**Impact of mental disorders on clinical outcomes of physical diseases: an umbrella review assessing population attributable fraction and generalized impact fraction**

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Empirical evidence indicates a significant bidirectional association between mental disorders and physical diseases, but the prospective impact of mental disorders on clinical outcomes of physical diseases has not been comprehensively outlined. In this PRISMA- and COSMOS-E-compliant umbrella review, we searched PubMed, PsycINFO, Embase and Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports, up to March 15, 2022, to identify systematic reviews with meta-analysis that examined the prospective association between any mental disorder and clinical outcomes of physical diseases. Primary outcomes were disease-specific mortality and all-cause mortality. Secondary outcomes were disease-specific incidence, functioning and/or disability, symptom severity, quality of life, recurrence or progression; major cardiac events, and treatment-related outcomes. Additional inclusion criteria were further applied to primary studies. Random effect models were employed, along with I2 statistic, 95% prediction intervals, small-study effects test, excess significance bias test, and risk of bias (ROBIS) assessment. Associations were classified into five credibility classes of evidence (I to IV and non-significant) according to established criteria, complemented by sensitivity and subgroup analyses to examine the robustness of the main analysis. Statistical analysis was performed using a new package for conducting umbrella reviews ([https://metaumbrella.org](https://metaumbrella.org/)). Population attributable fraction (PAF) and generalized impact fraction (GIF) were then calculated for class I-III associations. Forty-seven systematic reviews with meta-analysis, encompassing 251 non-overlapping primary studies and reporting 74 associations, were included (68% were at low risk of bias at the ROBIS assessment). Altogether, 43 primary outcomes (disease-specific mortality: n=17; all-cause mortality: n=26) and 31 secondary outcomes were investigated. Although 72% of associations were statistically significant (p<0.05), only two showed convincing (class I) evidence: that between depressive disorders and all-cause mortality in patients with heart failure (hazard ratio, HR=1.44, 95% CI: 1.26-1.65), and that between schizophrenia and cardiovascular mortality in patients with cardiovascular diseases (risk ratio, RR=1.54, 95% CI: 1.36-1.75). Six associations showed highly suggestive (class II) evidence: those between depressive disorders and all-cause mortality in patients with diabetes mellitus (HR=2.84, 95% CI:2.00-4.03) and with kidney failure (HR=1.41, 95% CI: 1.31-1.51); that between depressive disorders and major cardiac events in patients with myocardial infarction (odds ratio, OR=1.52, 95% CI: 1.36-1.70); that between depressive disorders and dementia in patients with diabetes mellitus (HR=2.11, 95% CI: 1.77-2.52); that between alcohol use disorder and decompensated liver cirrhosis in patients with hepatitis C (RR=3.15, 95% CI: 2.87-3.46); and that between schizophrenia and cancer mortality in patients with cancer (standardized mean ratio, SMR=1.74, 95% CI: 1.41-2.15). Sensitivity/subgroup analyses confirmed these results. The largest PAFs were 30.56% (95% CI: 27.67-33.49) for alcohol use disorder and decompensated liver cirrhosis in patients with hepatitis C, 26.81% (95% CI: 16.61-37.67) for depressive disorders and all-cause mortality in patients with diabetes mellitus, 13.68% (95% CI: 9.87-17.58) for depressive disorders and major cardiac events in patients with myocardial infarction, 11.99% (95% CI: 8.29-15.84) for schizophrenia and cardiovascular mortality in patients with cardiovascular diseases, and 11.59% (95% CI: 9.09-14.14) for depressive disorders and all-cause mortality in patients with kidney failure. The GIFs confirmed the preventive capacity of these associations. This umbrella review demonstrates that mental disorders increase the risk of a poor clinical outcome for several physical diseases. Prevention targeting mental disorders – particularly alcohol use disorders, depressive disorders and schizophrenia – can reduce the incidence of adverse clinical outcomes in people with physical diseases. These findings can inform clinical practice and trans-speciality preventive approaches cutting across psychiatric and somatic medicine.

**Key words:** Mental disorders, physical diseases, outcomes, disease-specific mortality, all-cause mortality, umbrella review, trans-speciality preventive approaches

Both physical diseases and mental disorders contribute significantly to the increasing burden on health care systems worldwide1,2. Cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes are accountable for more than 50% of global deaths1, while mental disorders are the third leading cause of disease burden, with depressive disorders accounting for 37% of all years of life lost to disability, followed by anxiety disorders (23%) and schizophrenia (12%)2.

The Cartesian dichotomy of mental disorder-physical disease is challenged by empirical evidence from primary studies3, meta-analyses3-7, and umbrella reviews8,9 showing significant prospective associations between the two realms. For instance, individuals with schizophrenia, compared to the general population, have a higher incidence of metabolic and cardiovascular diseases and of cancer10-13; those with mood disorders are at higher risk of developing cancer and diabetes mellitus7,14; and those with borderline personality disorder have a higher risk to develop a gastrointestinal disease, arthritis and chronic pain. Moreover, mental disorders have been found to increase the burden of physical diseases10,15,16.

Neurobiologically, the core mechanisms that are likely to drive the neuroprogression of mental disorders – such as inflammation, oxidative stress, apoptosis and mitochondrial dysfunction – overlap with the mechanisms driving somatoprogression17. Moreover, mental disorders interfere with adherence to healthy behaviors and treatment18. Consequently, the occurrence of mental disorders often worsens the prognosis of physical diseases. For example, depressive and anxiety disorders are associated with a higher mortality risk in people with cancer19,20, cardiovascular diseases21,22, chronic obstructive pulmonary disease23, and diabetes mellitus24,25. The recent COVID-19 pandemic has also indicated that mental disorders are associated with higher disease severity and mortality26-28.

Despite this accumulating evidence, studies concerning the impact of mental disorders on clinical outcomes of physical diseases are often restricted to small sets of associations, sometimes with conflicting results, and therefore hold limited clinical relevance9. Relevant confounders, such as differences in diagnostic methods, the timing of the diagnosis of mental disorders9 and the effect of psychiatric medications12, have not been systematically controlled for. Furthermore, the observed associations have generally not been appraised using established classification criteria to grade the credibility of the evidence and control for several types of biases.

Another limitation is that the reported associations are not directly informative for clinical practice. For example, it is unclear to what extent preventive approaches for mental disorders could reduce the incidence of clinical outcomes of physical diseases. To address this question, it is essential to quantify the proportional reduction in population-level disease that would occur if a given risk factor is eliminated (population attributable fraction, PAF)29,or partially reduced (generalized impact fraction, GIF)30-32. To our knowledge, no study has estimated the meta-analytic PAF or GIF of the most robust associations between mental disorders and physical diseases.

This is the first umbrella review comprehensively summarizing the evidence concerning the prospective impact of mental disorders on clinical outcomes of physical diseases using established classification criteria of evidence that address multiple biases33-35, controlling for relevant confounders, and estimating the related meta-analytic PAF and GIF. Providing a solid and rigorous synthesis of this evidence is crucial to promote sound etiopathological research and to implement effective preventive strategies cutting across psychiatry and somatic medicine36.

**METHODS**

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement37 and the Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) guidelines38. The study protocol is available at the Center for Open Science (<https://osf.io/dt4fu>).

**Search strategy and selection criteria**

We systematically searched PubMed, PsycINFO, Embase and Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports from inception to March 15, 2022, to identify systematic reviews with meta-analysis that examined the prospective association between any mental disorder and clinical outcomes of physical diseases. Primary outcomes were disease-specific and all-cause mortality. Secondary outcomes were disease-specific incidence, functioning and/or disability, symptom severity, quality of life, recurrence and progression; major cardiac events, and treatment-related outcomes.

Categories of mental disorders were stratified according to the corresponding ICD-10 diagnostic blocks, in line with previous studies39,40, and defined by standard diagnostic criteria or requirements (i.e., any version of the ICD or the DSM), or established diagnostic research criteria (e.g., Research Diagnostic Criteria41), or validated assessment instruments with cut-offs that map onto discrete ICD/DSM diagnoses (e.g., Patient Health Questionnaire, PHQ42).

We focused on categories of physical diseases associated with the highest burden according to the 2019 Global Burden of Disease (GBD) Study and other recent studies11: cardiovascular diseases (e.g., coronary heart disease), chronic respiratory diseases (e.g., chronic obstructive pulmonary disease), neurological diseases (e.g., multiple sclerosis), nutritional and metabolic diseases (e.g., obesity), endocrine system diseases (e.g., diabetes mellitus), kidney diseases, neoplasms, digestive diseases (e.g., liver cirrhosis), infectious diseases (e.g., human immunodeficiency virus, HIV infection), and musculoskeletal diseases (e.g., low back pain).

As a search strategy, we combined key terms and MeSH terms related to these categories of mental disorders and physical diseases with terms related to the clinical outcomes of interest and to systematic reviews or meta-analyses (full details are described in supplementary information). The reference lists of the records identified during the screening process were also searched. Four independent investigators screened the records based on title and abstract reading. After excluding those that were not relevant, the full texts of the remaining records were further assessed for inclusion. Any discrepancy was solved through discussions with a fifth senior investigator.

We included: a) systematic reviews with meta-analysis of observational studies with a prospective design, with meta-analytic summary estimates derived from at least two primary studies; b) primarily investigating the association between mental disorders and clinical outcomes of physical diseases (defined as above); c) published in English.

We excluded: a) systematic reviews without meta-analysis; b) systematic reviews with meta-analysis of individual participant data or network meta-analysis; c) systematic reviews with meta-analysis of randomized controlled trials, interventions, study designs other than prospective (cross-sectional and retrospective case-control studies are subject to recall bias and reverse causality); d) meta-analyses of data not identified via systematic reviews; e) meta-analyses mixing mental disorders and physical diseases without providing distinguishable association measures; e) systematic reviews or meta-analyses using unclear diagnostic criteria not operationalized as above; f) fully overlapping datasets.

When two systematic reviews or meta-analyses presented overlapping data on the same association, only the one with the largest dataset in terms of number of primary studies was retained for the specific association (the two meta-analyses could be non-overlapping for other associations). In the case of similar datasets, we selected the meta-analysis with the highest study quality. When two meta-analyses presented minimally overlapping or not overlapping datasets, nevertheless still addressing the same association, both meta-analyses were included.

Additional inclusion/exclusion criteria were applied to each of the primary studies included in the systematic reviews. Primary study-level inclusion criteria were: a) prospective cohort or longitudinal study (if a meta-analysis included multiple study designs such as randomized controlled trials and prospective studies, we only retained prospective studies); b) examining longitudinally the impact of a mental disorder on clinical outcomes of a physical disease (defined as above); c) distinguishing study participants with a mental disorder (exposed) or not (unexposed) who develop (cases) or not (controls) at least one clinical outcome of a physical disease.

Primary study-level exclusion criteria were: a) studies investigating psychiatric symptoms only but not mental disorders; b) studies reporting on clinical outcomes only for mixed categories of mental or physical diseases (e.g., anxiety and depressive disorders, or diabetes and stroke), without distinguishable estimates per pair of disorders; c) studies using unclear diagnostic criteria not operationalized as above (e.g., continuous psychometric scales without established cut-offs to estimate categorical diagnoses); d) studies reporting on outcomes other than those of interest.

**Risk of bias**

Four independent investigators assessed the risk of bias in the included systematic reviews by using the Risk of Bias in Systematic Reviews (ROBIS) tool43, which has shown good reliability and construct validity in systematic reviews44. Any discrepancy was solved through discussions with a fifth investigator.

The ROBIS tool is applied in three phases: 1) assess relevance (optional), 2) identify concerns with the review process, and 3) judge risk of bias in the review43. In this study, we employed phases 2 and 3. Phase 2 is divided into four domains. Domain 1 assesses concerns regarding the specification of study eligibility criteria; domain 2 evaluates any concerns regarding methods used to identify/select studies; domain 3 covers concerns regarding methods used to collect data and appraise studies; and domain 4 focuses on concerns regarding the synthesis of results. Phase 3 assesses the overall ROBIS risk of bias in the interpretation of review findings43,45.

**Data extraction**

Data extraction was performed independently by three investigators and verified by a fourth investigator.

For each eligible systematic review, we extracted the standard identifier (PubMed identifier, PMID, or digital object identifier, DOI), the first author, the year and journal of publication, the number of prospective primary studies, and the specific populations evaluated. We also extracted the study-specific association measures (odds ratio, OR; risk ratio, RR; hazard ratio, HR; and standardized mortality ratio, SMR), with their 95% confidence intervals (CIs), or the indirect information needed to estimate the association measure.

For each primary study, we extracted the specific population, the number of cases (number of outcome events in participants with a mental disorder), the number of non-cases (number of outcome events in participants without mental disorders), the sample size, the method used to diagnose physical diseases, and the confounders to be tested in subgroup analyses – i.e., the method used to diagnose mental disorders, the timing of mental disorder diagnosis (before or after the diagnosis of a physical disorder), the type of estimates (fully/partially adjusted or unadjusted), the age and sex of participants, and the exposure to psychiatric medications.

For primary studies, we extracted in decreasing order of preference the fully adjusted estimates (e.g., controlling for all available covariates), the partially adjusted estimates (e.g., controlling only for age and sex or some of the covariates reported in the study) and the unadjusted estimates. Whenever studies used multiple control groups, we only considered data from participants without a mental disorder (non-exposed).

We also recorded the quality score of the primary studies and the scale used (when reported) to assess quality; otherwise, we rated the study with the Newcastle‐Ottawa scale (NOS)46.

**Statistical analysis**

The main effect size of interest was the prospective association between mental disorders and clinical outcomes of physical diseases, indexed by the meta-analytic OR, RR, HR or SMR measures and eventually converted into equivalent odds ratios (eORs)33 for comparative purposes. The direction of the effect sizes was harmonized47: an eOR greater than 1 indexed an increased likelihood of the outcome, while an eOR less than 1 indexed a decreased likelihood of the outcome.

Whenever studies provided effect sizes for independent subgroups (e.g., they presented effect sizes for males and females separately), we pooled them using the Borenstein method48. When multiple outcomes (e.g., all-cause mortality and cardiovascular mortality) were assessed in the same primary study, we estimated a pooled effect size10, assuming a correlation of 0.8 between outcomes49,50.

Random effects models with the restricted maximum likelihood (REML) variance estimator were employed50. The I2 statistic was computed to evaluate inconsistency (I2>50% indicated high inconsistency)51, together with the 95% prediction intervals to estimate the plausible range in which the effect sizes of future studies are expected to fall52. The presence of small-study effects was tested with Egger’s regression asymmetry test (p≤0.0553).

The presence of excess significance bias was calculated by using the new Test for Excess Statistical Significance (TESS) and the Proportion of Statistical Significance Test (PSST)54. Both TESS and PSST have desirable statistical properties: adequate control of Type I errors and high statistical power, which takes inconsistency into account54. The presence of excess significance bias was assumed if either TESS or PSST was greater than the Z-score of 1.64554.

Associations were classified into five levels of evidence according to established classification criteria9,33-35,55: convincing (class I: >1000 cases, p<10-6, no evidence of small-study effects or excess significance bias, 95% prediction interval not including the null, and no large inconsistency); highly suggestive (class II: >1000 cases, p<10-6, largest study with a statistically significant effect, and class I criteria not met); suggestive (class III: >1000 cases, p<10-3, and class I and II criteria not met); weak (class IV: all other associations with p≤0.05); and non-significant (NS: all associations with p>0.05).

A sensitivity analysis was performed by removing the criterion of >1,000 cases to examine the robustness of the main analysis when smaller numbers of cases were included56. Subgroup analyses were also performed for associations supported by class I/II evidence to test confounders identified at the primary study level. We stratified the analyses by: a) diagnostic method (standard diagnostic criteria vs. research criteria vs. validated assessment instruments with cut-offs that map onto discrete categories); b) timing of mental diagnosis (diagnosis of mental disorder confirmed before or after the diagnosis of physical disease); c) follow-up duration (>5 vs. ≤5 years); d) type of estimates (adjusted vs. unadjusted); e) age of participants (<50 vs. ≥50 years old); f) exposure to psychiatric medications (yes/no); and g) sex (majority of males vs. majority of females).

The PAF analysis was conducted for each class I-III association, following a method previously established57. Prevalence data (± 95% CIs) of mental disorders in physical diseases were extracted from the primary studies as the total number of those exposed and those in the total population. The calculation of the PAF was based on Levin's formula58, which requires the RR estimate and the prevalence of the risk factor59. We converted all ORs to RRs using a standard formula60. 95% CIs for the PAFs were derived using a method previously validated40. For each association, we created 50,000 random RRs according to the RR 95% CI and 50,000 random prevalences according to the prevalence 95% CI. We then combined the random RRs and prevalences to derive 50,000 PAF estimations, from which we derived the PAF 95% CI.

While the PAF assumes a perfect intervention that eradicates the exposure (i.e., 100% reduction of the prevalence of the risk factors)61, complete removal of exposure is usually unrealistic. We thus performed additional analyses by computing the GIF for factors with the largest PAFs (since the GIF is ≤PAF, the GIF analysis would be futile for smaller PAFs). The GIF estimates the proportional reduction in disease incidence given a graded reduction in the prevalence of a risk factor61.

All analyses were performed in R software, version 4.1.2, using a new evidence synthesis package developed to conduct umbrella reviews: the metaumbrella package50,62, also available as a browser-based graphical app ([https://metaumbrella.org](https://metaumbrella.org/)).

**RESULTS**

**Database search results**

The search identified 21,612 potentially relevant records, and 18,610 titles/abstracts were screened after duplicate removal (see Figure 1). Altogether, 551 full-text papers were checked for eligibility, and 47 systematic reviews with meta-analysis were eventually included in the umbrella review13,19,20,22-24,26,63-102.

The systematic reviews were published between 2004 and 2022, including a total of 251 non-overlapping primary (prospective) studies. They reported on 43 primary outcomes (disease-specific mortality: n=17; all-cause mortality: n=26) and 31 secondary outcomes (disease-specific incidence: n=6; disease-specific functioning and/or disability: n=1; disease-specific symptom severity: n=7; disease-specific recurrence or progression: n=8; major cardiac events: n=7; and treatment-related outcomes: n=2). No disease-specific quality of life outcome was reported.

The total number of participants included in each systematic review ranged from 15975 to 10,757,43599 (median: 3,717, interquartile range, IQR: 480-14,938). The participants’ age ranged from 1772,85 to 99 years97, and all but one systematic review20 included both males and females. The number of primary (prospective) studies included in each systematic review ranged from 273,75,78,95,99 to 2776 (median: 5, IQR: 3-8); their follow-up duration ranged from three79 to 29 years86. About 79% of the primary studies in each systematic review were of high quality.

Most (n=38, 81%) systematic reviews examined associations between mood or anxiety disorders and clinical outcomes of physical diseases: 30 (63.8%) studied the associations of mood disorders19,24,63-65,67,68,71-74,81,82,84-94,96-100,102, and five (10.8%) the associations of anxiety disorders22,66,70,77,95, mostly with outcomes of cardiovascular, neoplastic, endocrine, infectious, neurological or respiratory diseases. Three studies (6.4%) investigated the associations of both anxiety and mood disorders with outcomes of neoplastic, neurological and respiratory diseases20,23,78.

The other diagnostic blocks were less investigated. Four systematic reviews (8.5%) studied organic, including symptomatic, mental disorders in relation to outcomes of cardiovascular, infectious or neurological diseases26,69,76,79. Two (4.2%) studied schizophrenia with regard to outcomes of neoplastic diseases83,101; one (2.1%) studied both mood disorders and schizophrenia in relation to outcomes of cardiovascular diseases13; one (2.1%) studied alcohol use disorders in regard to outcomes of liver diseases75; and one (2.1%) separately studied anxiety disorders, depressive disorders and Alzheimer's disease in relation to outcomes of a neurological disease75.

More than half (n=30, 63.8%) of the systematic reviews ascertained mental disorders using a combination of standard diagnostic criteria or requirements (DSM/ICD), research criteria and validated assessment measures with established cut-offs that map onto ICD/DSM diagnoses. Eleven (23.5%) ascertained mental disorders using exclusively the third of the above-mentioned approaches20,22,63,74,75,87,89,93,95,96,102. Only six (12.7%) used standard diagnostic criteria or requirements (any version of DSM or ICD) exclusively26,76,80,83,99,101 (for details, see supplementary information).

There were no systematic reviews with meta-analysis examining the impact of mental disorders from the other ICD-10 diagnostic blocks on clinical outcomes of physical diseases.

**Risk of bias**

An overall summary of the ROBIS assessment of the systematic reviews is provided in the supplementary information. A total of 26 (55.3%) reviews were at low risk of bias across all phase 2 domains. In Phase 2, 35 (74.5%) systematic reviews had a low risk of bias in domain 1, 34 (72.3%) in domain 2, 26 (55.3%) in domain 3, and 31 (66%) in domain 4. A total of 32 (68.1%) systematic reviews were rated as at low risk of bias in phase 3, which indexes the overall ROBIS risk of bias43,45.

**Summary of associations**

A total of 74 associations were analyzed. Fifty-three (71.6%) presented a statistically significant effect (p<0.05), but only 15 of those (28.3%) reached p<10-6. The number of cases was greater than 1,000 for 30 associations (40.5%). Twenty-eight associations (37.8%) presented large inconsistency (I2>50%), while for 12 (16.2%) the 95% prediction interval did not include the null hypothesis. Additionally, the evidence for small-study effects was noted for nine associations (12.1%), and excess significance bias was noted for 19 (25.6%) associations.

The summary of the associations for classes I-IV is shown in Figures 2 and 3. Only two associations (2.7%) showed a convincing level of evidence (class I), and six (8.1%) showed highly suggestive evidence (class II). Of the remaining associations, three (4.1%) showed suggestive evidence (class III), 42 (56.7%) weak evidence (class IV), and 21 (28.4%) had no evidence. In the following sections, we primarily describe the associations with the highest classes (I-III) of evidence.

**Associations of neurotic, stress-related and somatoform disorders with clinical outcomes of physical diseases**

None of the 13 associations in this diagnostic block was supported by convincing or highly suggestive evidence (class I and II) for either primary or secondary outcomes. Only the association between anxiety disorders and cardiovascular mortality in patients with cardiovascular diseases (RR=1.46, 95% CI: 1.17-1.82) presented a suggestive evidence level (class III). There was weak evidence (class IV) for four associations concerning secondary outcomes. No evidence was found for the remaining eight associations concerning primary and secondary outcomes (see Figures 2 and 3, Table 1 and supplementary information).

After removing the N>1000 cases criterion in sensitivity analysis, the two associations between anxiety disorders and major cardiac events were upgraded from weak (class IV) to suggestive evidence (class III). The level of evidence of the other associations remained unchanged (see Table 1 and supplementary information).

**Associations of mood disorders with clinical outcomes of physical diseases**

Among the 49 associations in this diagnostic block, only that between depressive disorders and all-cause mortality among patients with heart failure (HR=1.44, 95% CI: 1.26-1.65) presented a convincing level of association (class I) (see Figure 2 and Table 2).

Highly suggestive evidence (class II) was found for associations between depressive disorders and all-cause mortality in patients with kidney failure (HR=1.41, 95% CI: 1.31-1.51) and in those with diabetes mellitus (HR=2.84, 95% CI: 2.00-4.03); for the association between depressive disorders and major cardiac events in patients with myocardial infarction (OR=1.52, 95% CI: 1.36-1.70); and for the association between depressive disorders and dementia in patients with diabetes mellitus (HR=2.11, 95% CI: 1.77-2.52) (see Figure 2, Table 2 and supplementary information).

There was suggestive evidence (class III) for two associations: that between bipolar disorder and cardiovascular mortality in patients with cardiovascular diseases (RR=1.65, 95% CI: 1.32-2.06), and that between depressive disorders and all-cause mortality in patients with chronic kidney disease (RR=1.45, 95% CI: 1.22-1.73). There was either weak (class IV) or no evidence of association for all other primary and secondary outcomes (see Figure 3, Table 2 and supplementary information).

After removing the N>1000 cases criterion in sensitivity analysis, there was no change in the level of class I, II and III evidence (see Table 2).

Three associations between depressive disorders and primary outcomes were upgraded from weak (class IV) to highly suggestive evidence (class II): those with all-cause mortality in patients with myocardial infarction, percutaneous coronary intervention, and coronary artery disease (see Table 2). The same upgrade was observed for the associations between depressive disorders and two secondary outcomes: major cardiac events in patients with heart failure, and atrial fibrillation recurrence in patients with coronary artery disease (see supplementary information).

One association between depressive disorders and a primary outcome was upgraded from weak (class IV) to suggestive evidence (class III): that with cardiovascular mortality in patients with myocardial infarction (see Table 2). The same upgrade was observed for seven associations between depressive disorders and secondary outcomes: poor functional outcome and stroke recurrence in patients with stroke; major cardiac events in patients with percutaneous coronary intervention; ventricular tachycardia/fibrillation in patients with coronary artery disease; coronary artery disease in patients with diabetes mellitus; negative treatment outcomes in patients with tuberculosis; and pain in patients with HIV infection (see supplementary information).

**Associations of mental and behavioural disorders due to psychoactive substance use with clinical outcomes of physical diseases**

No association in this diagnostic block was supported by convincing evidence (class I), and there were no data on primary outcomes. The association between alcohol use disorder and decompensated liver cirrhosis in patients with hepatitis C (RR=3.15, 95% CI:2.87-3.46) presented highly suggestive evidence (class II). After removing the N>1000 cases criterion in sensitivity analysis, there was no change in the level of evidence (see supplementary information).

**Associations of schizophrenia with clinical outcomes of physical diseases**

In this diagnostic block, one association presented convincing evidence (class I): that between schizophrenia and cardiovascular mortality in patients with cardiovascular diseases (RR=1.54, 95% CI:1.36-1.75). One further association was supported by highly suggestive evidence (class II): that between schizophrenia and cancer mortality in patients with cancer (SMR=1.74, 95%CI: 1.41-2.15) (see Figure 2 and Table 3). Two associations presented weak evidence (class IV): those between schizophrenia and cancer mortality in patients with breast and lung cancer (see Figure 3 and Table 3).

After removing the N>1000 cases criterion in sensitivity analysis, the association between schizophrenia and cancer mortality was upgraded from weak (class IV) to highly suggestive (class II) in patients with lung cancer, and from weak (class IV) to suggestive (class III) in patients with breast cancer. The level of evidence of the other two associations remained unchanged (see Table 3).

**Associations of organic, including symptomatic, mental disorders with clinical outcomes of physical diseases**

No association in this diagnostic block was supported by convincing, highly suggestive, or suggestive evidence (classes I, II and III). There was weak evidence (class IV) of the association between both dementia and delirium with all-cause mortality in patients with hip fracture; of the association between dementia and all-cause mortality in patients with COVID-19 infection; and of the association between dementia and delirium in patients with stroke (see Table 3 and supplementary information).

After removing the N>1000 cases criterion in sensitivity analyses, the association between dementia and delirium in patients with stroke was upgraded from weak (class IV) to convincing evidence (class I), while the association between delirium and all-cause mortality in patients with hip fracture was upgraded from weak (class IV) to suggestive (class III) evidence (see Table 3 and supplementary information).

**Subgroup analyses**

Not all planned subgroup analyses were possible, due to the lack of data (see supplementary information).

When restricting the analyses to standard diagnostic criteria (any version of DSM or ICD), the class II association between depressive disorders and all-cause mortality in patients with diabetes mellitus was downgraded to weak (class IV) evidence. When restricting the analyses to studies formulating a diagnosis of mental disorder before the diagnosis of physical disease (of course, clinical outcomes always followed the diagnosis of a mental disorder), the level of evidence of class I and II associations remained unchanged.

When restricting the analyses to follow-up duration >5 years, the class I association between schizophrenia and cardiovascular mortality in patients with cardiovascular diseases, and the class II associations between depressive disorders and all-cause mortality in patients with kidney failure and diabetes mellitus were downgraded to suggestive or weak evidence (class III and IV). When restricting the analyses to adjusted estimates, only the class I association between schizophrenia and cardiovascular mortality in patients with cardiovascular diseases was downgraded to weak (class IV) evidence.

When restricting the analyses to age of participants <50 years, the class I association between schizophrenia and cardiovascular mortality in cardiovascular diseases was downgraded to weak (class IV) evidence. When restricting the analyses to samples exposed to psychiatric treatments, all class I and II associations were downgraded to either suggestive (class III) or weak (class IV) evidence.

When restricting the analyses to studies including in their samples a majority of males, the class I association between schizophrenia and cardiovascular mortality in patients with cardiovascular diseases, and between depressive disorders and all-cause mortality in patients with heart failure, were downgraded to highly suggestive (class II) or weak (class IV) evidence. The class II associations between depressive disorders and all-cause mortality in patients with kidney failure and diabetes mellitus were downgraded to suggestive or weak evidence (class III or IV).

It is important to note that all the subgroup analyses were conducted in a very small number of primary studies (see supplementary information) and are, therefore, highly underpowered.

**Population attributable fraction (PAF) and generalized impact fraction (GIF)**

The largest PAF was that for the association of alcohol use disorder with decompensated liver cirrhosis in patients with hepatitis C (30.56%, 95% CI: 27.67-33.49) (see Table 4). GIF analysis showed that alcohol use disorder should be reduced by 33% to prevent 10% of decompensated liver cirrhosis in hepatitis C (see also supplementary information).

The PAFs for the association of depressive disorders with all-cause mortality in patients with diabetes mellitus and kidney failure were respectively 26.81% (95% CI: 16.61-37.67) and 11.59% (95% CI: 9.09-14.14). The PAFs for the association of depressive disorders with cardiac events in patients with myocardial infarction was 13.68 (95% CI: 9.87-17.58) (see Table 4). GIF analyses showed that depressive disorders should be reduced by 37% and by 86% to prevent 10% of all-cause mortality in patients with diabetes mellitus and kidney failure, respectively, and be reduced by 73% to prevent 10% of major cardiac events in patients with myocardial infarction (see Figure 4 and supplementary information).

The PAF of the association of schizophrenia with cardiovascular mortality in patients with cardiovascular diseases was 11.99% (95% CI: 8.29-15.84) (see Table 4). GIF analysis showed that schizophrenia prevalence should be reduced by 83% to prevent 10% of cardiovascular mortality in patients with cardiovascular diseases (see supplementary information).

The PAFs for other class I-III associations are reported in Table 4. They were 7.53% (95% CI: 4.31-11.21) for the association between schizophrenia and cancer mortality in patients with cancer; 7.25% (95% CI: 4.38-10.34) for the association between depressive disorders and all-cause mortality in patients with heart failure; 4.53 (95% CI: 2.24-7.12) for the association between depressive disorders and all-cause mortality in patients with chronic kidney disease; 2.47% (95% CI: 0.93-4.33) for the association between anxiety disorders and cardiovascular mortality in patients with cardiovascular diseases; and 2.17% (95% CI: 1.16-3.76) for the association between bipolar disorder and cardiovascular mortality in patients with cardiovascular diseases.

**DISCUSSION**

In this umbrella review, we evaluated 47 systematic reviews with meta-analysis, including 251 non-overlapping primary studies, testing 74 prospective associations between mental disorders and 43 primary and 31 secondary clinical outcomes of physical diseases. This is the first attempt to comprehensively evaluate the impact of the entire spectrum of mental disorders on the clinical outcomes of physical diseases, using established grading criteria and a diagnostic block stratified approach. This is also the first study to employ *metaumbrella*, a comprehensive suite of statistical packages developed for conducting umbrella reviews50,62. We also estimated for the first time the meta-umbrella preventive capacity (meta-analytic PAFs) of the associations supported by class I-III evidence to establish reliable, evidence-based and actionable targets to be prioritized in clinical practice.

An additional strength of this work is the in-depth screening of primary studies included in each systematic review in order to selectively include only data reflecting prospective associations. This choice mitigates the reverse causality bias and ensures the temporality of the examined associations, where exposures (mental disorders) always preceded the event investigated (clinical outcomes of physical diseases). Furthermore, we also screened primary studies to include only those using robust diagnostic or research criteria, or validated instruments with specific cut-offs mapped to discrete categories of mental disorders. This approach overcomes the significant noise derived from studies that mistake continuous symptoms or self-reported subjective “experiences” for categorical mental disorders, which characterizes the existing transdiagnostic literature103,104. Our refined evidence synthesis method resulted in more than two-thirds (68%) of the included systematic reviews having a low risk of bias and nearly 80% of the selected primary studies scoring high on quality assessments.

Mood disorders (especially depressive disorders) emerged as credible risk factors for adverse clinical outcomes in cardiovascular diseases, as most associations in this class were supported by the largest evidence (classes I, II or III). The most robust association (class I) was that between depressive disorders and all-cause mortality among patients with heart failure, which remained at the same level of evidence after conducting subgroup analyses accounting for confounders. Other highly suggestive/suggestive associations were those between depressive disorders and the risk of major cardiac events in patients with myocardial infarction (class II), and between bipolar disorder and the risk of cardiovascular mortality in patients with cardiovascular disease (class III).

Overall, the association between depressive disorders and cardiovascular diseases is a consolidated area of research across psychiatry and somatic medicine7,105-108, although the underlying mechanisms are not fully understood107. The pathophysiology of these conditions may share common mechanisms, including behavioral, biological and medication-related ones108-112, forming an interdependent network113.

Behavioral mechanisms may include unhealthy habits (smoking, excessive alcohol consumption, physical inactivity, unhealthy diet, medication non-adherence) that accelerate pathophysiological processes, such as atherosclerosis, leading to poor health outcomes and increased mortality109,110,112-114.

Biological mechanisms may include alterations in the autonomic nervous system, plasminogen activator inhibitor-1 and fibrinogen levels, endothelial function, and neurohormonal factors, as well as diminished heart rate variability, and genetic alterations of the serotonin transporter109,110,112,113,114. Molecular inflammatory mechanisms involving interleukins (IL-6 and IL-1β) and C-reactive protein, as well as an oxidative stress imbalance, may also point to common pathways between mood and cardiovascular condictions109,115-118.

Mechanisms associated with treatment (for example, antidepressants use) may include cardiotoxicity109,110,113,114, or the alteration of platelet activation111 leading to an increased incidence of major cardiac events and sudden death109-111,113,114. However, the latter is unlikely a strong mechanism, especially when using selective serotonin reuptake inhibitors, which reduce platelet aggregation119,120.

We also found highly suggestive (class II) evidence that depressive disorders increase all-cause mortality risk in patients with diabetes mellitus and kidney failure. The increased mortality in diabetes mellitus is due to insulin resistance and metabolic factors (e.g., abdominal obesity and dyslipidaemia). These factors are aggravated by depressive disorders, which are independently associated with insulin resistance121 and metabolic syndrome (elevated adipose tissue and dyslipidemia122,123). The increased mortality in depressed patients with kidney failure may be due to suboptimal compliance with complex medication regimens123-125.

Highly suggestive (class II) evidence was similarly found for the association between depressive disorders and an increased risk of dementia in patients with diabetes mellitus67. Both depressive disorders and diabetes mellitus have been shown to increase the incidence of dementia individually and synergistically126, with the metabolic-brain axis as a key mediator connecting these conditions126. Depressive disorders are associated with micro/macro vascular alterations127,128, insulin resistance121 and neuroinflammation129; these factors may increase the risk of dementia in this patient population130,131. Stress and psychosocial determinants of health may also be key mediators in how these systems interact126.

These are clinically highly relevant findings, as depression prevention and/or treatment has great potential to improve overall health and outcomes in common physical diseases that are associated with severe biopsychosocial and societal burden (e.g., dementia is a rising problem in ageing societies132) and premature mortality. Our PAF analysis directly informs the prioritization of these approaches and associated resources on the basis of evidence-based potential preventive gains. For example, this study provides the first robust meta-umbrella evidence showing that preventing depressive disorders could reduce up to one-third of mortality rates across various physical conditions.

Screening for depression in patients with cardiovascular diseases is recommended by the US Preventive Services Task Force and the American Heart Association133,134. Furthermore, independent meta-analyses showed that psychotherapy/psychoeducation can have a preventive effect by reducing the severity of symptoms before the onset of depressive disorders135-137. Randomized controlled trials demonstrated that collaborative care, which includes patient preferences, cognitive intervention and/or lifestyle advice, drug treatment management, and relapse prevention138, or physical exercise139,140, can specifically reduce depression in patients with cardiovascular diseases or diabetes, including low and middle-income countries141,142. These interventions could, at the same time, have an impact on depressive disorders and improve self-management of physical diseases in patients with mental and physical multimorbidity143. Our GIF analysis confirms these benefits; the reduction of mortality rates remains clinically relevant even if preventive interventions are only partially effective. Taken together, these findings call for a new generation of translational research validating preventive approaches for depressive disorders in physical conditions.

The association between schizophrenia and increased cardiovascular and cancer mortality in patients with these physical diseases was also supported by convincing or highly suggestive evidence (class I and II, respectively). The higher mortality risk in schizophrenia compared to the general population is substantial and particularly marked during the early stages of the disorder144. The increased risk of cardiovascular and cancer mortality may be due to suboptimal cardiovascular145,146 and cancer screening147 in patients with schizophrenia, coupled with high cigarette smoking145, frequent metabolic syndrome (obesity, hypertension, diabetes, hyperlipidemia)148-152, physical inactivity, drug and alcohol use, and poor adherence to medication153-155.

Although antipsychotics can lead to adverse cardiometabolic effects that are a risk factor for cardiovascular mortality156, a recent meta-analysis showed that all-cause mortality risk at the population level is substantially reduced with antipsychotic use versus no antipsychotic use (RR=0.71)144. The reason for this paradoxical relationship can be found in a nationwide database within-subject analysis, where ongoing antipsychotic treatment was associated with higher adherence to statins, antihypertensive and antidiabetic medications157. Thus, greater psychiatric stability via antipsychotic treatment improves not only healthy lifestyle behaviors but also adherence to medications for secondary physical illness prevention144.

Furthermore, our PAF analysis suggests that preventing psychosis in young people at clinical high risk can produce physical health benefits in terms of reduced cardiovascular and cancer mortality, in addition to improved mental health outcomes158-165 (indicated prevention).

Highly suggestive evidence (class II) was also found for the association of alcohol use disorder with decompensated liver cirrhosis in patients infected with hepatitis C virus. Indeed, alcohol use disorder leads to alterations in cytokine production, lipopolysaccharide-TLR4 signalling, and reactive oxygen species166, factors that increase hepatotoxicity167,168. Patients with alcohol use disorder are also frequently medically ineligible for hepatitis C treatment169.

Our PAF analysis demonstrates that about one-third of decompensated liver cirrhosis in patients with hepatitis C could be averted by preventing alcohol use disorder (the largest PAF in our study). Thus, alcohol use disorder should be identified and managed as much as possible to improve psychiatric as well as physical health outcomes. Screening for unhealthy alcohol use in primary care settings in adults, including pregnant women, and providing brief behavioral counselling interventions is an evidence-based approach to reducing unhealthy alcohol use, as recommended by the US Preventive Services Task Force170.

There are some limitations to this study. First, while we avoided the limitations of retrospective or case-control study designs by selecting only prospective systematic reviews with meta-analysis and prospective primary studies, the observed associations do not represent pathophysiological causality. For example, although we preferably focused on adjusted estimates, we could not specifically address the role of single confounders, such as genetic effects, body mass index or metabolic risk factors, which may at least partially account for the observed associations. Second, there were few relevant systematic reviews with meta-analysis in non-adult populations and for mental disorders other than depressive disorders. For example, we did not find any relevant meta-analysis that considered children or adolescents, anorexia nervosa or personality disorders. Third, the results of the subgroup analyses should be viewed with caution due to the granularity of the reported data and the very limited statistical power. Finally, our PAF findings are specific to the populations affected with physical diseases and cannot be applied to the general population.

Acknowledging these caveats, our study has several implications. We demonstrated at a meta-umbrella review level that mental disorders significantly impair the health and life expectancy of individuals with physical diseases, and quantified for the first time the associated preventive capacity. Our findings may be particularly relevant for informing the prioritization of preventive approaches for physical diseases via improved detection and management of mental disorders, with currently the best evidence and actionable targets for alcohol use disorders, depression and schizophrenia.

These approaches are likely to be particularly relevant for young people, given the early age at onset of most mental disorders40,171. Prevention for youth is currently driven by initiatives siloed in physical diseases, such as cancer and obesity143,165. However, preventing the onset of mental disorders can become a tantalizing strategy for reducing at the same time the risk of developing physical diseases143. Indeed, the cost and risk associated with preventive approaches (e.g., ethical concerns172) can be offset by concurrently reducing the burden of both psychiatric disorders and physical diseases165,173. Integrating early detection and prevention of mental health and physical conditions may be particularly cost-effective in resource-constrained settings142.

This strategy would require innovative integrated or, at least, co-located clinical services for emerging mental and physical conditions, overcoming the limited preventive capacity of current health care services165. Indeed, youth-friendly mental and physical health care services are being developed and tested worldwide174-177, and promise to achieve the much-needed cross-disciplinary fertilization of expertise which is essential to reduce the Cartesian dichotomy between mental and physical knowledge, education and research.

In conclusion, this umbrella review demonstrates that mental disorders increase the risk of several poor clinical outcomes in patients with physical diseases. Prevention targeting mental disorders, particularly alcohol use disorders, depressive disorders and schizophrenia, can reduce the incidence of adverse clinical outcomes in physical diseases. These findings can inform clinical practice and trans-speciality preventive approaches cutting across psychiatric and somatic medicine.

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Records identified through database searching (n=21,612) (PubMed, n=8,431; PsycINFO, n=2,976; Embase, n=10,171; JBI Database, n=34)

Records removed before screening (n=3,002)

Records screened

(n=18,610)

Records excluded

(n=18,056)

Records not retrieved

(n=3)

Records sought for retrieval

(n=554)

Records excluded (n=501)

* Meta-analysis with outcomes or associations other than those of interest (n=321)
* No meta-analysis (n=129)
* Meta-analyses of randomized controlled trials, interventions, study designs other than prospective (n=33)
* Meta-analyses of individual participant data or network meta-analyses (n=11)
* Overlapping meta-analyses (n=7)

Records assessed for eligibility (n=551)

Systematic reviews eligible (n=50, including a total of k=287 non-overlapping primary studies)

Records excluded (n=3)

Primary studies excluded (k=36)

* Only one prospective cohort (k=13)
* No distinguishable mental/physical estimates (k=8)
* Unclear diagnostic criteria (k=8)
* Investigating psychiatric symptoms, not disorders (k=7)

Systematic reviews included in umbrella review (n=47, with a total of k=251 non-overlapping primary studies and 74 associations)

**Figure 1** PRISMA flow chart, JBI - Joanna Briggs Institute

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**Figure 2**  Forest plot of prospective associations between mental disorders and clinical outcomes of physical diseases, stratified by class I, II and III of evidence

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**Figure 3** Forest plot of prospective associations between mental disorders and clinical outcomes of physical diseases, stratified by class IV of evidence

**Table 1** Level of evidence for the association of neurotic, stress-related and somatoform disorders with primary outcomes of physical diseases

| **Study** | **Mental disorder** | **Physical disease** | **Outcome** | **k** | **Effect size****(95% CI)** | **N****cases** | **p random****effects** | **I2 %** | **PI (95% CI)** | **SSE/ ESB** | **LS** | **eOR** | **CE** | **CES** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Neurotic, stress-related and somatoform disorders in patients with cardiovascular diseases*** |  |
| Emdin et al70 | Anxiety disorders  | Cardiovascular diseases  | Cardiovascular mortality | 3 | RR: 1.46(1.17-1.82) | 3,475 | 7.2e-04 | 0.00 | 0.35-6.04 | No/No | No  | 1.46 | III | III |
| Celano et al66 | Anxiety disorders  | Coronary artery disease | All-cause mortality  | 8 | OR: 1.25(0.96-1.64) | 904 | >0.05 | 43.85  | 0.7-2.26  | No/Yes  | No | 1.25 | NS | NS |
| Li et al77 | Anxiety disorders  | Acute coronary syndrome | All-cause mortality | 5 | RR: 1.03(0.7-1.51) | 961 | >0.05 | 44.05 | 0.35-3.05  | No/No | No  | 1.03 | NS | NS |
| ***Neurotic, stress-related and somatoform disorders in patients with other physical diseases*** |  |
| Atlantis et al23 | Anxiety disorders  | Chronic obstructive pulmonary disease | All-cause mortality | 3 | RR: 1.11(0.9-1.36) | 32 | >0.05 | 0.00 | 0.29-4.17  | No/No | No | 1.11 | NS | NS |
| Wang et al20 | Anxiety disorders  | Breast cancer | All-cause mortality | 3 | HR: 1.07(0.92-1.23) | 1,049 | >0.05 | 0.00 | 0.42-2.69 | No/No | No  | 1.07 | NS | NS |

CE – class of evidence, CES – class of evidence after sensitivity analysis (removing the N>1,000 cases criterion), CI – confidence interval, eOR – equivalent odds ratio, ESB – excess significance bias, HR – hazard ratio, LS – largest study with significant effect, NS – not significant, OR – odds ratio, RR – risk ratio, PI – prediction interval, SSE – small study effect

**Table 2** Level of evidence for the association of mood disorders with primary outcomes of physical diseases

| **Study** | **Mental disorder** | **Physical****disease** | **Outcome** | **k** | **Effect size****(95% CI)** | **N****cases** | **p random****effects** | **I2%** | **PI (95% CI)** | **SSE/****ESB** | **LS** | **eOR** | **CE** | **CES** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Mood disorders in patients with cardiovascular diseases*** |  |
| Sokoreli et al93 | Depressive disorders | Heart failure | All-cause mortality | 4 | HR: 1.44(1.26-1.65) | 1,377 | 1.4e-07 | 0.00 | 1.07-1.94 | No/No | Yes  | 1.44 | I | I |
| Gathright et al74 | 9 | HR: 1.49(1.05, 2.1) | 1,283 | 2.5e-02 | 79.85 | 0.46-4.79 | Yes/Yes | No | 1.49 | IV | IV |
| Correll et al13 | Bipolar disorder | Cardiovascular diseases | Cardiovascular mortality | 6 | RR: 1.65(1.32, 2.06) | 8,923 | 9.0e-06 | 80.43 | 0.86-3.14 | No/No | Yes | 1.65 | III | III |
| Meijer et al81 | Depressive disorders | Myocardial infarction | Cardiovascular mortality | 5 | OR: 2.37(1.47, 3.82) | 107 | 3.8e-04 | 13.58 | 0.78-7.22 | No/No | No | 2.37 | IV | III |
| Meijer et al81 | Depressive disorders | Myocardial infarction | All-cause mortality | 15 | OR: 2.24(1.65, 3.03) | 725 | 2.0e-07 | 48.11 | 0.92-5.44 | No/No | Yes | 2.24 | IV | II |
| Song et al94 | Depressive disorders | Percutaneous coronary intervention | All-cause mortality | 6 | RR: 1.76(1.45, 2.13) | 265 | 1.1e-08 | 0.00 | 1.28-2.41 | No/Yes | Yes | 1.76 | IV | II |
| Barth et al63 | Depressive disorders | Coronary artery disease | All-cause mortality | 6 | HR: 1.73(1.16, 2.57) | 1,097 | 7.1e-03 | 72.4 | 0.49-6.12 | No/Yes | Yes | 1.73 | IV | IV |
| Nicholson et al84 | 10 | RR: 1.59(1.36, 1.87) | 412 | 1.3e-08 | 9.42 | 1.32-1.93 | No/Yes | Yes  | 1.59 | IV | II |
| Yuan et al99 | Bipolar disorder | Stroke | Stroke mortality  | 2 | HR: 1.69(1.11, 2.55) | 1,816 | 3.2e-02 | 96.52 | NA | NA/NA | Yes  | 1.69 | IV | IV |
| Bartoli et al64 | Depressive disorders | Stroke | All-cause mortality | 5 | RR: 1.63(1.10, 2.41) | 237 | 1.5e-02 | 58.87 | 0.49-5.39 | No/No | No | 1.63 | IV | IV |
| Cai et al65 | 8 | HR: 1.55(1.19, 2.02) | 24,022 | 1.0e-03 | 74.47 | 0.69-3.5 | Yes/Yes | Yes | 1.55 | IV | IV |
| Wu et al97 | Depressive disorders | Coronary artery disease | Cardiovascular mortality | 5 | HR: 1.59(1.08, 2.35) | 1,654 | 1.9e-02 | 82.00 | 0.41-6.23 | Yes/Yes | Yes | 1.59 | IV | IV |
| Correll et al13 | Depressive disorders | Cardiovascular diseases | Cardiovascular mortality | 5 | OR: 1.44(1.04, 1.98) | 8,319 | 2.6e-02 | 86.29 | 0.46-4.44 | No/No | No | 1.44 | IV | IV |
| Pan et al86 | Depressive disorders | Stroke | Stroke mortality | 4 | HR: 1.41(1.06, 1.86) | 5,007 | 1.7e-02 | 36.91 | 0.76-2.59 | No/No | No | 1.41 | IV | IV |
| Flaherty et al73 | Depressive disorders | Coronary artery bypass graft | All-cause mortality | 2 | HR: 1.36(1.05, 1.77) | 239 | 2.1e-02 | 0.00 | NA | NA/NA | Yes | 1.36 | IV | IV |

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| --- |
| ***Mood disorders in patients with chronic respiratory diseases*** |
| Atlantis et al23 | Depressive disorders | Chronic obstructive pulmonary disease | All-cause mortality | 6 | RR: 2.04(0.87-4.77) | 215 | >0.05 | 73.8 | 0.12-34.24 | No/Yes | Yes | 2.04 | NS | NS |
| Courtwright et al68 | Depressive disorders | Lung transplant  | Posttransplant mortality  | 2 | HR: 1.01 (0.99-1.04) | 218 | >0.05 | 0.00 | NA | NA/NA | No | 1.01 | NS | NS |
| ***Mood disorders in patients with endocrine system diseases*** |  |
| Farrokhi et al72 | Depressive disorders | Kidney failure  | All-cause mortality | 6 | HR: 1.41(1.31, 1.51) | 1,834 | 1.0e-22 | 12.85 | 1.28-1.55 | Yes/Yes | Yes  | 1.41 | II | II |
| Hofmann et al24 | Depressive disorders | Diabetes mellitus | All-cause mortality | 7 | HR: 2.84(2.00, 4.03) | 2,108 | 4.7e-09 | 88.81 | 0.88-9.15 | No/No | Yes | 1.93 | II | II |
| Hofmann et al24 | 6 | HR: 1.54 (1.09, 2.18) | 3,725 | 1.4e-02 | 85.18 | 0.48-4.99 | No/Yes | No  | 1.54 | IV | IV |
| Palmer et al85  | Depressive disorders | Chronic kidney disease  | All-cause mortality | 13 | HR: 1.45 (1.22, 1,.73) | 2,066 | 2.0e-05 | 40.69 | 0.95-2.22 | Yes/Yes | Yes | 1.45 | III | III |
| Farooqi et al71 | Depressive disorders | Diabetes mellitus | Cardiovascular mortality | 3 | HR: 1.33(1.04, 1.71) | 468 | 2.3e-02 | 14.51 | 0.27-6.66 | No/No | No | 1.33 | IV | IV |
| van Dooren et al96 | 2 | HR: 1.60(0.69, 3.72) | 169 | >0.05 | 77.41  | NA | NA/NA | No  | 1.60 | NS | NS |
| ***Mood disorders in patients with cancer*** |
| Satin et al19 | Depressive disorders | Cancer | All-cause mortality | 3 | RR: 1.39(1.02, 1.89) | 55 | 3.5e-02 | 0.00 | 0.19-10.08 | No/No | No | 1.39 | IV | IV |
| Satin et al19 | 8 | HR: 1.09 (1.02, 1.15) | 1,490 | 5.2e-03 | 60.07 | 0.95-1.24 | Yes/No | No  | 1.09 | IV | IV |
| Wang et al20 | Depressive disorders | Breast cancer | Breast cancer mortality | 2 | HR: 1.45(1.04, 2.01) | 313 | 2.7e-02 | 0.00 | NA | NA/NA | No  | 1.45 | IV | IV |
| Wang et al20 | Depressive disorders | Breast cancer | All-cause mortality | 6 | HR: 1.26(1.09, 1.45) | 2,021 | 1.3e-03 | 0.00 | 1.03-1.53 | No/No | No  | 1.26 | IV  | IV |
| Shi et al91 | Depressive disorders | High-grade brain tumor | All-cause mortality | 3 | HR: 1.31(0.86, 1.99) | 836 | >0.05 | 0.00 | 0.09-19.69 | No/No | No  | 1.31 | NS | NS |
| Shi et al91 | Depressive disorders | Glioma | Glioma mortality | 5 | RR: 0.74 (0.54, 1.02) | 627 | >0.05 | 48.61 | 0.27-2.07 | No/No | No  | 0.74 | NS | NS |
| ***Mood disorders in patients with other physical diseases*** |
| Ruiz-Grosso et al87 | Depressive disorders | Tuberculosis | Tuberculosis mortality  | 2 | OR: 2.85(1.52, 5.36) | 53 | 1.1e-03 | 0.00 | NA | NA/NA | Yes | 2.85 | IV | IV |

CE – class of evidence, CES – class of evidence after sensitivity analysis (removing the N>1,000 cases criterion), CI – confidence interval, eOR – equivalent odds ratio, ESB – excess significance bias, HR – hazard ratio, LS – largest study with significant effect, NA – not assessable, NS – not significant, OR – odds ratio, RR – risk ratio, PI – prediction interval, SSE – small study effect

**Table 3**  Level of evidence for the association of schizophrenia and organic, including symptomatic, mental disorders with primary outcomes of physical diseases

| **Study** | **Mental disorder** | **Physical****disease** | **Outcome** | **k** | **Effect size****(95% CI)** | **N****cases** | **p random****effects** | **I2%** | **PI (95% CI)** | **SSE/ESB** | **LS** | **eOR** | **CE** | **CES** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  ***Schizophrenia in patients with cardiovascular diseases and cancer*** |  |
| Correll et al13 | Schizophrenia | Cardiovascular diseases  | Cardiovascular mortality | 7 | RR: 1.54(1.36-1.75) | 9,097 | 2.2e-11 | 27.82 | 1.19-2.00 | No/No | No | 1.54 | I | I |
| Zhuo et al101 | Schizophrenia |  Cancer  | Cancer mortality | 3 | SMR: 1.74 (1.41, 2.15) | 6,145 | 2.9e-07 | 66.53 | 0.17-17.56 | No/No | Yes  | 1.72 | II | II |
| Ni et al83 | Schizophrenia | Breast cancer | Breast cancer mortality | 2 | RR, 2.54 (1.56, 4.14) | 175 | 1.7e-04 | 0.00 | NA | NA/NA | Yes | 2.54 | IV | III |
| Ni et al83 | Schizophrenia | Lung cancer | Lung cancer mortality | 2 | RR, 2.24(1.67, 3.01) | 192 | 9.0e-08 | 0.00 | NA | NA/NA | Yes | 2.24 | IV | II |
| ***Organic, including symptomatic, mental disorders in patients with infectious and musculoskeletal system diseases*** |
| Liu et al79 | Dementia | Hip fracture | All-cause mortality |  2 | HR, 3.72(1.6, 8.67) | 384 | 2.3e-03 | 72.52 | NA | NA/NA | Yes | 3.72 | IV | IV |
| Liu et al79 | Delirium | Hip fracture | All-cause mortality |  6 | HR, 2.21(1.49, 3.27) | 638 | 7.5e-05 | 64.54 | 0.65-7.51 | No/No | Yes | 2.21 | IV | III |
| Hariyanto et al76 | Dementia | COVID-19 | All-cause mortality  |  2 | RR, 2.24 (1.26, 3.98) | 4,417 | 5.8e-03 | 89.51 | NA | NA/NA | Yes | 2.24 | IV | IV |
| Liu et al26 |  2 | OR, 3.27 (0.34, 31.43) | 148 | >0.05 | 47.02 | NA | NA/NA | Yes | 3.27 | NS | NS |

CE – class of evidence, CES – class of evidence after sensitivity analysis (removing the N>1,000 cases criterion), CI – confidence interval, eOR – equivalent odds ratio, ESB – excess significance bias, HR – hazard ratio, LS – largest study with significant effect, NA – not assessable, NS – not significant, OR – odds ratio, RR – risk ratio, PI – prediction interval, SMR – standardized mortality ratio, SSE – small study effect

**Table 4**  Meta-analytical population attributable fraction (PAF) for the associations supported by the largest evidence (classes I, II and III)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Mental disorder** | **Physical disease** | **Outcome** | **Risk ratio****(95% CI)** | **Prevalence of mental disorder in** **physical disease (95% CI)** | **PAF****(95% CI)** |
| Depressive disorders | Heart failure | All-cause mortality | 1.44(1.26-1.65) | 17.72%(16.89-18.56) | 7.25%(4.38-10.34) |
| Schizophrenia | Cardiovascular diseases | Cardiovascular mortality | 1.54(1.36-1.75) | 25.17%(25.08-25.30) | 11.99%(8.29-15.84) |
| Depressive disorders | Diabetes mellitus | Dementia | 2.11(1.77-2.52) | 6.66%(6.60-6.71) | 6.89%(4.87-9.19) |
| Depressive disorders | Kidney failure | All-cause mortality | 1.41(1.31-1.51) | 32.11%(31.30-32.93) | 11.59%(9.09-14.14) |
| Depressive disorders | Diabetes mellitus | All-cause mortality | 2.84(2.00-4.03) | 19.91%(19.07-20.79) | 26.81%(16.61-37.67) |
| Alcohol use disorder | Hepatitis C  | Decompensated liver cirrhosis | 3.15(2.87-3.46) | 20.50%(20.30-20.70) | 30.56%(27.67-33.49) |
| Depressive disorders | Myocardial infarction | Major cardiac events | 1.52(1.36-1.70) | 30.58%(29.62-31.56) | 13.68%(9.87-17.58) |
| Schizophrenia | Cancer | Cancer mortality | 1.74(1.41-2.14) | 11.05%(10.75-11.36) | 7.53%(4.31-11.21) |
| Bipolar disorder | Cardiovascular diseases | Cardiovascular mortality | 1.65(1.32-2.06) | 3.41%(3.81-4.10) | 2.17%(1.16-3.76) |
| Anxiety disorders | Cardiovascular diseases | Cardiovascular mortality | 1.46(1.17-1.82) | 5.50%(5.41-5.64) | 2.47%(0.93-4.33) |
| Depressive disorders | Chronic kidney disease | All-cause mortality | 1.45(1.22-1.73) | 10.50%(10.01-10.96) | 4.53%(2.24-7.12) |

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**Figure 4** Meta-analytic generalized impact fraction (GIF) of depressive disorders for all-cause mortality and major cardiac events in several physical diseases