500** | 0.104 |
| Y | **17** | **2.287** | **1.844-2.836** | **0.0001** | **99.436** |
| P | N | **6** | **1.720** | **1.239-2.387** | **0.001** | **98.089** | 0.346 |
| Y | **14** | **2.080** | **1.667-2.595** | **0.0001** | **99.056** |  |
| SCZ-GP | I + P | N | **7** | **1.945** | **1.557-2.430** | **0.0001** | **96.910** | 0.225 |
| Y | **12** | **2.398** | **1.858-3.094** | **0.0001** | **99.582** |  |
| I | N | **2** | **1.832** | **1.297-2.589** | **0.001** | **91.901** | **0.0001** |
| Y | **3** | **3.804** | **3.734-3.875** | **0.0001** | **0** |  |
| P | N | **5** | **1.989** | **1.459-2.711** | **0.0001** | **97.671** | 0.798 |
| Y | **9** | **2.101** | **1.583-2.787** | **0.0001** | **99.387** |  |
| SCZ-noSCZ | P | N | 1 | 0.880 | 0.722-1.073 | 0.206 | 0 | **0.0001** |
| Y | **6** | **2.101** | **1.670-2.642** | **0.0001** | **82.414** |  |
| **Cerebrovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | N | **6** | **1.622** | **1.352-1.945** | **0.0001** | **34.536** | 0.275 |
| Y | **10** | **1.341** | **1.004-1.791** | **0.047** | **98.414** |
| P | N | **4** | **1.727** | **1.273-2.345** | **0.0001** | **49.853** | 0.178 |
| Y | 7 | 1.206 | 0.790-1.843 | 0.385 | 98.800 |
| SCZ-GP | I + P | N | **5** | **1.668** | **1.311-2.122** | **0.0001** | **45.213** | 0.675 |
| Y | **8** | **1.531** | **1.115-2.104** | **0.009** | **98.651** |
| I | N | **2** | **1.552** | **1.179-2.043** | **0.002** | **39.247** | **0.011** |
| Y | **3** | **2.229** | **2.147-2.313** | **0.0001** | **0** |
| P | N | **3** | **1.912** | **1.180-3.098** | **0.008** | **62.474** | 0.405 |
| Y | 5 | 1.424 | 0.866-2.342 | 0.163 | 99.136 |
| SCZ-noSCZ | P | N | **1** | **1.510** | **1.148-1.986** | **0.003** | **0** | 0.324 |
| Y | 2 | 0.724 | 0.173-3.038 | 0.659 | 95.719 |
| **MEAN AGE** | | | | | | | | |
| **Any cardio-cerebrovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | P | < 40 | **2** | **2.012** | **1.268-3.190** | **0.003** | **87.454** | 0.743 |
| ≥ 40 | **8** | **2.261** | **1.338-3.820** | **0.002** | **99.298** |
| SCZ-GP | P | < 40 | **2** | **2.012** | **1.268-3.190** | **0.003** | **87.454** | 0.384 |
| ≥ 40 | **6** | **2.714** | **1.659-4.440** | **0.0001** | **98.528** |
| **Cardiovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | < 40 | 4 | 1.796 | 0.902-3.575 | 0.096 | 91.520 | 0.935 |
| ≥ 40 | **7** | **1.852** | **1.386-2.474** | **0.0001** | **92.276** |
| P | < 40 | **3** | **1.179** | **1.080-1.287** | **0.0001** | **0** | **0.003** |
| ≥ 40 | **7** | **1.852** | **1.386-2.474** | **0.0001** | **92.276** |
| SCZ-GP | I + P | < 40 | 4 | 1.796 | 0.902-3.575 | 0.096 | 91.520 | 0.325 |
| ≥ 40 | **1** | **2.670** | **1.815-3.928** | **0.0001** | **0** |
| P | < 40 | **3** | **1.179** | **1.080-1.287** | **0.0001** | **0** | **0.0001** |
| ≥ 40 | **1** | **2.670** | **1.815-3.928** | **0.0001** | **0** |
| **Cerebrovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | < 40 | 2 | 1.291 | 0.869-1.918 | 0.205 | 0 | 0.554 |
| ≥ 40 | 4 | 1.083 | 0.706-1.661 | 0.715 | 87.861 |
| P | < 40 | 1 | 1.300 | 0.860-1.965 | 0.213 | 0 | 0.547 |
| ≥ 40 | 4 | 1.083 | 0.706-1.661 | 0.715 | 87.861 |
| SCZ-GP | I + P | < 40 | 2 | 1.291 | 0.869-1.918 | 0.205 | 0 | 0.883 |
| ≥ 40 | **1** | **1.340** | **1.002-1.793** | **0.049** | **0** |
| P | < 40 | 1 | 1.300 | 0.860-1.965 | 0.213 | 0 | 0.906 |
| ≥ 40 | **1** | **1.340** | **1.002-1.793** | **0.049** | **0** |
| **INCIDENT VS PREVALENT** | | | | | | | | |
| **Any cardio-cerebrovascular** | | | | | | | | |
| SCZ-GP | I + P | Incident | **4** | **3.470** | **1.792-6.719** | **0.0001** | **97.883** | 0.104 |
| Prevalent | **24** | **1.984** | **1.729-2.275** | **0.0001** | **97.690** |
| withinSCZ anyAP-noAP | I + P | Incident | **2** | **0.964** | **0.740-1.257** | **0.789** | **57.480** | **0.001** |
| Prevalent | **2** | **0.606** | **0.583-0.629** | **0.0001** | **0** |
| **Cardiovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | Incident | **5** | **2.701** | **1.802-4.050** | **0.0001** | **98.514** | 0.155 |
| Prevalent | **20** | **1.963** | **1.653-2.331** | **0.0001** | **98.841** |
| SCZ-GP | I + P | Incident | **5** | **2.701** | **1.802-4.050** | **0.0001** | **98.514** | 0.240 |
| Prevalent | **14** | **2.058** | **1.680-2.522** | **0.0001** | **99.120** |
| **Cerebrovascular** | | | | | | | | |
| SCZ-GP + SCZ-noSCZ | I + P | **Incident** | **5** | **1.764** | **1.357-2.292** | **0.0001** | **72.580** | 0.266 |
| **Prevalent** | 11 | 1.386 | 0.993-1.936 | 0.055 | 98.027 |
| SCZ-GP | I + P | **Incident** | **5** | **1.764** | **1.357-2.292** | **0.0001** | **72.580** | 0.657 |
| **Prevalent** | **8** | **1.583** | **1.062-2.359** | **0.024** | **98.505** |

**Legend. AP, antipsychotic; FGA, first generation antipsychotic; GP, general population; k, number of studies; LAI, long acting injection; N, number of comparisons; SCZ, schizophrenia; SGA, second generation antipsychotic; RR, relative risk; 95%CI, 95% confidence interval; p, p-value; I2, heterogeneity measure.**

Table 4. Meta-regression analyses.

| **Comparison** | **Incident / Prevalent** | **k/N** | **Beta** | **95%CI** | **p** |
| --- | --- | --- | --- | --- | --- |
| **Any cardio-cerebrovascular disease** | | | | | |
| **Follow-up time** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 26/43 | -0.01 | -0.03-0.008 | 0.29 |
| Prevalent | 22/36 | -0.01 | -0.03-0.01 | 0.33 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 24/39 | -0.01 | -0.03-0.006 | 0.19 |
| Prevalent | 20/32 | -0.01 | -0.03-0.007 | 0.23 |
| *Factors within schizophrenia* | | | | | |
| Any AP-no AP | Incident + prevalent | **3/35** | **-0.04** | **-0.05- -0.02** | **0.0001** |
| Incident | 2/12 | -0.02 | -0.04-0.005 | 0.13 |
| Prevalent | 2/23 | 0.02 | -0.04-0.07 | 0.55 |
| Any FGA-no AP | Incident + prevalent | **2/16** | **-0.07** | **-0.10- 0.04** | **0.0001** |
| Any SGA-no AP | Incident + prevalent | 2/10 | -0.02 | -0.05-0.002 | 0.07 |
| **Median study year** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | **26/43** | **0.02** | **0.002-0.03** | **0.02** |
| Prevalent | **22/36** | **0.02** | **0.001-0.03** | **0.03** |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | **24/39** | **0.02** | **0.008-0.03** | **0.001** |
| Prevalent | **20/32** | **0.02** | **0.007-0.04** | **0.003** |
| *Factors within schizophrenia* | | | | | |
| Any AP-no AP | Incident + prevalent | **3/35** | **-0.09** | **-0.14- -0.04** | **0.0001** |
| Incident | 2/12 | -0.07 | -0.15-0.02 | 0.13 |
| Prevalent | 2/23 | -0.02 | -0.09-0.05 | 0.55 |
| Any FGA-no AP | Incident + prevalent | 2/16 | **-0.23** | **-0.33- -0.13** | **0.0001** |
| Any SGA-no AP | Incident + prevalent | 2/10 | -0.08 | -0.17-0.006 | 0.07 |
| **NOS score** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 26/43 | 0.19 | -0.004-0.38 | 0.055 |
| Prevalent | 22/36 | 0.19 | -0.08-0.47 | 0.16 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 24/39 | **0.22** | **0.03-0.40** | **0.02** |
| Prevalent | 20/32 | 0.22 | -0.04-0.49 | 0.10 |
| **Number of variables adjusted for** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 26/43 | **-0.02** | **-0.03- -0.004** | **0.01** |
| Prevalent | 22/36 | **-0.02** | **-0.03- -0.004** | **0.01** |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 24/39 | -0.05 | -0.14-0.04 | 0.26 |
| Prevalent | 20/32 | -0.08 | -0.18-0.008 | 0.07 |
| *Factors within schizophrenia* | | | | | |
| Any AP-no AP | Incident + prevalent | 3/35 | **-0.06** | **-0.09- -0.03** | **0.0001** |
| Incident | 2/12 | -0.03 | -0.07-0.009 | 0.13 |
| Prevalent | 2/23 | 0.03 | -0.07-0.14 | 0.55 |
| Any FGA-no AP | Incident + prevalent | 2/16 | **-0.12** | **-0.17- -0.07** | **0.0001** |
| Any SGA-no AP | Incident + prevalent | 2/10 | -0.04 | -0.09-0.003 | 0.07 |
| **Age** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Prevalent | 9/13 | -0.03 | -0.07-0.003 | 0.07 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Prevalent | 7/11 | -0.01 | -0.07-0.04 | 0.67 |
| **Sample size** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 24/41 | 0.000001 | -0.000001-0.000001 | 0.09 |
| Prevalent | 20/34 | 0.000001 | -0.000001-0.000001 | 0.97 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 21/37 | 0.000001 | -0.000001-0.000001 | 0.13 |
| Prevalent | 17/30 | -0.000001 | -0.000001-0.000001 | 0.13 |
| *Factors within schizophrenia* | | | | | |
| Any AP-no AP | Incident + prevalent | 3/16 | **-0.00001** | **-0.00001- -0.000001** | **0.00001** |
| Incident | 2/13 | -0.0001 | -0.0003-0.00004 | 0.13 |
| **% female** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 20/32 | -0.0005 | -0.007-0.006 | 0.87 |
| Prevalent | 16/25 | -0.002 | -0.01-0.006 | 0.67 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 18/30 | -0.0008 | -0.007-0.006 | 0.82 |
| Prevalent | 14/23 | -0.002 | -0.01-0.006 | 0.61 |
| **Cardiovascular disease** | | | | | |
| **Follow-up time** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | **24/48** | **-0.01** | **-0.03- -0.0004** | **0.04** |
| Prevalent | **19/39** | **-0.02** | **-0.03- -0.0001** | **0.049** |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 18/40 | -0.01 | -0.03-0.0002 | 0.053 |
|  | Prevalent | 13/32 | -0.02 | -0.03-0.002 | 0.08 |
| **Median study year** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 25/48 | 0.008 | -0.004-0.02 | 0.20 |
| Prevalent | 20/40 | 0.003 | -0.01-0.02 | 0.68 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 19/41 | 0.01 | -0.0001-0.02 | 0.053 |
|  | Prevalent | 14/33 | 0.007 | -0.008-0.02 | 0.37 |
| **NOS score** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 25/48 | 0.0009 | -0.11-0.11 | 0.99 |
| Prevalent | 20/40 | -0.08 | -0.21-0.05 | 0.21 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 19/41 | 0.02 | -0.09-0.13 | 0.67 |
|  | Prevalent | 14/33 | -0.06 | -0.19-0.07 | 0.37 |
| **Number of variables adjusted for** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 25/48 | 0.02 | -0.008-0.04 | 0.17 |
| Prevalent | 20/40 | 0.02 | -0.01-0.04 | 0.25 |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP | Incident + prevalent | 19/41 | 0.02 | -0.009-0.04 | 0.21 |
|  | Prevalent | 14/33 | 0.01 | -0.01-0.04 | 0.35 |
| **Age** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 11/12 | -0.006 | -0.02-0.01 | 0.49 |
|  | Prevalent | 10/11 | 0.0003 | -0.02-0.02 | 0.97 |
| **Sample size** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 25/48 | **0.000001** | **0.0000001-0.000001** | **0.049** |
| Prevalent | 20/40 | 0.000001 | -0.000001-0.000001 | 0.77 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 19/41 | 0.000001 | -0.000001-0.000001 | 0.07 |
|  | Prevalent | 14/33 | -0.000001 | -0.000001-0.000001 | 0.95 |
| *Schizophrenia versus without schizophrenia matched by comorbid condition* | | | | | |
| **% female** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 20/38 | 0.0004 | -0.005-0.005 | 0.89 |
|  | Prevalent | 15/30 | 0.002 | -0.005-0.009 | 0.62 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 14/32 | 0.001 | -0.004-0.003 | 0.69 |
| Prevalent | 10/25 | 0.004 | -0.003-0.01 | 0.28 |
| **Cerebrovascular disease** | | | | | |
| **Follow-up time** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 16/25 | -0.002 | -0.02-0.02 | 0.81 |
| Prevalent | 11/16 | 0.005 | -0.02-0.03 | 0.76 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 13/22 | -0.02 | -0.03-0.002 | 0.09 |
| Prevalent | 8/13 | -0.01 | -0.04-0.01 | 0.34 |
| **Median study year** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 16/25 | 0.01 | -0.004-0.02 | 0.16 |
| Prevalent | 11/16 | 0.008 | -0.01-0.03 | 0.43 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 13/22 | **0.02** | **0.003-0.03** | **0.01** |
| Prevalent | 8/13 | 0.01 | -0.003-0.03 | 0.12 |
| **NOS score** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 16/25 | **0.18** | **0.04-0.33** | **0.01** |
| Prevalent | 11/16 | 0.22 | -0.002-0.44 | 0.052 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 13/22 | **0.23** | **0.12-0.35** | **0.0001** |
| Prevalent | 8/13 | **0.27** | **0.12-0.43** | **0.0006** |
| **Number of variables adjusted for** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 16/25 | **-0.08** | **-0.13- -0.02** | **0.006** |
| Prevalent | 11/16 | **-0.10** | **-0.16- -0.05** | **0.0004** |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 13/22 | 0.03 | -0.08-0.14 | 0.64 |
| Prevalent | 8/13 | -0.14 | -0.37-0.10 | 0.26 |
| **Sample size** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 16/25 | 0.000001 | -0.000001-0.000001 | 0.12 |
| Prevalent | 11/16 | 0.000001 | -0.000001-0.000001 | 0.20 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 13/22 | 0.000001 | -0.000001-0.000001 | 0.18 |
| Prevalent | 8/13 | 0.000001 | -0.000001-0.000001 | 0.29 |
| **% female** | | | | | |
| *Schizophrenia versus any other population* | | | | | |
| SCZ-GP + SCZ-noSCZ | Incident + prevalent | 12/21 | 0.0002 | -0.005-0.005 | 0.95 |
| Prevalent | 8/13 | -0.0005 | -0.009-0.008 | 0.92 |
| *Schizophrenia versus general population* | | | | | |
| SCZ-GP | Incident + prevalent | 10/19 | -0.0001 | -0.004-0.004 | 0.96 |
| Prevalent | 6/11 | -0.001 | -0.008-0.006 | 0.77 |

*Legend. AP, antipsychotic; FGA, first generation antipsychotic; GP, general population; k, number of studies; LAI, long acting injection; N, number of comparisons; SCZ, schizophrenia; SGA, second generation antipsychotic; RR, relative risk; 95%CI, 95% confidence interval; p, p-value; I2, heterogeneity measure.*