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Regional differences in mortality risk and in attenuating or aggravating factors in schizophrenia: a systematic review and meta-analysis

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Summary (249/250 words)

People with schizophrenia die prematurely, yet regional differences are unclear.
PRISMA 2020-compliant systematic review/random-effects meta-analysis of cohort studies assessing mortality relative risk (RR) versus any control group, and moderators, in people with ICD/DSM-defined schizophrenia, comparing countries and continents. We conducted subgroup, meta-regression analyses, and quality assessment. The primary outcome was all-cause mortality. Secondary outcomes were suicide-, /natural-cause- and other-cause-related mortality.
We included 135 studies from Europe (n=70), North-America (n=29), Asia (n=33), Oceania (n=2), Africa (n=1). In incident plus prevalent schizophrenia, differences across continents emerged for all-cause mortality (highest in Africa, RR=5.98, 95%C.I.=4.09-8.74, k=1, lowest in North-America, RR=2.14, 95%C.I.=1.92-2.38, k=16), suicide (highest in Oceania, RR=13.5, 95%C.I.=10.08-18.07, k=1, lowest in North-America, RR=4.4, 95%C.I.=4.07-4.76, k=6), but not for natural-cause mortality. Europe had the largest association between antipsychotics and lower all-cause mortality/suicide (Asia had the smallest or no significant association, respectively), without differences for natural-cause mortality. Higher country socio-demographic index significantly moderated larger suicide-related and smaller natural-cause-related mortality risk in incident schizophrenia, with reversed associations in prevalent schizophrenia. Antipsychotics had a larger/smaller protective association in incident/prevalent schizophrenia regarding all-cause mortality, and smaller protective association for suicide-related mortality in prevalent schizophrenia. Additional regional differences emerged in incident schizophrenia, across countries, and secondary outcomes.
Significant regional differences emerged for all-cause, cause-specific and suicide-related mortality. Natural-cause death was homogeneously increased globally. Moderators differed across countries. Global initiatives are needed to improve physical health in people with schizophrenia, local studies to identify actionable moderators.

Keywords

Schizophrenia; mortality; geographical regions; antipsychotic; systematic review; meta-analysis.

Introduction

Schizophrenia ranks high among 369 diseases and injuries in terms of burden due to premature mortality, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs) across 204 countries and territories worldwide(Abbafati et al., 2020) and severely disrupts the subjective life of the affected persons and their families(Estradé et al., 2023; Fusar-Poli et al., 2022). This ranking has been consistent(Charlson et al., 2018) since 2010(Whiteford et al., 2013). Moreover, epidemiological and burden estimates associated with schizophrenia are underrated compared to other mental disorders due to its relatively low prevalence(GBD and Collaborators, 2022).

People with schizophrenia have, on average, a shortened lifespan of approximately 10-25 years compared to the general population(Crump et al., 2013; Tanskanen et al., 2018). Schizophrenia is associated with sedentary behavior(Vancampfort et al., 2017), which can additionally worsen clinical outcomes of several physical disease(Dragioti et al., 2023).

A recent large-scale systematic review and meta-analysis of 135 prospective and retrospective nationwide, and targeted cohort studies published between 1957 and 2021, which assessed mortality risk among people with schizophrenia vs. the general population or other controls, established a 2.5-fold (95% confidence interval(CI): 2.4 - 2.7-fold) increased risk in all-cause mortality vs. any control group based on 79 studies(Correll et al., 2022b).

This previous meta-analysis also reported cause-specific mortality risk estimates, showing a 9.8-fold (95%CI=7.6-12.6-fold) risk increase of for suicide/injury-poisoning/undetermined non-natural cause risk, 7.0-fold (95%CI=6.8-7.2-fold) for pneumonia, 3.2-3.8-fold for infectious, endocrine, respiratory, urogenital or diabetes causes, 2.1-2.9-fold for alcohol, gastrointestinal, renal, nervous system, cardio-cerebrovascular, liver or any natural causes, and a 1.3-1.6-fold increase for mortality related to cerebrovascular, breast, colon, pancreas or any cancer causes(Correll et al., 2022b). Additionally, incident schizophrenia was associated with relatively higher all-cause and suicide mortality risks than prevalent schizophrenia. Importantly, antipsychotics were associated with lower mortality risk, while comorbid substance use disorder was associated with higher mortality risk(Correll et al., 2022b), which has been confirmed recently(Correll et al., 2022a).

Furthermore, that meta-analysis showed that the mortality gap between people with schizophrenia and the general population increased slightly but significantly with time, despite the development and implementation of new methods for reducing cardiovascular mortality in the general population(Correll et al., 2022b). While the general population may have benefitted from such novel interventions, chances are that people with schizophrenia have benefitted less so because the mortality rate in the general population decreased more rapidly than in people with schizophrenia, thus increasing the mortality gap(Saha et al., 2007). Consistent with and likely contributing to this finding, people with severe mental disorders, including patients with schizophrenia, have limited access to cancer screening(Solmi et al., 2020) and to screening and treatment for cardiovascular disorders

compared to the general population(Solmi et al., 2021). Moreover, there are differences in lifestyle behaviors across regions.

However, currently no meta-analysis of the mortality risk in people with schizophrenia has explored whether mortality risk and mitigating or risk factors differ across different geographical areas(Correll et al., 2022b).

Detecting potential geographical disparities in standardized mortality ratios (SMRs) among people with schizophrenia vs. the general population or other matched control groups can pave the ground towards data-guided studies for the potential underlying causes, ideally driving the implementation of targeted programs to address potentially involved socio-demographic or other factors. Regional differences in epidemiology, burden, and mortality of many conditions are freely available from the Global Burden of Disease initiative. However, the GBD report does not measure mortality due to mental disorders (apart from anorexia nervosa), as all deaths are re-assigned to cause-specific natural death or suicide, so that GBD report cannot inform on geographic differences in mortality risk associated with schizophrenia(GBD and Collaborators, 2022; Haro and McGrath, 2022; Solmi et al., 2022). Hence, an atlas of regional differences in mortality risk in schizophrenia is currently missing. Nevertheless, differences across countries might be expected, given the heterogeneous distribution of early intervention services for schizophrenia across the globe(Kumar et al., 2020; Rukat et al., 2014), which have shown to improve outcomes(Correll et al., 2018), the differential access to antipsychotic medications across regions, and the heterogeneous integration of psychiatric care with primary and physical care in different healthcare settings(Hung et al., 2021). Therefore, the present systematic review and meta-analysis aimed at assessing all-cause and specific-cause mortality risks in individuals with schizophrenia versus several control groups and their mitigating or risk factors by continent, country, and socio-demographic index.

Methods

Search

We used the same methods by the recently published PRISMA 2020-compliant systematic review(Correll et al., 2022b), which searched Medline, PubMed, and PsycINFO for relevant records indexed up to 09/09/2021. We 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 eTables 1-2.

Inclusion and exclusion criteria

We included: i) peer-reviewed publications of a cohort study (prospective or retrospective; nationwide or not); ii) including ≥70% of participants with ICD/DSM-defined schizophrenia and in ≥100 patients; 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. We excluded: i) non-cohort studies, such as case-control studies, reviews, meta-analyses, and systematic reviews; ii) studies not providing quantitative data on mortality; iii) publications containing non-peer-reviewed data (such as proceedings, poster abstracts, or posters). No language or time restrictions were applied.

Screening, data extraction, and quality assessment

Four independent raters (GC, LKS, MS, NS) conducted the title, abstract, and full-text screening and extracted the data, each in duplicate. A third author (CUC) resolved any conflict.

Details on the overall data extraction procedure are available elsewhere(Correll et al., 2022b). We used the Newcastle-Ottawa Scale(Wells et al., 2009) to measure the quality of the studies. Authors were contacted to provide missing data for the relevant original studies.

Outcomes

The primary outcome was all-cause mortality. Key secondary outcomes were: i) mortality due to suicide and ii) natural cause(s). Additional secondary outcomes included other specific-cause mortality.

Data analysis

Main analyses examined author-defined incident plus prevalent cohorts together versus any control group, comparing by continent. We conducted a random-effects meta-analysis(Serghiou and Goodman, 2019) calculating the pooled risk ratio (RR) of primary and secondary outcomes. 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 extent of heterogeneity(Egger et al., 1997).

We conducted random-effects meta-regression analyses between primary and key secondary outcomes and the socio-demographic index (SDI), a metric ranging from 0-1, whose decile increase predicts a 1.68-fold variation in the risk for a given outcome, as reported by GBD 2019(Solmi et al., 2022). Sensitivity analyses were conducted within the incident and prevalent populations, as well as comparing the general population and the control groups matched by underlying conditions and estimates by country.

All analyses were conducted using Comprehensive Meta-Analysis Version 2.0(Borenstein et al., 2005).

Results

Search results

Details on the search results and characteristics of the included studies are reported in the main report of the present meta-analysis and in eTable 3(Correll et al., 2022b).

Out of 8,345 abstracts, after removal of duplicates, we reviewed 6,390 titles and abstracts and ultimately included 135 studies(Correll et al., 2022b) (Figure 1), reporting on 4,136,128 people with schizophrenia and 1,231,669,106 controls.

The included studies encompassed 23 countries across six continents: Europe or Israel (n=70), North-America (n=29), Asia (n=33), Oceania (n=2), and Africa (n=1). Additionally, the distribution of evidence across countries is reported in Figure 2.

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Overall, 22 studies included first-episode or incident schizophrenia, and five studies included treatment-resistant schizophrenia; all other studies included patients with prevalent schizophrenia. Forty-nine studies only reported on all-cause mortality, the primary outcome of this meta-analysis, 25 only on a specific cause of mortality, and 63 on both all-cause and specific-cause mortality.

Mortality risk among people with schizophrenia versus any control group across continents

Incident plus prevalent, incident, and prevalent risks for all-cause, suicide-related, and natural cause mortality in schizophrenia versus the general population are reported in Figures 3A-C. Additional details are displayed in eTable 4.

For schizophrenia vs. any control group (general population or psychiatric controls without schizophrenia), incident plus prevalent *all-cause* mortality was highest in Africa (RR=5.98, 95%C.I.=4.09-8.74, k=1) and lowest in North-America (RR=2.14, 95%C.I.=1.92-2.38, k=16, I^2=99%), continent differences p=<.001.

Suicide-related mortality was highest in Oceania (RR=13.5, 95%C.I.=10.08-18.07, k=1) and lowest in North-America (RR=4.4, 95%C.I.=4.07-4.76, k=6, I^2=67.41%), continent differences p=<.001.

Natural-cause mortality was highest in Europe (RR=2.08, 95%C.I.=1.88-2.31, k=33, I^2=99.04%) and the lowest in North-America (RR=1.77, 95%C.I.=1.50-2.11, k=12, I^2=99.18%), continent differences p=.29.

For *specific causes* of mortality, only diabetes differed statistically significantly across different continents", with the highest mortality in North-America (RR=4.20, 95%C.I.=4.07-4.33, k=1) and the lowest in Europe (RR=1.72, 95%C.I.=1.21-2.43, k=3, I^2=71.88%), continent differences p=<.001.

For incident schizophrenia, the risk for *all-cause* mortality was highest in North-America (RR=10.0, 95%C.I.=9.04-11.06, k=1) and lowest in Europe (RR=5.33, 95%C.I.=3.91-7.28, k=1), continent differences p=<.001.

For prevalent schizophrenia, *all-cause* mortality was highest in Africa (RR=5.98, 95%C.I.=4.09-8.74, k=1) and lowest in North-America (RR=2.05, 95%C.I.=1.71-2.46, k=15, I^2=98.97%), continent differences p=<.001.

Natural-cause mortality was highest in Europe (RR=2.04, 95%C.I.=1.82-2.29, k=28, I^2=99.14%), and the lowest in North-America (RR=1.74, 95%C.I.=1.35-2.25, k=12, I^2=99.14%), continent differences p=.525.

Mortality risk among people with schizophrenia versus the general population across continents

Incident plus prevalent risk for *all-cause* mortality was highest in Africa (RR=5.98, 95%C.I.=4.09-8.74, k=1) and lowest in North-America (RR=2.72, 95%C.I.=2.50-2.97, k=11, I^2=98.2%) (continent differences p<.001).

Suicide-related mortality was highest in Oceania (RR=13.5, 95%CI=10.08-18.08, k=1), and lowest in North-America (RR=4.40, 95%C.I.=4.07-4.76, k=6, I^2=67.41%), continent differences p=<.001.

Natural-cause mortality risk was highest in Asia (RR=2.28, 95%C.I.=1.93-2.68, k=12, I^2=98.66%) and lowest in North-America (RR=1.90, 95%C.I.=1.61-2.24, k=10, I^2=98.77%), continent differences p=0.248.

The following *specific causes* of mortality statistically significantly differed across continents: i) "any cancer": highest mortality in Europe (RR=1.47, 95%C.I.=1.25-1.72, k=15, I^2=95.87%) and lowest in Asia (RR=1.02, 95%C.I.=0.83-1.25, k=5, I^2=95.56%), continent difference p=0.025; ii) "colon cancer": highest in Europe (RR=2.20, 95%C.I.=0.95-5.09, k=1), and lowest in Asia (RR=1.10, 95%C.I.=0.89-1.35, k=1), continent difference, p=<.001; iii) "liver cancer": highest in North-America (RR=1.40, 95%C.I.=1.20-1.63, k=1) and lowest in Europe (RR=0.50, 95%C.I.=0.24-1.05, k=1), continent difference, p=0.007; iv) "lung cancer": highest in Europe (RR=2.10, 95%C.I.=1.48-2.97, k=1) and lowest in Asia (RR=0.77, 95%C.I.=0.67-0.89, k=1), continent difference=<.001; v) "endocrine disease": highest in Europe (RR=4.83, 95%C.I.=1.98-11.8, k=7, I^2=97.89%) and lowest in Asia (RR=0.97, 95%C.I.=0.66-1.42, k=1), continent difference, p=<.01; vi) "injury (accident)": highest in Asia (RR=6.60, C.I.=4.29-10.2, k=1) and lowest in Oceania (RR=1.80, 95%C.I.=0.91-3.55, k=1), continent difference, p=<.01; vii) "respiratory disease (COPD - chronic obstructive pulmonary disease): highest in North-America (RR=7.47, 95%C.I.=3.11-17.9, k=2, I^2=57.59%) and lowest in Asia (RR=0.64, 95%C.I.=0.48-0.85, k=1), continent difference, p=<.001; viii) "undetermined non-natural causes": highest in Europe (RR=8.76, 95%C.I.=6.97-11.0, k=10, I^2=93.47%) and lowest in North-America (RR=5.96, 95%C.I.=5.69-6.23, k=3, I^2=0%), continent difference, p=.01; and ix) "urogenital disease (renal failure)": highest in North-America (RR=3.62, 95%C.I.=3.33-3.93, k=1) and lowest in Asia (RR=1.93, 95%C.I.=1.66-2.25, k=1), continent difference, p=<.001.

For incident schizophrenia, the highest *all-cause* mortality risk emerged in Europe (RR=3.73, 95%C.I.=2.88-4.84, k=4, I^2=97.89%) being lowest in North-America (RR=3.300, 95%C.I.=3.299-3.301, k=1), continent differences, p=.649.

Suicide-related mortality was highest in Europe (RR=16.8, 95%CI=14.1-20.1, k=4, I^2=86.22%) and lowest in North-America (RR=4.28, 95%C.I.=4.19-4.37, k=1), continent differences, p=<.001.

Natural-cause mortality risk was highest in Europe (RR=2.32, 95%C.I.=1.77-3.03, k=5, I^2=95.06%) and lowest in North-America (RR=1.807, 95%C.I.=1.806-1.808, k=1), continent differences, p=.07.

The following *specific causes* of mortality statistically significantly differed across continents: i) "cardiovascular disease": highest in North-America (RR=3.80, 95%C.I.=3.73-3.88, k=1) and lowest in Europe (RR=2.37, 95%C.I.=1.71-3.30, k=4, I^2=88.12%), continent differences, p=.005; ii) "cerebrovascular disease": highest in North-America (RR=2.23, 95%C.I.=2.15-2.32, k=1) and lowest in Europe (RR=1.60, 95%C.I.=1.35-1.91, k=4, I^2=0%), continent differences, p=<.001; iii) "any cancer": highest in North-America (RR=1.800, 95%C.I.=1.799-1.801, k=1) and lowest in Europe (RR=1.17, 95%C.I.=0.97-1.41, k=4, I^2=47.94%), continent difference, p=<.001; iv) "homicide": highest in Europe (RR=9.04, 95%C.I.=3.65-22.4, k=1) and lowest in North-America (RR=1.12, 95%C.I.=1.05-1.20, k=1), continent difference, p=<.001; v) "undetermined non-natural causes": highest in Europe (RR=9.28, 95%C.I.=6.38-13.5, k=3, I^2=40.25%) and lowest in North-America (RR=5.96, 95%C.I.=5.69-6.24, k=1), continent difference, p=0.01.

For prevalent schizophrenia, *all-cause* mortality risk was highest in Africa (RR=5.98, 95%C.I.=4.09-8.74, k=1) and the lowest in North-America (RR=2.64, 95%C.I.=2.26-3.07, k=10, I^2=98.3%), continent differences, p=<.001.

Suicide-related mortality was highest in Oceania (RR=13.5, 95%CI=10.1-18.1, k=1) and lowest in North-America (RR=4.94, 95%C.I.=2.90-8.43, k=5, I^2=57.45%), continent differences, p=.009.

Natural-cause mortality risk was numerically highest in Asia (RR=2.28, 95%C.I.=1.93-2.68, k=12, I^2=98.66%) and lowest in North-America (RR=1.97, 95%C.I.=1.47-2.62, k=8, I^2=98.97%), continent differences, p=.678.

The following *specific causes* of mortality statistically significantly differed across continents: i) "any cancer": highest in Europe (RR=1.57, 95%C.I.=1.30-1.89, k=11, I^2=96.67%) and lowest in Asia (RR=1.02, 95%C.I.=0.83-1.25, k=5, I^2=95.56%), continent differences, p=.009; ii) "lung cancer": highest in Europe (RR=2.10, 95%C.I.=1.48-2.97, k=1) and lowest in Asia (RR=0.77, 95%C.I.=0.67-0.89, k=1), continent difference, p=<.001; iii) "any infectious disease": highest in Asia (RR=3.82, 95%C.I.=2.30-6.34, k=3, I^2=85.13%) and lowest in North-America (RR=1.61, 95%C.I.=0.96-2.68, k=2, I^2=0), continent difference, p=0.04; iv) "injury (accidents)": highest in North-America (RR=7.50, 95%C.I.=2.52-22.3, k=1) and lowest in Europe (RR=1.65, 95%C.I.=1.48-1.85, k=1), continent difference, p=<.001; v) "musculoskeletal disease": highest in Asia (RR=8.82, 95%C.I.=4.94-15.7, I^2=0%) and lowest in Europe (RR=2.85, 95%C.I.=2.67-3.04, I^2=0%), continent difference, p=<.001; vi) "respiratory disease (COPD)": highest in Europe (RR=4.35, 95%C.I.=3.38-5.59, k=2, I^2=0%) and lowest in Asia (RR=0.64, 95%C.I.=0.48-0.85, k=1), continent difference, p=<.001; and vii) "skin/subcutaneous disease": highest in Asia (RR=12.1, 95%C.I.=8.10-18.1, k=1) and lowest in Europe (RR=2.85, 95%C.I.=2.64-3.08, k=1), continent difference, p=<.001.

Mortality risk in people with schizophrenia versus matched controls without schizophrenia (i.e. with the same physical condition), in prevalent schizophrenia, across continents

For prevalent schizophrenia, all-*cause mortality* was highest in Oceania (RR=2.52, 95%C.I.=1.83-3.48, k=1) and lowest in North-America (RR=1.24, 95%C.I.=1.08-1.42, k=5, I^2=73.15%), continent differences p=<.001.

For *natural-cause mortality*, the highest mortality risk emerged in Europe (RR=1.76, 95%C.I.=1.53-2.03, k=9, I^2=86.45%), being lowest in Asia (RR=1.14, 95%C.I.=0.54-2.41, k=4, I^2=90.53%), continent differences p=.09.

The following *specific causes* of mortality statistically significantly differed across different continents: i)"cardio-cerebrovascular disease": highest in Europe (RR=1.62, 95%C.I.=1.45-1.81, k=1) and lowest in North-America (RR=1.10, 95%C.I.=1.06-1.14, k=1), continent differences p=<.001; ii) "cerebrovascular disease": highest in Europe (RR=1.51, 95%C.I.=1.15-1.99, k=1) and lowest in Asia (RR=0.34, 95%C.I.=0.19-0.59, k=1), continent differences p=<.001; iii) "diabetes": highest mortality in Europe (RR=1.78, 95%C.I.=1.62-1.96, k=1) and lowest in Asia (RR=1.23, 95%C.I.=1.10-1.38, k=1), continent differences p=<.001; and iv) "infectious disease (COVID-19)": highest in Asia (RR=2.51, 95%C.I.=1.65-3.80, k=2, I^2=0%) and lowest in Europe (RR=1.30, 95%C.I.=1.14-1.48, k=2, I^2=0%), continent differences p=0.003.

Mortality risk in people with schizophrenia exposed to antipsychotics vs. people with schizophrenia unexposed to antipsychotics, across continents

The association between antipsychotics and all-cause, suicide-related, and natural-cause mortality, in incident plus prevalent, incident, prevalent schizophrenia versus any control group is reported in Figures 4A-C.

For incident plus prevalent *all-cause* mortality, risk reduction with antipsychotics was highest in Europe (RR=0.63, 95%C.I.=0.52-0.75, k=7, I^2=96.85%) and lowest for Asia (RR=0.80, 95%C.I.=0.75-0.85, k=2, I^2=0), continent difference, p=.01.

For *suicide*-related mortality, risk reduction with antipsychotics was numerically highest in Europe (RR=0.72, 95%C.I.=0.38-1.34, k=2, I^2=97.67%) and numerically lowest for Asia (RR=1.07, 95%C.I.=0.76-1.52, k=1), continent difference, p=0.269.

For natural-cause mortality, risk reduction with antipsychotics was highest in Asia (RR=0.64, 95%C.I.=0.55-0.75, k=1) and numerically lowest in Europe (RR=0.81, 95%C.I.=0.46-1.42, k=2, I^2=96.33%), continent difference, p=0.431.

In prevalent schizophrenia, for *all-cause* mortality risk reduction with antipsychotics was highest in Europe (RR=0.54, 95%C.I.=0.48-0.59, k=5, I^2=87.1%) and lowest in Asia, (RR=0.80, 95%C.I.=0.75-0.85, k=2, I^2=0), between continent p<.001.

For suicide-related mortality risk reduction with antipsychotics was highest in Europe (RR=0.52, 95%C.I.=0.48-0.57, k=1), without risk reduction in Asia (RR=1.07, 95%C.I.=0.76-1.52, k=1), continent difference, p<.001.
For natural-cause mortality, risk reduction with antipsychotics was highest in Europe (RR=0.61, 95%C.I.=0.58-0.63, k=1) and lowest in Asia (RR=0.64, 95%C.I.=0.55-0.75, k=1), continent difference, p=0.546.

Risk for mortality-related outcomes across specific countries

All-cause mortality risk in schizophrenia versus any control group *by country* is outlined in Figure 5A-C, and in detail in eTable 3 (vs. the general population).

Meta-regression analysis between primary and key secondary outcomes and socio-demographic index
All results of the meta-regression analysis between primary and key secondary outcomes and SDI are detailed in eTable 5.
Comparing people with schizophrenia with the general population, a higher socio-demographic index did not significantly moderate all-cause mortality risk. However, a higher socio-demographic index significantly moderated a higher suicide-related mortality risk in incident schizophrenia (beta=41.1, p=0.002, k=5), yet a lower suicide-related mortality risk for prevalent schizophrenia (beta=-6.74, p=0.02, k=23). The opposite finding emerged for natural-cause mortality risk, with a lower risk in incident schizophrenia (beta==-15.3, p=0.002, k=6), but a higher risk in prevalent schizophrenia (beta=1.79, p=0.04, k=34).
Considering protective effects of antipsychotics, for all-cause mortality, a higher socio-demographic index moderated a larger protective effect in incident plus prevalent schizophrenia for any second-generation antipsychotic (SGA) (beta=-18.0, p=0.03, k=3), any long-acting injectable antipsychotic (LAI) (beta=-14.5, p=0.001, k=2), any first-generation antipsychotic (FGA)-LAI (beta=-10.1, p=0.02, k=2); in incident schizophrenia for any antipsychotic (beta=-37.7, p=0.03, k=3); in prevalent schizophrenia for any LAI (beta=-14.8, p=0.001, k=2), any FGA-LAI (beta=-10.9, p=0.02, k=2), while, conversely, in prevalent schizophrenia a lowering of the protective effect emerged for any antipsychotic (beta=13.2, p=0.003, k=7). Regarding suicide-related mortality risk, a higher socio-demographic index significantly reduced the protective effect of any antipsychotic in prevalent schizophrenia (beta=31.3, p=0.008, k=2). Finally, for natural-cause mortality, no moderating effect emerged.

Discussion

To the best of our knowledge, this is the largest and most comprehensive meta-analysis providing a global atlas of differences across countries and continents in the risk of death in schizophrenia versus

the general population with/without other psychiatrically ill groups, and on the association between antipsychotic treatments and mortality risk in subjects with incident and prevalent schizophrenia. While most evidence comes from Western and Northern European countries or Israel, the U.S. was the single country with the highest number of individual studies (N=20) contributing to the analyses. On the other hand, only one or no studies at all were retrieved for Central- and South-America, Eastern Europe, Africa, the Middle East, and South-Eastern Asia. This result reflects a significant lack of information that should be filled in the future.

Compared with the general population, in incident plus prevalent schizophrenia, differences across regions emerged for all-cause and suicide-related mortality but not for natural-cause-related mortality. People with schizophrenia had a 2.8-fold increased risk of all-cause mortality in Africa (RR=5.98) compared to North-America (RR=2.14). People with schizophrenia had a 3.1-fold increased suicide-related mortality risk in Oceania (RR=13.5) compared to North-America (RR=4.4).
In incident schizophrenia, the highest risk of death relative to the general population due to suicide, homicide, and undetermined non-natural causes emerged in Europe, while North-American patients had the lowest risk. The lowest risk in North America might be related with high rates of suicide even in the general population in the US(Pritchard et al., 2023). It has been shown that increased state guns restrictions and decreased gun ownership rates are associated with lower deaths by suicide within USA(Gunn III et al., 2022; Paul and Coakley, 2023), and broad access to firearms in USA might be mitigating the relative risk of suicide in persons with schizophrenia compared with the general population(Pritchard et al., 2023). Conversely, death relative to the general population due to cardiovascular and cerebrovascular diseases and any cancer was highest in North-American and lowest in European patients. This difference might be related with a larger gap in quality of care for cardiometabolic risk factors and conditions in the US compared with Europe. Insurance-based healthcare systems might amplify the gap in physical healthcare in people with schizophrenia who are frequently unemployed and have less consistent and lower quality health insurance coverage(Wilson et al., 2022). Lack of insurance coverage is associated with lower access to care, which can lead to premature mortality(Murphy et al., 2021).
In prevalent schizophrenia, relative to the respective general population, African patients showed the highest risk of death due to any cause, while North-American patients had the lowest. This is possibly due to structural limitations in healthcare system in Africa, and the association between severe mental illness and food insecurity, which in turn is linked to earlier mortality compared with the general population(Beyene, 2023; Tirfessa et al., 2019; Trudell et al., 2021; Weobong et al., 2023). North American patients also exhibited the lowest risk of suicide relative to the general population, while Oceania ranked highest. Low relative risk on North America is probably driven by high rates of suicide in the general population(WHO, The Global Health Observatory). The European patients had the highest risk of death from any cancer, lung cancer, and COPD, while Asian patients had the

lowest. This finding can be driven by poor cancer screening in Asia (with the exception of high-income countries), cancer features at diagnosis and temporal trends of cancer risk factors which might contribute to higher mortality from cancer in the general population(Sankaranarayanan et al., 2014; Sung et al., 2021; Yang et al., 2019). Asian patients instead ranked highest for death due to infectious disease, while North-American patients had the lowest risk, possibly due to lower hygiene practices in vulnerable populations(Freeman et al., 2014). Conversely, North-American patients had the highest risk of death relative to the general population due to injury, while European patients had the lowest, possibly due to lower unintentional accidents rate in North America in the general population(Chandran et al., 2010). Finally, the risk of death due to musculoskeletal disease and skin/subcutaneous disease was highest in Asia and lowest in Europe, with incidence rates of musculoskeletal diseases in the general population having decreased the most in Asia over the last decades, possibly without a parallel decrease in persons with schizophrenia(Liu et al., 2022).
These results suggest that there are differences across continents regarding causes of death in incident and prevalent schizophrenia. For instance, violent causes of death (suicide, homicide, injury) affect younger patients with schizophrenia in Europe and older patients with schizophrenia in the US, while the opposite was observed for medical diseases, especially cardiovascular issues and cancer. Overall though, no differences emerged across continents regarding natural-cause mortality. Two recent meta-analyses reported the absence of substantial differences between countries in disadvantage of people with schizophrenia in receiving adequate screening for cardiovascular diseases(Solmi et al., 2021) and cancer(Solmi et al., 2020). A rise in the prevalence of cardiovascular-related comorbidities in younger people has been observed both in the US(Hirode and Wong, 2020) and in Europe(Mattsson et al., 2007). Despite the fact that differences exist across regions with respect to access to healthcare, lifestyle, and screening for physical conditions(McCarthy, 2016; Solmi et al., 2020), the gap in mortality due to natural causes relative to the respective general population appears to be largely homogeneous across the globe. Several factors could drive such a gap, which range from almost uniformly low socioeconomic status in people with schizophrenia precluding the access to care in insurance-based healthcare systems, negative symptoms as a barrier to outreach for receiving proper screening and treatment for physical conditions, lower education, or paranoid delusions as a barrier to trust healthcare systems(Wilson et al., 2022).

Compared with matched controls (i.e. with the same physical condition), in prevalent schizophrenia, the risk of death due to any cause was highest in Oceania and lowest in North-America. Relative to their general population controls, North-American patients also had the lowest risk of death due to cardio-cerebrovascular diseases, while European patients had the highest, probably due to lower quality of care for obesity and cardiometabolic conditions in North America where they are highly prevalent(Danaei et al., 2011; Ng et al., 2014). In addition, European patients had the highest risk of death due to cerebrovascular diseases and diabetes, while Asians had the lowest, possibly reflecting

benign epidemiology figures regarding hypertension in Asia(Zhou et al., 2021). Finally, Asian patients had the highest risk of death due to COVID-19 infection, while Europeans had the lowest risk, reflecting the epidemiology of COVID-19 pandemic(Govind et al., 2022; Hassan et al., 2022; Vita and Barlati, 2022).

Altogether, matching control groups did not alter significantly regional differences observed in comparisons versus general population, a higher burden for specific medical causes of death was further confirmed in European versus North-American patients relative to their respective general population. This reduced gap in the US could also possibly be explained by a higher prevalence of medical comorbidities among the general population compared to European subjects (especially Western Europe which was mostly represented among the European countries included in this study), as shown by GBD data(Abbafati et al., 2020), which might mitigate the gap stemming from low access to insurance-based healthcare of patient with schizophrenia.

Regarding the role of antipsychotics, a larger protective effect in prevalent samples for treatment with any antipsychotic emerged in European versus Asian patients across all-cause and suicide-related mortality, but no differences emerged for natural-cause mortality across continents. Data for incident samples and for antipsychotics subclasses came from Northern-European studies only, thus preventing further comparative analyses by region. Since different antipsychotic regimens and formulations could be more commonly prescribed in some regions compared to others(Gallini et al., 2013), a deeper understanding of the impact of antipsychotics on mortality within and across regions and health-care systems would be useful to replicate and expand findings from the overall sample(Correll et al., 2022b). For instance studies set in Asia reported on subjects prescribed 25 to 100mg of clozapine, which might not be at therapeutic range, despite differences in indicated doses of clozapine across different ethnicities(Correll et al., 2022; de Leon et al., 2021). Also, the use of clozapine varies across countries(Bachmann et al., 2017), as do the incidence and severity/handling of side effects(Chan et al., 2021).

Sociodemographic index and mortality risk across continents

SDI is a composite proxy measure of the rankings of the income per capita, average educational attainment, and fertility rates for a country. A previous meta-analysis reported an increasing all-cause mortality SMR in patients with severe mental illness in more developed countries, albeit not being statistically significant in that broader population(Saha et al., 2007). Our analyses provide a more fine-grained picture, with a higher SDI being associated with a higher suicide-related mortality risk in incident schizophrenia and a higher natural-cause mortality risk in prevalent schizophrenia. Moreover, the protective effect of antipsychotic treatment towards suicide-related mortality was also reduced with increasing SDI. This finding might suggest the presence of different cultural/social/environmental risk factors in more developed countries, which go beyond psychopathology alone and that need to be

better understood and corrected in order to contrast suicide risk. For example, in a meta-analysis of 50-years of research studies, the only significant moderating variable for greater attainment of recovery in schizophrenia was residing in a developing country(Jääskeläinen et al., 2013). Hence, it is possible that several factors could reduce stress and provide protective factors against suicide and (some) natural causes of mortality. Such factors include the greater level of family cohesion and support in lower-SDI countries, the presence of cultural rituals, stigma-related factors that may be protective against suicide(Alemu et al., 2023; Mugisha et al., 2018), and, possibly, less demands and greater opportunity to participate in social and even lower-level job-related vocational settings. Conversely, the increase of natural-cause mortality with higher country SDI in prevalent schizophrenia might reflect better general healthcare quality for the general population, which patients with schizophrenia have limited access to(Kerrison et al., 2023; Solmi et al., 2021, 2020). Nevertheless, these results further confirm the need of better prevention and treatment of unhealthy lifestyle behaviors that often characterize people with schizophrenia(Vancampfort et al., 2019), and to improve their often poor access to physical healthcare(O'Connor et al., 2023; Solmi et al., 2021, 2020).

Critical appraisal of the evidence and limitations of the study

While the present report represents a primer, it must be remarked that a considerable number of comparisons relied on a handful of studies for specific continents, especially Africa and Oceania. In contrast, those comparisons involving multiple records often exhibited high heterogeneity. In addition, chances are that the differences across different regions may depend on differential trends in the diagnosis of schizophrenia, which is now less common than it used to be in the past, especially in North-American and European countries compared to African or Asian countries(Charlson et al., 2018). Similarly, people with schizophrenia may receive delayed general medical diagnoses and interventions compared to the general population, especially in those countries with limited resources(Solmi et al., 2020), thus inflating the risk of death due to specific cancers, among others. Furthermore, differences in the results for patients with schizophrenia versus the general population across different regions may also depend on differential trends in the all-cause and specific-cause mortality rates in the respective general population, rather than differences across schizophrenia samples per se. Future studies should delineate this in more detail. Finally, while exposure to any antipsychotic predicted lower mortality due to any cause as the SDI increased(Correll et al., 2022b), the finding of higher rates of suicide-related mortality in countries with higher SDI in people with schizophrenia warrants additional research (i.e., providing clear-cut stratification of the proportion of first- vs. SGAs exposed cases, in the view of the differential impact on mood and overall suicide risk as well as additional potential confounding factors such as urbanization, as well as substance use which is increased with premature mortality). Similarly, the lack of evidence about LAIs should prompt further primary research.

This study has general limitations and strengths, which are alike those reported for the previous large-scale meta-analysis on mortality in schizophrenia(Correll et al., 2022b), and include, but are not limited to, the following. First, this work included observational studies, which are limited regarding any causal inference. However, they are representative of the clinical population. Second, many meta-analyses and meta-regression analyses, in particular for secondary outcomes, included only few studies, and results should be considered exploratory. However, this meta-analysis still represents the largest evidence synthesis conducted on this topic so far. Third, we did not account for age in this work, nor for first-episode or treatment-resistant course, as too few studies focused on these relevant subpopulations, yet we accounted for disease stage (i.e., incident, prevalent), which would be highly collinear with age. Finally, we imputed the population size for studies reporting on standardized mortality ratio, and we pooled different effect sizes under the assumption that studies had the same population, design, and outcome.

In conclusion, across 23 countries in six continents, a mortality gap for patients with schizophrenia was globally present, but notable significant differences in all-cause, suicide-related, and specific-cause mortality risk, and its moderators emerged across different continents and countries. An increase in natural-cause mortality was more homogeneously distributed globally. Improving psychological as well as physical health of people with schizophrenia worldwide is paramount(O'Connor et al., 2023), and local studies are much needed in order to identify actionable factors to mitigate the risk of premature all-cause, suicide-related, and cause-specific death in people with schizophrenia. Specifically, studies aiming to identify moderating and mediating modifiable and non-modifiable factors of all-cause specific and cause-specific premature mortality in people with schizophrenia are needed.

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Authors' contributions: CUC, GC, MS designed the study and wrote the protocol. CUC, GC, MS, SCRM, LF managed literature search and data extraction. GC, MS conducted statistical analyses. GC, MF, MS wrote the first draft of the paper. All authors contributed to and have approved the final manuscript.

Conflict of interest statement*:*

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