European Neuropsychopharmacology 88 (2024) 6–20

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

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

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https://doi.org/10.1016/j.euroneuro.2024.07.009
Received 20 April 2024; Received in revised form 16 July 2024; Accepted 19 July 2024
Available online 8 August 2024

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ARTICLE INFO

Keywords:
Schizophrenia
Mortality
Cardiovascular
Cerebrovascular
Antipsychotic
Systematic review
Meta-analysis

ABSTRACT

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.

1. 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) (GBD 2019 Diseases and Injuries Collaborators 2020; Fusar-Poli et al., 2022). This high burden has not changed substantially in the last decade (Charlson et al., 2018; Whiteford et al., 2013). Also, partially due to its relatively low prevalence, the epidemiological and burden estimates associated with schizophrenia are underestimated compared to other mental disorders (GBD 2019 Mental Disorders Collaborators 2022).

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 (Crump et al., 2013; Tanskanen et al., 2018). 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 (Correll et al., 2022; Solmi et al., 2024).

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 (Correll et al., 2022). 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 (Correll et al., 2022).

Also, the previous meta-analysis showed that the mortality gap between people with schizophrenia and the general population increased

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despite the development and implementation of new methods for reducing cardiovascular mortality in the general population over time (Correll et al., 2022). 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 (Saha et al., 2007). 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.

2. Methods

2.1. Search

We used data from the recently published (Correll et al., 2022) PRISMA 2020-compliant systematic review (Page et al., 2021), 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).

2.2. 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.

2.3. 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 (Correll et al., 2022) and the Newcastle-Ottawa Scale (Wells et al., n.d.) was used to measure the quality of the studies. Authors were contacted to provide missing data for the relevant original studies.

2.4. 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 (Correll et al., 2022). 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).

2.5. 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 (Serghiou and Goodman, 2019) calculating the pooled risk ratio (RR). We pooled raw numbers, odds ratio, RR, hazard ratio, and SMR in the same analyses, given the study design, population, and outcomes were homogeneous across studies. The events of interest were rare (i.e., <10 %). We preferred adjusted effect sizes over non-adjusted ones or raw data. I^2 was used to measure the proportion of variability (Seagroatt and Stratton, 1998) 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 (Pierce et al., 2006).

3. Results

3.1. Search results

The literature search of the previous systematic review considered 8345 abstracts that were reduced to 6390 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 (Fig. 1, Table 1), reporting on 2513,359 people with schizophrenia. The list of studies and reasons for exclusion of the studies evaluated at full text are reported fully elsewhere (Correll et al., 2022), 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 (Oh et al., 2021) specifically reported data for cardiovascular and cerebrovascular disorder mortality separately, we performed the analyses on all the studies providing data for any cardio-cerebrovascular disorder.

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

Incident plus prevalent, incident, and prevalent risks for cardio-

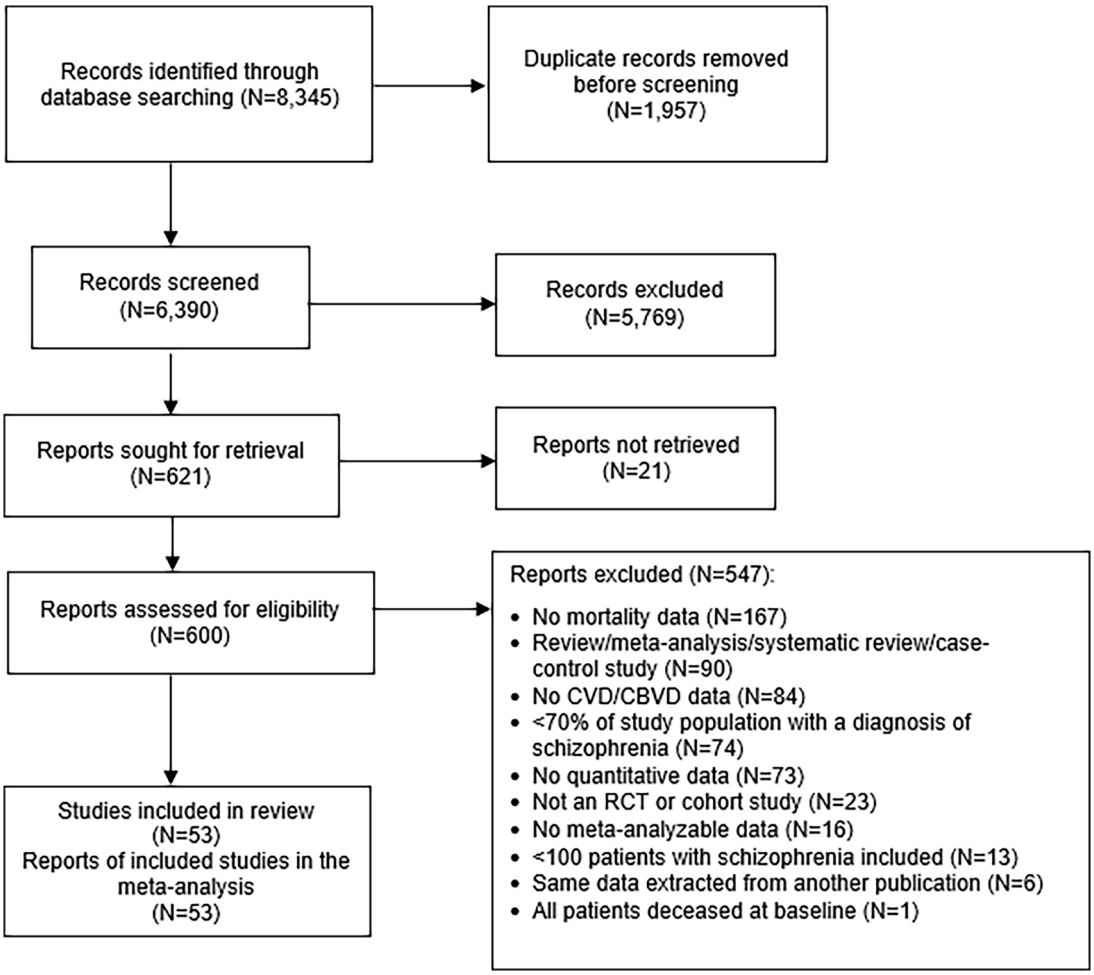

Fig. 1. PRISMA flow chart. RCT – randomized controlled trial.

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, I^2=21.3), followed by any oral second-generation antipsychotic (SGA) (RR=0.57, 95 %CI=0.52–0.62, k= 2, I^2=0), any SGA (RR=0.65, 95 % CI=0.48–0.89, k= 2, I^2=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).

3.3. 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.

3.4. Meta-regression analyses

Meta-regression analyses are available in Table 4. For any cardio-cerebrovascular disorder, when comparing people with schizophrenia

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 (Allebeck and Wistedt, 1986)	Sweden	1971–1981	Schizophrenia vs general population	P	1190	16,902	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	9
Brown 2010 (Brown et al., 2010)	UK	1981–2006	Schizophrenia vs general population	P	370	24,328,853	Any cardio-cerebrovascular, cardiovascular	9
Buda 1988 (Buda et al., 1988)	US	1934–1974	Schizophrenia vs general population	P	332	na	Any cardio-cerebrovascular	9
Cheng 2014 (Cheng et al., 2014)	Taiwan	1998–2008	Schizophrenia vs general population	P	2457	22,561,450	Any cardio-cerebrovascular	9
Crump 2013 (Crump et al., 2013)	Sweden	2003–2009	Schizophrenia vs general population	P	8277	6097,834	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	9
Fors 2007 (Fors et al., 2007)	Sweden	1991–2000	Schizophrenia vs general population	P	255	1530	Any cardio-cerebrovascular	9
Hayes 2017 (Hayes et al., 2017)	UK	2000–2014	Schizophrenia vs general population	P	22,497	241,884	Any cardio-cerebrovascular	9
Kredentser 2014 (Kredentser et al., 2014)	Canada	1999–2008	Schizophrenia vs general population	P	9038	978,128	Any cardio-cerebrovascular	9
Kugathasan 2019 (Kugathasan et al., 2019)	Denmark	1995–2015	Schizophrenia vs general population	P	30,210	5432,821	Any cardio-cerebrovascular	9
Lahti 2012 (Lahti et al., 2012)	Finland	1969–2004	Schizophrenia vs general population	I	204	12,735	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	9
Laursen 2013 (Laursen et al., 2013)	Denmark, Finland, Sweden	2000–2007	Schizophrenia vs general population	P	66,088	4490,039	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	9
Mortensen 1990 (Mortensen and Juel, 1990)	Denmark	1957–1986	Schizophrenia vs general population	P	6178	2494,178	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	6
Mortensen 1993 (Mortensen and Juel, 1993)	Denmark	1970–1987	Schizophrenia vs general population	I	9156	2561,000	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	6
Newman 1991 (Newman and Bland, 1991)	Canada	1976–1985	Schizophrenia vs general population	P	3623	2238,000	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	6
Olfson 2015 (Olfson et al., 2015)	US	2001–2007	Schizophrenia vs general population	I	1138,853	173,699,853	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	9
Talaslahti 2012 (Talaslahti et al., 2012)	Finland	1992–2008	Schizophrenia vs general population	P	9461	941,041	Any cardio-cerebrovascular	9
Tanskanen 2018 (Tanskanen et al., 2018)	Finland	1984–2014	Schizophrenia vs general population	P	42,343	4515,838	Any cardio-cerebrovascular	9
Westman 2017 (Westman et al., 2018)	Sweden	1987–2010	Schizophrenia vs general population	P	46,911	10,678,728	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	9
Zilber 1989 (Zilber et al., 1989)	Israel	1978–1983	Schizophrenia vs general population	P	9282	na	Any cardio-cerebrovascular	9
Torniainen 2015 (Torniainen et al., 2015)	Sweden	2006–2010	Schizophrenia vs general population	P	20,262	214,670	Any cardio-cerebrovascular	9
Berardi 2021 (Berardi et al., 2021)	Italy	2008–2017	Schizophrenia vs general population	P	7940	4250,075	Any cardio-cerebrovascular	9
Pan 2020 (Pan et al., 2020)	Taiwan	2005–2013	Schizophrenia vs general population	P	200,193	2521,200	Any cardio-cerebrovascular	9
Yung 2020 (Yung et al., 2020)	Hong Kong	2006–2016	Schizophrenia vs general population	P	46,896	7500,000	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	9

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Table 1 (*continued*)

	Country	Years	Comparison	Incident/ prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Curkendall 2004 (Curkendall et al., 2004)	Canada	1994–1998	Schizophrenia vs general population	P	3022	13,110	Any cardio-cerebrovascular	8
Kiviniemi 2010 (Kiviniemi et al., 2010)	Finland	1995–2001	Schizophrenia vs general population	I	7591	5120,000	Any cardio-cerebrovascular	9
Girardi 2021 (Girardi et al., 2021)	Italy	2008–2018	Schizophrenia vs general population	P	12,196	4887,004	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	9
Enger 2004 (Enger et al., 2004)	US	1995–1999	Schizophrenia vs general population	P	1920	11,520	Cardiovascular	9
Kilbourne 2009 (Kilbourne et al., 2009)	US	1999–2006	Schizophrenia vs general population	P	22,817	38,859	Cardiovascular	9
Laursen 2011 (Laursen and Nordentoft, 2011)	Denmark	1992–2006	Schizophrenia vs general population	P	30,614	8999,225	Cardiovascular	9
Boden 2015 (Bodén et al., 2015)	Sweden	1997–2010	Schizophrenia vs without schizophrenia matched for comorbid condition	P	541	209,592	Cardiovascular	9
Chen 2020 (Chen et al., 2021)	Taiwan	2000–2016	Schizophrenia vs general population	P	170,322	22,710,322	Cardiovascular	9
Wellejus Albertsen 2020 (Wellejus Albertsen et al., 2020)	Denmark	2000–2013	Schizophrenia vs without schizophrenia matched for comorbid condition	P	1160	36,685	Cardiovascular	9
Castagnini 2013 (Castagnini et al., 2013)	Denmark	1995–2008	Schizophrenia vs general population	I	4576	3565,833	Cardiovascular, cerebrovascular	9
Daumit 2010 (Daumit et al., 2010)	US	1992–2001	Schizophrenia vs general population	P	2303	5171,640	Cardiovascular	8
Osby 2000 (Osby et al., 2000)	Sweden	1973–1995	Schizophrenia vs general population	I	7784	1792,216	Cardiovascular, cerebrovascular	9
Chen 2021 (Chen et al., 2021)	Taiwan	2001–2016	Schizophrenia vs general population	P	170,322	22,829,678	Cardiovascular	9
Hennessy 2002 (Hennessy et al., 2002)	US	1993–1996	Schizophrenia vs general population; Schizophrenia with different antipsychotic regimens	P	136,927	29,086	Cardiovascular	7
Attar 2018 (Attar et al., 2019)	Denmark	1995–2013	Schizophrenia vs without schizophrenia matched for comorbid condition	P	726	2178	Any cardio-cerebrovascular, cardiovascular	9
Fleetwood 2021 (Fleetwood et al., 2021)	UK	1991–2014	Schizophrenia vs without schizophrenia matched for comorbid condition	P	923	235,310	Cardiovascular	9
Kang 2011 (Kang et al., 2011)	Taiwan	2002–2004	Schizophrenia vs without schizophrenia matched for comorbid condition	P	485	2910	Cerebrovascular	9
Kapral 2021 (Kapral et al., 2021)	Canada	2002–2012	Schizophrenia vs without schizophrenia matched for comorbid condition	P	612	52,473	Cerebrovascular	9
Kurdyak 2012 (Kurdyak et al., 2012)	Canada	2002–2006	Schizophrenia vs without schizophrenia matched for comorbid condition	P	842	70,826	Cardiovascular	9
Mohamed 2019 (Mohamed et al., 2019)	US	2004–2014	Schizophrenia vs without schizophrenia matched for comorbid condition	P	23,582	6322,796	Any cardio-cerebrovascular, cardiovascular	9
Sogaard 2017 (Søgaard et al., 2017)	Denmark	2000–2015	Schizophrenia vs without schizophrenia matched for comorbid condition	P	534	2552,772	Cardiovascular	9
Kiviniemi 2013 (Kiviniemi et al., 2013)	Finland	1998–2003	Schizophrenia treated with antipsychotics vs not treated	I	5266	6713	Any cardio-cerebrovascular	9
Oh 2021 (Oh et al., 2021)	Korea	2003–2017	Schizophrenia treated with antipsychotics vs not treated	P	77,139	9784	Any cardio-cerebrovascular, cardiovascular, cerebrovascular	9
Taipale 2020 (Taipale et al., 2020)	Finland	1996–2015	Schizophrenia treated with antipsychotics vs not treated	I, P	62,250	na	Any cardio-cerebrovascular	9
Strom 2011 (Strom et al., 2011)	Multi-nation	2002–2006	Schizophrenia with different antipsychotic regimens	P	9077	9077	Cardiovascular	9
Tang 2021 (Tang et al., 2021)	Taiwan	2001–2015	Schizophrenia with different antipsychotic regimens	P	58,615	9544	Any cardio-cerebrovascular	9

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Table 1 (*continued*)

	Country	Years	Comparison	Incident/ prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Chan 2021 (Chan et al., 2022)	Hong Kong	2006–2016	Schizophrenia with versus without multiple physical comorbidities	I	395	13,545	Any cardio-cerebrovascular	9
Kugathasan 2019 (Kugathasan et al., 2020)	UK	2013–2017	Schizophrenia with vs without cardiovascular disease	P	na	1798	Any cardio-cerebrovascular	9
Hjorthoj 2015 (Hjorthøj et al., 2015)	Denmark	1969–2013	Schizophrenia with vs without substance use disorder	P	18,561	22,909	Any cardio-cerebrovascular	9
Chong 2009 (Chong et al., 2009)	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	I^2	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.

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).

4. 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 (Kiviniemi et al., 2013). 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 (Koponen et al., 2008). 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 (Ray et al., 2001). 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 (Viron et al., 2012). Hence, while prevalent samples may have established care plans or relationships, incident cases may not have had sufficient time to achieve those necessary components

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	I^2	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**	**1.266–2964**	**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

(*continued on next page*)

Table 3 (*continued*)

Comparison	I/P	Group	k	RR	95 %CI	p	I^2	Between groups p
		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.

to effective care, leading to higher rates of antipsychotic treatment discontinuation (Rubio et al., 2021) and cardio-cerebrovascular mortality (Viron et al., 2012). 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 (Ray et al., 2001), which may be due to autonomic system dysfunction, direct cardiac repolarization effects or, even depressogenic effects of FGAs (Voruganti and Awad, 2004). 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 emerged as potentially 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 (Solmi and Correll, 2022). Previous consensus guidelines for diabetes-monitoring among patients with schizophrenia recommended more frequent testing and monitoring as compared to the general population (Suvisaari et al., 2016). 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 (Viron et al., 2012). Likewise, in cases of clozapine titration, patients have received as frequent as daily or weekly follow-up, which may better facilitate comorbidity treatment (Correll et al., 2022; Bhamidipati and Divadeenam, 2021). 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 (Taipale et al., 2020). In another Finnish nation-wide cohort, clozapine was associated with the lowest risk of developing a substance use disorder among patients with schizophrenia (Lähteenvuo et al., 2022). 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 (Kuipers et al., 2014). 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 (Ilzarbe and Vieta, 2023). 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 (Zhang et al., 2013). 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 (De Prisco and Vieta, 2024), longitudinal follow-up, standardized outcomes documentation, comprehensive covariate data collection, and robust methods to minimize the impact of reporting or selection bias.

5. 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

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**

(*continued on next page*)

Table 4 (*continued*)

Comparison	Incident / Prevalent	k/N	Beta	95 %CI	p
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

(*continued on next page*)

Table 4 (*continued*)

Comparison	Incident / Prevalent	k/N	Beta	95 %CI	p
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; I^2, heterogeneity measure.

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.

Role of the funding source

There was no funding for this manuscript.

Contributors

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

Declaration of competing interest

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

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

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

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

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

JF is supported by a UK Research and Innovation Future Leaders Fellowship (MR/T021780/1) and has received honoraria / consultancy fees from Atheneum, Informa, Gillian Kenny Associates, Bayer, Big Health, Hedonia, Strive Coaching, Wood For Trees, Nutritional Medicine Institute, Angelini, ParachuteBH, Richmond Foundation and Nirakara, independent of this work.

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

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

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

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

HL reports receiving grants from Shire Pharmaceuticals; personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB; all outside the submitted work. Henrik Larsson is editor-in-chief of JCPP Advances.

CUC has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Tolmar, Vertex, Viatris and Xenon Pharmaceuticals. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Mindpax, and Quantic.

PL reports institutional grants from AstraZeneca, Biogen, Jansen, MSD and Novartis.

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

submitted work.

Acknowledgments

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2024.07.009.

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