





Relationship between severe mental illness and physical multimorbidity: a meta-analysis and call for action

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ABSTRACT

Background People with severe mental illness (SMI) have a higher prevalence of several chronic physical health conditions, and the prevalence of physical multimorbidity is expected to rise. The aim of this study was to assess the strength of the association between SMI and physical multimorbidity.

Study selection and analysis We systematically searched PubMed/Medline, Scopus, Embase, Web of Science, PsycINFO and the behavioural sciences collection databases, from inception to 31 January 2023, for studies that investigated the association between SMI and physical multimorbidity. Humans of any age either clinically diagnosed and/or currently receiving treatment for SMI, specified as schizophrenia (and related psychotic disorders), bipolar disorder and psychotic depression, were eligible. Data from studies selected for inclusion were converted into ORs, with a subsequent meta-analysis conducted.

Findings We included 19 studies with a total of 194 123 patients with SMI with different diagnoses and drawn from the general population. The pooled OR for physical multimorbidity in people with versus without SMI was 1.84 (95% CI 1.33 to 2.54), with the analysis indicating a high level of heterogeneity (98.38%). The other 15 studies included in the systematic review for which it was not possible to conduct a meta-analysis showed strong associations between SMI and physical multimorbidity.

Conclusions The current evidence highlights the link between SMI and physical multimorbidity. A multidisciplinary approach is now urgent to develop the best models of services tailored to patients with SMI with physical multimorbidities to improve physical, mental and social outcomes.

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INTRODUCTION

Mental health is a human right, crucial to personal, community and socioeconomic development, and is defined as a state of mental well-being that enables people to cope with the stresses of life, realise their abilities, learn and work well, and contribute to their community.¹ Mental health is an integral component of health and well-being that underpins our

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ People with severe mental illness have a higher prevalence of several chronic physical health conditions, and the prevalence of physical multimorbidity is expected to rise.

WHAT THIS STUDY ADDS

⇒ The current evidence highlights the link between severe mental illness and physical multimorbidity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A multidisciplinary approach for those with severe mental illness and physical multimorbidity is now urgent to improve physical, mental and social outcomes.

individual and collective abilities to make decisions, build relationships and shape the world we live in.¹ Mental health conditions include mental disorders and psychosocial disabilities, as well as other mental states associated with significant distress, impaired functioning or risk of self-harm.¹ Moreover, people with mental illness have an increased risk of physical disease, as well as reduced access to adequate healthcare.² Indeed, growing evidence suggests that people with mental disorders have a higher prevalence of several chronic physical health conditions, including HIV, diabetes mellitus, and gastrointestinal, cardiovascular and respiratory diseases.²⁻³ The prevalence of physical multimorbidity, defined as any combination of chronic disease with at least one other disease (acute or chronic),⁴ is expected to rise, according to the ageing population and increased exposure to risk factors for chronic conditions.⁵ However, this association is not linear and the poor physical health of people with mental illness is a multifaceted, transdiagnostic and global problem. As a result, physical health disparities are observed across the entire spectrum of mental illnesses in low-income, middle-income and high-income countries.⁶ The poor clinical management of physical comorbidity and multimorbidity in people with mental illnesses results in drastically



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reduced life expectancy and increases the personal, social and economic burden of mental illnesses across the lifespan.⁷ Moreover, reduced life expectancy among this population is also attributed to several other factors, including for example social and behavioural factors (eg, loneliness^{8,9} and reduced levels of physical activity^{10,11}) and socioeconomic status. Indeed, those of a lower socioeconomic status are more likely to experience mental illness and multimorbidity^{12,13} and have lower life expectancy.¹⁴ Long-term physical conditions and mental health problems often co-occur, act synergistically and have negative effects on levels of disability, with longer hospital stays and increased costs and mortality.¹⁵ To date, no attempt has been made to collate and evaluate the existing literature on the relationship between severe mental illness and physical multimorbidity. The aim of this systematic review and meta-analysis was to assess the strength of the association between severe mental illness and physical multimorbidity.

METHODS

The present review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses¹⁶ and the Meta-Analysis of Observational Studies in Epidemiology¹⁷ guidelines and a structured protocol preregistered on PROSPERO (CRD42023395165).

Search strategy

Two investigators (MT and DP) independently conducted the same literature search using PubMed/Medline, Scopus, Embase, Web of Science, PsycINFO and the behavioural sciences collection databases from inception to 31 January 2023. The following search strategy was employed: (“bipolar disorder” OR mania OR schizophrenia OR schizoaffective OR psychosis OR psychotic OR “psychotic depression” OR “psychotic depressive” OR “serious mental illness” OR “severe mental illness” OR “psychiatric”) AND (“multimorbidity” OR “multi-morbidity” OR “multi morbidity” OR multimorbidities OR “multi-morbidities” OR “multi morbidities” OR multimorbid OR “multi-morbid” OR “multi morbid” OR comorbidity OR “co-morbidity” OR “co morbidity” OR comorbidities OR “co-morbidities” OR “co morbidities” OR comorbid OR “co-morbid” OR “co morbid” OR “multiple chronic conditions” OR “multiple chronic illnesses” OR “multiple chronic diseases” OR “multiple conditions” OR “multiple illnesses” OR “multiple diseases” OR “multiple diagnoses” OR “morbidity pattern” OR “morbidity patterns” OR polymorbidity OR “poly-morbidity” OR “poly morbidity” OR polymorbidities OR “poly-morbidities” OR “poly morbidities” OR poly pathology OR “poly-pathology” OR “poly pathology” OR poly pathologies OR “poly-pathologies” OR “poly pathologies” OR pluripathology OR “pluri-pathology” OR “pluri pathology” OR multipathology OR “multi-pathology” OR “multi pathology” OR multipathologies OR “multi-pathologies” OR “multi pathologies” OR “multiple pathologies” OR “disease cluster” OR “disease clusters”). The reference lists of the retrieved articles were then searched to identify other potentially eligible articles to include in the analysis which may have been missed in the initial search. Database search, review of inclusion and exclusion criteria, quality of studies, and extraction of data were carried out by two investigators (MT, DP), meaning each investigator carried out the procedure and then compared their results, and in the case of any disagreement a consensus was reached through discussion with a third senior investigator (LS). There was no language restriction applied.

Type of studies and inclusion and exclusion criteria

Following the PICOS (participants, intervention, controls, outcomes, study design) framework, we included studies assessing the following:

- ▶ P: humans of any age either clinically diagnosed and/or currently receiving treatment for a severe mental illness, specified as schizophrenia (and related psychotic disorders), bipolar disorder and psychotic depression.
- ▶ I: none.
- ▶ C: humans without mental illness (eg, psychotic depression vs no psychotic depression).
- ▶ O: physical multimorbidity, defined as any combination of chronic disease with at least one other disease (acute or chronic),⁴ as the the primary outcome. Specifically, studies which explicitly reported on the incidence of physical multimorbidity or a change in physical multimorbidity over time were considered.
- ▶ S: all articles of an observational nature on severe mental illness and physical multimorbidity (cross-sectional, cohort studies, retrospective studies, case-control studies and longitudinal).
- ▶ Articles published in any language (but only English-written articles were identified), on humans only, and across all age groups, severe mental illnesses and groupings of physical multimorbidity. Theoretical-only articles, those of qualitative nature, case studies, conference abstracts and experimental trials were excluded.

Data extraction

For each eligible study, two investigators (MT, DP) extracted the following data independently for each study: name of the first author, year of publication, country, study design, sample size, sample characteristics and outcomes. In the case of any disagreement, consensus was reached through discussion with a third senior investigator (LS).

Assessment of study quality

The quality of studies was assessed using the Newcastle-Ottawa Scale (NOS) by two authors (DP, MT),¹⁸ independently for each study. In the case of any disagreement, consensus was reached through discussion with a third senior investigator (LS). Based on three quality parameters—selection, comparability and outcome—the NOS assigns a maximum of 9 points. Following standard protocol, studies were graded as having high (<5 stars), moderate (5–7 stars) or low (≥8 stars) risk of bias.¹⁹

Assessment of the certainty of evidence

To measure the certainty of evidence, the Grading of Recommendations, Assessment, Development and Evaluation framework was employed.²⁰

Statistical analysis

To be eligible for inclusion in the meta-analysis, primary data from retrieved articles were required to have the following information: number of participants with no severe mental illness (a) with physical multimorbidity (any combination of chronic disease with at least one other disease (acute or chronic⁴)) and (b) without physical multimorbidity; and number of people with severe mental illness (a) with and (b) without physical multimorbidity. These data were then used to calculate an OR for each primary study, indicating the odds of multimorbidity in people with versus without severe mental illness. The meta-analysis was performed on the Comprehensive Meta-Analysis software

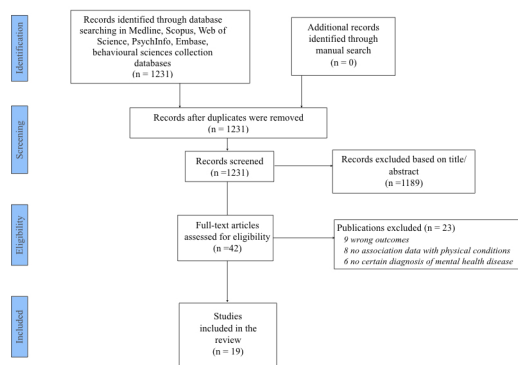


Figure 1 PRISMA flow chart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

by employing the DerSimonian and Laird method, weighting studies based on the inverse variance and calculating the prevalence proportions with 95% CIs. Because of anticipated heterogeneity, a random-effects model was chosen. Heterogeneity was assessed using the I^2 statistic, with $<50\%$ being deemed as low, $50\%–75\%$ moderate and $>75\%$ high heterogeneity.²¹ To assess for publication bias, a visual inspection of funnel plots and the Egger regression test were carried out.²² Following recommendations from Fu *et al*²³ and Sterne *et al*,²⁴ the Egger regression was carried out only when the number of studies in each analysis was greater than 10.

RESULTS

Literature search

As shown in [figure 1](#), we initially found 1231 possibly eligible articles. After removing 1189 articles through the title/abstract screening, 42 were retrieved as full text. Of the 42 full-text articles, 23 articles were excluded due to lack of relevant outcomes, not including analysis on the association between severe mental illness and physical multimorbidity, and mental health diagnoses were not obtained. This left 19 articles to be included in the systematic review.^{25–41}

Descriptive data

The 19 articles (14 cohort, 3 case–control and 2 cross-sectional in study design) included a total of 194 123 psychiatric patients with various diagnoses, and a total of 7 660 590 participants in the control groups of the articles that reported on control

groups (see online supplemental table S1). The majority of articles determined the presence of mental illness using psychiatrist diagnoses based on the respective severe mental health codes in International Classification of Disease version 10. Regarding the presence of morbidities, the majority of articles used medical records as indicators. Online supplemental table S1 also includes the main physical morbidities associated with respective mental illnesses. Other physical morbidities that are not reported in the table include viral hepatitis, HIV infection, tuberculosis, generic infections, hypertriglyceridaemia, metabolic not specified diseases, extrapyramidal diseases, status epilepticus, migraine, trigeminal neuropathy, facial pain, spinal and back pain, sciatica, sinusitis, anaemia, chronic obstructive pulmonary disease, not specified respiratory tract diseases, gingivitis, urinary incontinence, urinary tract diseases, menopausal syndrome, jaundice, arthritis, skin diseases, psoriasis, eczema, transitory ischaemic attack, aneurysm, ischaemic heart disease, heart failure, atrial fibrillation, cardiac arrhythmia, Parkinson disease, dementia, multiple sclerosis, inflammatory bowel disease, neurological diseases, haematological and rheumatological diseases, osteoporosis, allergies, thyroid disorders, immune diseases, blindness and vision disorders, hearing loss, prostatic hyperplasia, diverticular disease, gout, not specified musculoskeletal, endocrinological and gynaecological diseases, and chronic pain.

Studies were predominantly carried out in Europe, where 14 studies were performed, followed by Asia with 3 and North America and Middle East with 1 each.

Meta-analysis

Four articles were eligible for meta-analysis. The pooled OR for multimorbidity in people with versus without severe mental illness was 1.84 (95% CI 1.33 to 2.54), with the analysis indicating a high level of heterogeneity (98.38%; [figure 2](#)). Due to the limited number of studies, the Egger regression test was not performed; however, visual inspection of the funnel plot suggested no publication bias.

Risk of bias

The median quality of the included studies was 6.6 (range: 5–8), indicating an overall satisfactory quality.

DISCUSSION

The findings from our systematic review and meta-analysis suggest an increased risk of physical multimorbidity among people with severe mental illness. In particular, the pooled

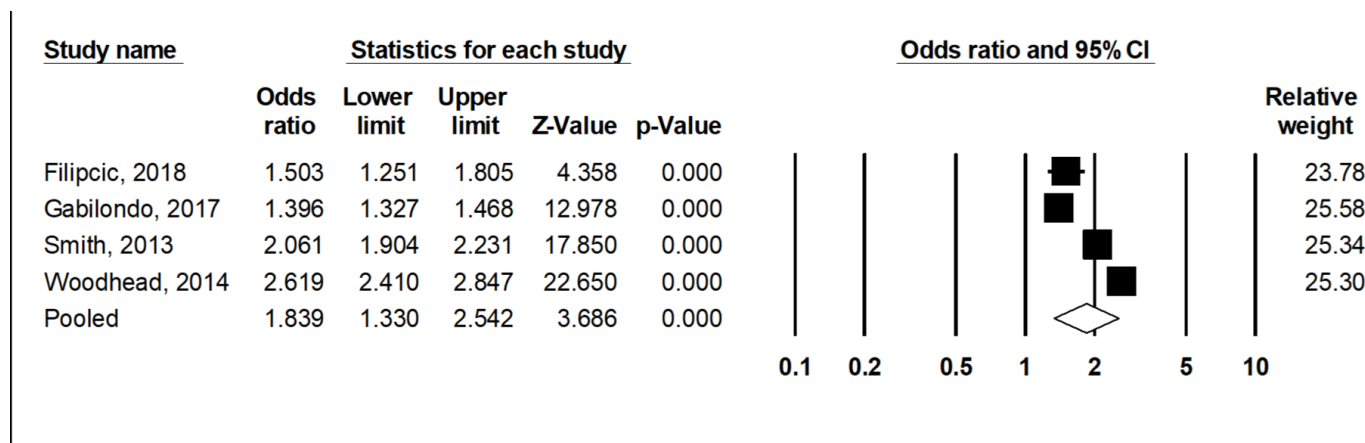


Figure 2

OR for physical multimorbidity in people with versus without severe mental illness was 1.84 (95% CI 1.33 to 2.54), suggesting an almost double risk. Moreover, although it was possible to include relatively few papers in the meta-analysis (mainly due to insufficient data reported in primary studies), the other 15 studies included in the systematic review showed strong associations between severe mental illness and physical multimorbidity. As shown in online supplemental table S1, the main associated conditions were metabolic diseases such as diabetes and obesity; hypertension; epilepsy; respiratory, vascular, kidney and gastrointestinal diseases; and cancer. In addition, physical illnesses affecting all organs were reported. These results are in line with the growing evidence highlighting the increased risk of multiple physical conditions in people who suffer from severe mental health problems. Although these data are significant in and of themselves, they must be considered in light of the increasing number of mental health problems and the reduced and unequal healthcare offered to patients suffering from severe mental health problems. On one hand, in 2019, almost one billion people were living with a mental disorder, which represents the leading cause of disability, causing 1 in 6 years lived with disability.⁴² Moreover, it is reported that people with severe mental health conditions die on average 10–20 years earlier than the general population, mostly due to preventable physical diseases.⁴² On the other hand, just a small fraction of people in need of mental health services have access to effective, affordable and quality mental healthcare, especially in low-income countries.⁴³ For instance, 71% of those with psychosis worldwide do not receive mental health services (70% of people with psychosis are treated in high-income countries vs 12% in low-income countries). These data are more alarming for depression (23% effectively treated in high-income countries vs 3% in low-income and lower-middle-income).⁴²

Independent from the mechanism, to address physical multimorbidity in those with severe mental illness, it is urgent to find integrated and multidisciplinary solutions which consider the complexity of care and the interaction of different health professionals and specialists across different types of care. Indeed, it is crucial to find shared and proper solutions; such approaches will help avoid fragmented and inconsistent care, particularly important for patients with severe mental illness. It is desirable to develop models of care that allow for an integrated approach to diagnosing, monitoring and treating physical multimorbidity in patients with mental illness, particularly in areas of social and economic deprivation. In fact, only through this could healthcare delivery be achieved along a continuum of preventive services and treatment, according to patient needs over time and across different levels of the health system. In this regard, also considering the greatest difficulty in adhering to therapy of people with mental illness, more efforts should be made to prevent, rather than to treat, potential physical diseases. Moreover, integrated care could be cost-effective, patient-centred and equitable. Finally, it is also desirable to adopt a sectorial approach, focusing on common groups of diagnoses in order to facilitate thematic working groups, to consider specific service needs and to design the best approach for mental health patients.

This is the first systematic review and meta-analysis to collate the literature on severe mental illness and physical multimorbidity. However, findings must be interpreted in light of the study's limitations. First, across the included studies, there is considerable variation in the types of included conditions, and cut-offs include two or more multimorbidities. This heterogeneity is perceived to be the result of contextual variation in consideration of multimorbidity across clinical and public

health settings. Moreover, the diagnosis of physical diseases was wide, followed different criteria and was not standardised. This suggests that there is a need for further and more homogeneous studies in order to have a clear picture of the burden of this disease association and to clarify the mechanisms supporting this interaction. Although multiple factors and mechanisms are likely involved in the association between severe mental illness and physical multimorbidity, current hypotheses include shared genetic susceptibility, pathophysiological overlaps such as immuno-inflammatory dysregulation, and the side effects of psychiatric drugs.^{44 45}

In conclusion, the present work demonstrates the link between severe mental illness and physical multimorbidity, which has the potential to lead to a decreased chance of treatment compliance, increased risk of treatment failure, relapsing disease, worsening prognosis and increased treatment costs.¹⁵ Thus, it is urgent for psychiatrists, health professionals, researchers and policy makers to collaborate to develop the best models of services tailored to patients with severe mental illnesses with physical multimorbidities in order to improve physical, mental and social outcomes for all patients.

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