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All-cause and cause-specific mortality in people with depression: a large-scale systematic review and meta-analysis of relative risk and aggravating or attenuating factors, including antidepressant treatment

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Depression has been reported to be associated with premature mortality. However, no meta-analysis has comprehensively examined all-cause and cause-specific mortality risk in people with this condition, focusing also on possible aggravating and attenuating factors, including antidepressant treatment. We conducted a systematic review and meta-analysis of cohort studies to synthesize mortality risk estimates associated with depression (major depressive disorder and dysthymia) due to any and specific causes, and when depression is accompanied by comorbid conditions. Effects of antidepressant medication and electroconvulsive therapy (ECT), and other potential moderators of mortality risk, were evaluated. We searched EMBASE, Medline and PsycINFO databases up to January 26, 2025, pooling mortality estimates using random-effect models. Publication bias, subgroup and meta-regression analyses, and quality assessment (Newcastle-Ottawa Scale) were performed. Across 268 studies, 10,842,094 individuals with depression and 2,837,933,536 control subjects were included. All-cause mortality was doubled in people with depression versus no depression/general population controls (relative risk, RR=2.10, 95% CI: 1.87-2.35, I^2=99.9%), being especially high for suicide (RR=9.89, 95% CI: 7.59-12.88, I^2=99.6%), but also elevated for natural causes (RR=1.63, 95% CI: 1.51-1.75, I^2=99.6%). Among individuals with versus without depression matched for comorbid conditions, the depression-associated mortality risk was also significantly elevated (RR=1.29, 95% CI: 1.21-1.37, I^2=99.9%). Depression with versus without psychotic symptoms (RR=1.61, 95% CI: 1.45-1.78, I^2=6.3%), and treatment-resistant versus non-treatment-resistant depression (RR=1.27, 95% CI: 1.16-1.39, I^2=85.3%), conferred an incremental mortality risk. Antidepressant use (versus no antidepressant use) was associated with significantly lower all-cause mortality in people with depression (RR=0.79, 95% CI: 0.68-0.93, I^2=99.2%). ECT use (versus no ECT use) was associated with reduced all-cause mortality (RR=0.73, 95% CI: 0.66-0.82, I^2=0%), natural-cause mortality (RR=0.76, 95% CI: 0.59-0.97, I^2=12.0%), and suicide (RR=0.67, 95% CI: 0.53-0.85, I^2=32.3%). Our results affirm heightened mortality risk in depression, identify clinically relevant patient subgroups with increased mortality risk, and highlight mortality-reducing effects of antidepressant treatment and ECT. Multipronged intervention approaches targeting physical health improvement and suicide risk alleviation, optimizing antidepressant treatment, and pursuing early identification and effective interventions for psychotic and treatment-resistant depression, could help reduce this mortality gap, which is still growing.

Key words: Depression, mortality, suicide, major depressive disorder, dysthymia, psychotic depression, treatment-resistant depression, antidepressant treatment, electroconvulsive therapy

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Depression is a potentially chronic[1,2] and treatable[3,4] mental disorder, with a lifetime prevalence of 15-18%[1,2], which represents one of the leading causes of global disease burden[1,5], involving substantial health care and societal costs. The disorder is also highly prevalent in people with a wide range of chronic physical diseases, with an average point prevalence of 25%[6,7]. Critically, accumulating data have shown that people with depression have an increased risk of premature mortality relative to the general population[8], with a reduced life expectancy of 13 years[9]. Despite markedly elevated risk of suicide, the excess death in individuals with depression is mainly attributable to natural causes[10,11]. Considering the persistent mortality gap associated with depression in recent decades[10,12], the health inequalities experienced by people with this condition represent a serious public health concern.

Several studies have investigated premature mortality patterns associated with depression, aiming to enhance the understanding of mechanisms underlying this excess mortality, as well as to identify modifiable factors that can inform policy formulation, resource allocation and health care enhancement. Some meta-analyses have been conducted in this respect[8], but they are hampered by significant methodological limitations.

First, a majority of the studies included in previous meta-analyses ascertained depression by self-report tools, which are actually intended to be used as a screening instrument for probable depression[12-15]. This procedure may increase the likelihood of misclassifying individuals with subthreshold depressive symptoms as having a psychiatric diagnosis of depression, potentially underestimating the excess mortality risk associated with depression. Misclassification bias may be more pronounced when self-rating instruments are used to ascertain comorbid depression among individuals with severe physical diseases, in whom physical symptoms can overlap with or mimic depressive symptoms[16]. Cross-study variations in cut-off scores used with the same tool introduce even greater heterogeneity, and further compromise accuracy in depression case ascertainment[17]. Thus far, there has been no meta-analysis only including studies which defined depression according to ICD or

DSM, based on diagnostic interviews or clinician-assigned diagnosis ascertained from health-record databases.

Second, evaluation of mortality risk was often restricted to a subgroup of patients with a specific physical morbidity, such as cardiovascular disease[18-20], cancer[21,22] or diabetes mellitus[23,24], comparing people with depression to those with the same physical morbidity but without depression. Third, prior analyses did not take into consideration the incident and prevalent depression status, precluding the investigation of the association between mortality risk and duration of depression[8,20,21,22]. Fourth, most prior meta-analyses focused on all-cause mortality risk, without a comprehensive evaluation of risk for cause-specific deaths in people with depression[12,15,18-20,23,25]. Fifth, evaluation of the relationships of mortality risk with subtypes of the condition, such as psychotic and treatment-resistant depression, is limited.

Notably, despite the mixed findings reported in the literature concerning the association of antidepressant or electroconvulsive therapy (ECT) use with excess mortality in people with depression [26-45], there has been no meta-analysis including the evaluation of the impact of these treatments on mortality risk.

To fill this research gap, we conducted the most comprehensive systematic review and meta-analysis to date examining the risk of all-cause and cause-specific mortality in people with depression versus those with no depression or the general population. We also evaluated mortality risk associated with depression in people with any or specific comorbid conditions. We only included studies that ascertained depression according to ICD or DSM, using diagnostic interviews or health-record database-derived clinician-assigned diagnosis. In addition, associations of antidepressant treatment (any antidepressant, drug classes, and individual agents) and ECT with mortality risk were assessed. To explore potential sources of heterogeneity and factors that may aggravate or attenuate mortality risk associated with depression, we performed subgroup and meta-regression analyses stratified by a range of study characteristics and depression-related factors, such as incident/prevalent sample, time intervals of observation after depression diagnosis, presence of psychotic symptoms, and treatment-resistant status.

METHODS

This study was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020)[46]. The study protocol was registered with PROSPERO (CRD42023451258).

Search strategy and selection criteria

We searched EMBASE, Medline and PsycINFO for articles published from inception to January 26, 2025, without language restrictions. The search key words included terms related to depression, antidepressant treatment and mortality (see supplementary information for details). We also hand-searched references of all selected papers and relevant reviews to identify additional eligible studies. Two reviewers performed the search independently and compared the results. Disagreement was resolved by consensus.

Studies were selected if they: a) included patients of any age with depression (i.e., major depressive disorder or dysthymia) defined according to any version of ICD or DSM, based on a diagnostic interview or a clinician-assigned coded diagnosis derived from health-record databases; b) reported data on all-cause and cause-specific mortality; and c) were cohort studies. Publications that adopted non-cohort designs, such as case-control studies; reviews and meta-analyses; studies containing qualitative or non-meta-analyzable data, or restricted to population subgroups (e.g., homeless or incarcerated people), or with sample sizes <100 were excluded. Two authors independently screened titles and abstracts of relevant papers for inclusion, and disagreements were resolved through discussion with two other authors.

Outcomes, data extraction and assessment of study quality

The primary outcome was risk of all-cause mortality in individuals with depression. The secondary outcomes included mortality due to natural, unnatural and more specific causes. Analyses were performed in prevalent plus incident cohorts, where prevalent cases were individuals living with depression, regardless of diagnosis date, while incident cases included individuals with newly-diagnosed depression within the period of observation. Comparison groups included the general population, people without depression, and psychiatric controls. Individuals with any/specific comorbid conditions with and without depression were also compared.

To investigate mortality risk associated with antidepressant use and ECT, people with depression treated with any/specific antidepressants (drug classes or individual agents) or ECT were compared to those with depression not receiving treatment with antidepressants or ECT, respectively. Additional comparisons in relation to other depression-related characteristics, including dysthymia/no depression, various time intervals of observation after depression diagnosis, late-life depression/no depression, early-life depression/no depression, depression with/without psychotic symptoms, and treatment-resistant versus non-treatment-resistant depression, were performed.

Data were extracted independently by two authors using a predefined form, with discrepancies resolved by consensus. Since the current study focused on depression, studies pooling data of people with other psychiatric diagnoses (e.g., combining patients with depression and schizophrenia) were excluded, unless the study provided stratified analyses only for people with depression. If several adjusted risk estimates were reported, the one controlling for the most comprehensive set of covariates was chosen.

When studies presented findings graphically, we extracted the data from figures using WebPlotDigitizer, a web-based tool for numerical data extraction from plots and graph images. For studies that only reported data on point estimates without standard errors (SE) or 95% confidence intervals (CIs), we extrapolated the SE as the

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mean from studies that reported SE. Following previous research[9,47], for studies using the general population as the reference with standardized mortality ratios (SMRs) for mortality risk, we estimated the sample size of the control group as the size of the general population in that country or region and in the age range of the depression group, based on census-based data for the median year of the study period.

Risk of bias was assessed independently by two reviewers using the Newcastle-Ottawa Scale[48], which covers the following three domains: a) selection (representativeness, selection of non-exposed cohort, ascertainment of exposure, outcome of interest not present at baseline); b) comparability (control for covariates); and c) outcome (assessment of mortality; follow-up duration ≥3 years, unless predefined time frame for investigation). Disagreements were resolved through consultation with other members of the research team.

Data analysis

Given the generally rare cumulative incidence of mortality in included studies (i.e., <10%)[49], SMRs, hazard ratios, odds ratios, risk ratios, and incidence rate ratios were treated as equivalent measures of risk, with an aim to give an overview of relative associations[47,50,51], and the term relative risk (RR) is then used thereafter. Random-effects meta-analytic models were applied to generate pooled estimates of RR for depression versus no depression/general population, depression versus no depression matched for any comorbid conditions, and major depressive disorder versus no depression/general population.

I^2 statistic was used to measure the total variation due to heterogeneity[52]. Additionally, Cochran's Q test was performed to assess the statistical significance of the heterogeneity across studies. Publication bias was assessed using Egger's test[53], with p values <0.1 considered significant. In case of publication bias, we also calculated the fail-safe number as the estimated number of studies needed to move the mortality risk from significant to non-significant, and performed the Duval and Tweedie's trim-and-fill procedure[54].

Aggravating or attenuating factors and sources of heterogeneity were explored with subgroup and meta-regression analyses. Subgroup analyses were stratified by: control group (general population and people with no depression); prevalent/incident depression sample; sex; age categories (<25 years, 25-60 years, and >60 years); diagnostic system (ICD and DSM); geographical location in terms of continents; source of study samples (health-system case registers, health-insurance databases, hospital/clinic samples or records, community surveys); population of people with depression (community, inpatient, outpatient, or inpatient and outpatient); other depression-related characteristics (dysthymia, time intervals of observation after depression diagnosis, late-life depression, early-life depression, depression with psychotic symptoms, and treatment-resistant depression); and use of antidepressants (any antidepressant, drug classes, individual agents) and ECT.

Random-effects meta-regression analyses were performed on potential moderators, including characteristics of the overall sample (median year of observation period, number of years in observation period, mean follow-up duration, number of adjusted covariates, human development index[55], socio-demographic index[56], and Newcastle-Ottawa Scale score); characteristics of the depression sample (sample size, and proportion of people with major depressive disorder, dysthymia and antidepressant treatment); and difference in characteristics between depression and non-depression samples (mean age, body mass index, proportion of people being female, White, current smoker, and married; and percentage of people with obesity, alcohol use disorders, substance use disorders, diabetes mellitus, cancers, and renal diseases).

Meta-analysis models were performed in R (version 4.1.2) with *metafor* package. For all analyses, except Egger's test, p values <0.05 were considered significant.

RESULTS

Search results

The PRISMA flow diagram describing the process of study identification and selection is shown in Figure 1. The literature search identified 18,056 papers (18,026 from database searching and 30 from manual search), of which 16,860 remained after removal of duplicates. Upon exclusion of irrelevant studies, we retrieved 653 full-text papers to be assessed for eligibility. Of these, 385 were excluded, mainly due to lack of relevant outcomes, no depression, or ascertainment of depression based on self-report measures or depressive symptoms (see supplementary information).

Altogether, 268 publications met inclusion criteria[10,30-36,43,45,57-314], comprising 10,842,094 individuals with depression and 2,837,933,536 control subjects. Comparisons included people with depression (N=1,900,317) versus the general population (N=2,650,612,526); individuals with depression (N=5,455,521) versus no depression (N=43,415,950); people with depression (N=5,881,116) versus no depression (N=40,284,386) matched for comorbid conditions; and individuals with depression (N=76,751) versus other mental disorders (N=37,421). Other mental disorders included schizophrenia (one study, N=861), bipolar disorder (three studies, N=5,192), adjustment disorder (one study, N=31), and alcohol use disorders (one study, N=31,337). Only data on depression versus bipolar disorder were sufficient for meta-analysis. The characteristics of individual studies are provided in the supplementary information.

Studies were conducted in the US (n=79), the UK (n=31), South Korea (n=24), Sweden (n=24), Taiwan (n=21), Denmark (n=17), Canada (n=12), The Netherlands (n=10), Finland (n=9), Germany (n=5), Spain (n=5), Australia (n=4), Hong Kong (n=4), Switzerland (n=4), Italy (n=3), France (n=2); Brazil, China, Ethiopia, Hungary, Israel, Japan, Lithuania, Norway, Portugal, Singapore and South Africa (n=1 each). Two studies were conducted using data from multiple countries worldwide, and one using data from multiple countries in Europe.

Data of study samples were mainly derived from health-system case registers (n=135). Other data sources included health-insurance databases (n=52), hospital/clinic samples or records (n=50),

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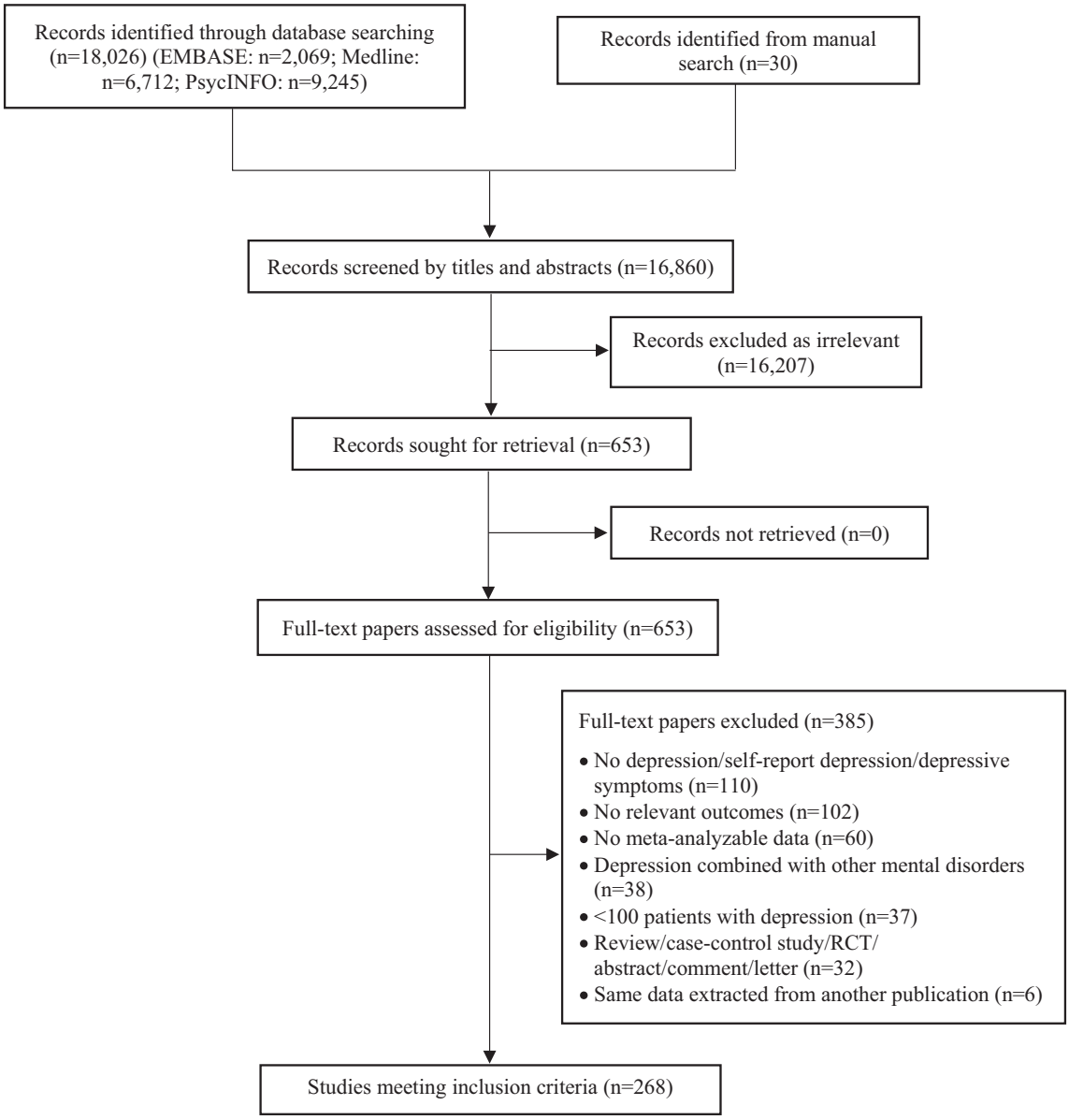


Figure 1 PRISMA 2020 flow chart. RCT – randomized controlled trial

and community surveys (n=31). The length of observation period ranged from 1 to 65 years. All studies examined cases following the ICD (n=200), DSM (n=62) or ICD/DSM (n=6). People with depression were identified in outpatient or inpatient/outpatient settings (n=187), inpatient settings (n=53), or the community (n=28).

Primary outcome: all-cause mortality

The pooled RR for all-cause mortality of individuals with depression versus no depression/general population was 2.10 (95% CI: 1.87-2.35; I^2=99.9%, n=128) (see Figure 2). The mortality risk was not significantly different in patients with incident (RR=2.04, 95% CI: 1.60-2.60, I^2=99.9%, n=20) versus prevalent (RR=2.05, 95% CI: 1.81-2.33, I^2=99.9%, n=110) depression (between-group p=0.974) (see Table 1). The pooled RRs for all-cause mortality of people with depression versus the general population (RR=2.38, 95% CI: 1.74-3.25, I^2=100.0%, n=37), and individuals with depression versus no depression (RR=2.01, 95% CI: 1.80-2.24, I^2=99.7%, n=92) were similar in magnitude (between-group p=0.782) (see supplementary information).

Among individuals with depression versus no depression matched for comorbid conditions, the depression-mortality association was significant (RR=1.29, 95% CI: 1.21-1.37, I^2=99.9%, n=98) (see Figure 3). The all-cause mortality risk was increased in people with depression versus no depression matched for comorbid alcohol/substance use disorders (RR=2.59, 95% CI: 1.71-3.93, I^2=99.8%, n=5); colorectal cancer (RR=1.80, 95% CI: 1.28-2.55, I^2=82.5%, n=2);

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Death causes	n	Sample size for depression group/comparison group	RR (95% CI)	I^2 (%)
All causes	128	7,410,593/2,797,649,150	**2.10 (1.87-2.35)**	99.87
Natural causes	58	15,706,165/2,115,890,845	**1.63 (1.51-1.75)**	99.59
Unnatural causes	49	5,159,404/1,677,640,085	**5.81 (4.55-7.43)**	99.77
Suicide	44	2,687,171/1,487,047,309	**9.89 (7.59-12.88)**	99.59
Non-suicide unnatural causes	15	2,712,694/569,661,047	**2.06 (1.70-2.50)**	96.87
Accidents	8	994,802/462,323,299	**2.19 (1.38-3.47)**	98.81
Neurological diseases	6	2,104,035/16,994,013	**2.28 (1.81-2.88)**	96.20
Respiratory diseases	14	1,679,058/442,741,489	**2.34 (1.94-2.83)**	99.02
Endocrine diseases	5	1,764,197/121,544,138	**2.01 (1.34-3.01)**	99.36
Diabetes mellitus	3	1,700,885/113,086,772	**1.82 (1.12-2.96)**	99.58
Infectious diseases	7	1,210,291/19,795,495	**1.65 (1.21-2.24)**	96.41
Gastrointestinal diseases	9	2,928,690/1,400,830,974	**1.64 (1.25-2.15)**	98.42
Liver diseases	4	1,145,866/19,621,608	1.49 (0.98-2.27)	98.62
Cardiovascular diseases	36	3,849,896/844,677,849	**1.47 (1.35-1.60)**	98.89
Genitourinary diseases	6	1,866,232/565,557,974	**1.45 (1.19-1.76)**	93.95
Cancers	25	2,518,185/567,911,595	**1.35 (1.20-1.52)**	98.84
Cerebrovascular diseases	10	1,515,008/362,275,370	**1.27 (1.10-1.47)**	95.34
COVID-19	6	1981,456/26,917,222	1.13 (0.94-1.35)	95.68

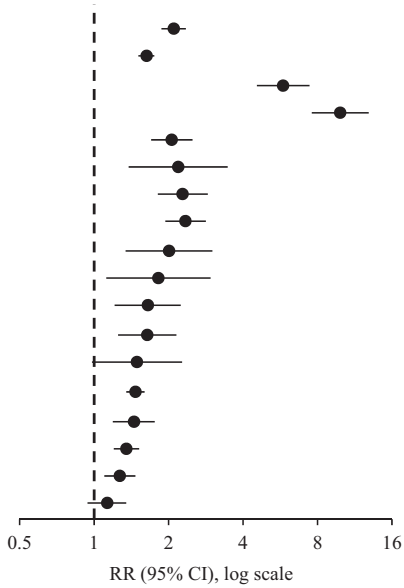


Figure 2 All-cause and cause-specific mortality risk in people with depression versus no depression/general population. RR – relative risk, COVID-19 – coronavirus 19 disease. Significant values are highlighted in bold prints.

peripheral vascular diseases (RR=1.42, 95% CI: 1.22-1.65, I^2=98.0%, n=3); myocardial infarction (RR=1.41, 95% CI: 1.16-1.71, I^2=97.3%, n=10); stroke (RR=1.40, 95% CI: 1.16-1.68, I^2=98.8%, n=7); prostate cancer (RR=1.38, 95% CI: 1.01-1.89, I^2=97.5%, n=3); diabetes mellitus (RR=1.33, 95% CI: 1.22-1.46, I^2=99.0%, n=11); any cardiovascular diseases (RR=1.32, 95% CI: 1.24-1.41, I^2=98.3%, n=35); chronic pulmonary diseases (RR=1.32, 95% CI: 1.09-1.61, I^2=98.7%, n=3); ischemic heart diseases (RR=1.29, 95% CI: 1.06-1.57, I^2=97.8%, n=13); non-ischemic cardiovascular diseases (RR=1.28; 95% CI: 1.18-1.39, I^2=95.9%, n=9); any cancers (RR=1.27, 95% CI: 1.16-1.39, I^2=98.0%, n=21); heart failure (RR=1.26, 95% CI: 1.16-1.37, I^2=95.9%, n=8); renal diseases (RR=1.20, 95% CI: 1.09-1.33, I^2=97.1%, n=5); respiratory diseases (RR=1.20, 95% CI: 1.06-1.36, I^2=97.8%, n=6); breast cancer (RR=1.20, 95% CI: 1.04-1.39, I^2=84.6%, n=8); and coronavirus disease 2019 (COVID-19) (RR=1.14, 95% CI: 1.02-1.28, I^2=99.8%, n=4) (see Figure 3).

In the analyses on people with major depressive disorder compared to no depression/general population, the pooled RR was 2.17 (95% CI: 1.69-2.79, I^2=99.7%, n=36), with evidence of publication bias (Egger's test p<0.001) (see Figure 4). The risk of all-cause mortality associated with major depressive disorder versus the general population (RR=2.41, 95% CI: 1.43-4.04, I^2=99.6%, n=8) was comparable to that versus no depression (RR=2.13, 95% CI: 1.61-2.83, I^2=99.7%, n=29) (between-group p=0.751). The magnitude of depression-associated all-cause mortality risk was significant in individuals matched for any comorbid conditions with major depressive disorder versus no depression (RR=1.33, 95% CI: 1.25-1.41, I^2=98.7%, n=25) (see supplementary information).

Individuals with dysthymia had an increased all-cause mortality risk compared to those with no depression (RR=1.40, 95% CI: 1.30-1.51, I^2=0%, n=3). All-cause mortality risk was markedly elevated in the 0-180 days after depression diagnosis (RR=10.80, 95% CI: 6.21-18.77, I^2=98.5, n=2); and lower but still significantly elevated in the observation periods of 180-365 days (RR=3.29, 95% CI: 1.51-7.17, I^2=98.0, Egger's test p<0.001, n=2), and 1-5 years (RR=4.23, 95% CI: 2.25-7.97, I^2=99.8, n=4) following depression diagnosis (see Figure 4).

Psychotic depression (versus non-psychotic depression: RR=1.61, 95% CI: 1.45-1.78, I^2=6.3%, n=2) and treatment-resistant depression (versus non-treatment-resistant depression: RR=1.27, 95% CI: 1.16-1.39, I^2=85.3%, Egger's test p<0.001, n=9) further increased depression-associated mortality risk. Both late-life depression (versus no depression: RR=2.11, 95% CI: 1.11-4.00, I^2=64.1%, n=3) and early-life depression (versus no depression: RR=1.73, 95% CI: 1.38-2.17, I^2=0.0%, n=2) were associated with increased mortality risk (see Figure 4).

Secondary outcomes: natural, unnatural and other cause-specific mortality

The RR for natural-cause mortality was 1.63 (95% CI: 1.51-1.75, I^2=99.6%, n=58) for depression relative to no depression/general population (see Figure 2). The depression-mortality association was consistent when compared to the general population (RR=1.74, 95% CI: 1.54-1.98, I^2=99.7%, n=19) and to individuals with no depression (RR=1.57, 95% CI: 1.43-1.73, I^2=99.4%, n=39) (between-group p=0.755). The association was also significant in individuals matched for any comorbid conditions (RR=1.20, 95% CI: 1.14-1.27, I^2=97.6%, n=22) (see supplementary information).

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Table 1 Subgroup analyses on risk of all-cause mortality in patients with depression versus no depression/general population

Subgroup	n	Sample size for depression group/comparison group	RR (95% CI)	I^2 (%)	Between groups p	p for differences
Sex					0.615	
Male	65	4,990,780/1,946,058,373	2.37 (2.06-2.71)	99.9		Ref.
Female	58	5,267,202/2,162,929,399	2.27 (1.90-2.71)	99.9		0.615
Age					0.139	
<25 years	5	75,335/4,287,267	3.28 (1.79-6.02)	98.1		Ref.
25–60 years	8	2,697,902/61,509,449	3.54 (2.30-5.44)	99.9		0.942
>60 years	32	1,375,463/87,212,436	2.17 (1.67-2.83)	99.9		0.252
Depression sample nature					0.974	
Prevalent	110	4,964,453/2,457,348,522	2.05 (1.81-2.33)	99.9		Ref.
Incident	20	2,461,401/230,300,779	2.04 (1.60-2.60)	99.9		0.974
Diagnostic system					0.002	
ICD	75	7,268,131/995,528,374	2.41 (2.06-2.82)	99.9		Ref.
DSM	47	86,428/984,715,642	1.66 (1.47-1.87)	92.1		0.004
ICD/DSM	4	650/381,342,460	1.06 (0.69-1.64)	92.3		0.028
Continent					0.278	
Africa	2	143,614/838,526	2.00 (0.71-5.64)	92.0		Ref.
Asia	16	2,140,725/177,689,675	2.39 (1.53-3.74)	100.0		0.893
Australia	4	1,299/28,615,691	3.13 (0.91-10.84)	98.9		0.499
Europe	71	1,265,030/580,795,483	2.26 (1.97-2.59)	99.7		0.830
North America	30	1,586,594/1,573,503,906	1.51 (1.25-1.83)	99.8		0.703
South America	1	2,201,147/NA	2.35 (1.60-3.46)	99.6		0.784
Source of study samples					0.043	
Community surveys	30	61,195/302,131	1.58 (1.36-1.84)	90.3		Ref.
Health-system case registers	55	4,006,290/1,134,611,614	2.23 (1.94-2.56)	99.9		0.036
Health-insurance databases	15	2,218,351/188,888,363	2.80 (1.65-4.75)	100.0		0.041
Hospital/clinic samples or records	27	1,069,373/594,016,368	1.96 (1.49-2.59)	98.9		0.161
Population of depression sample					<0.001	
Community	28	60,917/578,747	1.57 (1.34-1.85)	91.1		Ref.
Outpatient or inpatient and outpatient	69	3,752,495/1,095,159,416	1.89 (1.65-2.16)	99.9		0.175
Inpatient	29	3,391,983/1,265,545,640	2.95 (2.31-3.76)	99.8		0.001

RR – relative risk, NA – not available

Depression was associated with increased unnatural-cause mortality risk relative to no depression/general population (RR=5.81, 95% CI: 4.55-7.43, I^2=99.8%, n=49) (see Figure 2). Depression-associated mortality risk estimates for unnatural causes were significantly higher when compared to the general population (RR=9.69, 95% CI: 6.02-15.59, I^2=99.9%, n=20) than compared to no depression (RR=4.36, 95% CI: 3.41-5.58, I^2=99.4%, n=28) (between-group p<0.001). The associations were also significant in individuals matched for any comorbid conditions (RR=2.57, 95% CI: 1.89-3.50, I^2=97.5%, n=9). Treatment-resistant status conferred an incremental effect on the depression-associated unnatural-cause mortality risk (RR=2.30, 95% CI: 1.68-3.14, I^2=92.6%, n=4), compared to non-treatment-resistant depression (see supplementary information).

Individuals with depression exhibited increased mortality risk compared to no depression/general population for suicide (RR=9.89, 95% CI: 7.59-12.88, I^2=99.6%, n=44); any non-suicide unnatural cause (RR=2.06, 95% CI: 1.70-2.50, I^2=96.9%, n=15); accidents (RR=2.19, 95% CI: 1.38-3.47, I^2=99.8%, n=8); neurological diseases (RR=2.28, 95% CI: 1.81-2.88, I^2=96.2%, n=6); respiratory diseases (RR=2.34, 95% CI: 1.94-2.83, I^2=99.0%, n=14); endocrine diseases (RR=2.01, 95% CI: 1.34-3.01, I^2=99.4%, n=5); diabetes mellitus (RR=1.82, 95% CI: 1.12-2.96, I^2=99.6%, n=3); infectious diseases (RR=1.65, 95% CI: 1.21-2.24, I^2=99.4%, n=7); gastrointestinal diseases (RR=1.64, 95% CI: 1.25-2.15, I^2=98.4%, n=9); cardiovascular

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Comorbid conditions	n	Sample size for depression group/comparison group	RR (95% CI)	I^2 (%)
Any comorbid conditions	98	5,881,116/40,284,386	**1.29 (1.21-1.37)**	99.85
Alcohol/substance use disorders	5	67,540/538,232	**2.59 (1.71-3.93)**	99.84
Colorectal cancer	2	9,101/38,564	**1.80 (1.28-2.55)**	82.54
Peripheral vascular diseases	3	35,826/133,527	**1.42 (1.22-1.65)**	97.98
Myocardial infarction	10	18,952/171,040	**1.41 (1.16-1.71)**	97.27
Stroke	7	41,392/320,874	**1.40 (1.16-1.68)**	98.75
Prostate cancer	3	6,242/132,621	**1.38 (1.01-1.89)**	97.51
Angina	2	8,567/22,874	1.36 (0.76-2.43)	97.68
Diabetes mellitus	11	542,856/4,288,006	**1.33 (1.22-1.46)**	99.05
Cardiovascular diseases	35	224,187/1,455,452	**1.32 (1.24-1.41)**	98.32
Chronic pulmonary diseases	3	43,234/70,177	**1.32 (1.09-1.61)**	98.66
Ischemic heart diseases (IHD)	13	32,312/284,293	**1.29 (1.06-1.57)**	97.80
AIDS/HIV	3	9,360/38,944	1.29 (0.68-2.45)	98.12
Non-IHD cardiovascular diseases	9	36,195/469,815	**1.28 (1.18-1.39)**	95.85
Cancers	21	100,282/670,646	**1.27 (1.16-1.39)**	98.02
Heart failure	8	35,944/467,693	**1.26 (1.16-1.37)**	95.92
Infectious diseases	5	210,085/622,475	1.22 (0.96-1.55)	99.11
Renal diseases	5	58,972/893,327	**1.20 (1.09-1.33)**	97.12
Respiratory diseases	6	429,170/187,102	**1.20 (1.06-1.36)**	97.78
Breast cancer	8	20,378/243,339	**1.20 (1.04-1.39)**	84.60
Lung cancer	3	9,671/50,160	1.17 (0.98-1.40)	89.29
COVID-19	4	3,848,244/26,019,000	**1.14 (1.02-1.28)**	99.75
Neurological diseases	2	13,460/3,127	1.11 (0.94-1.31)	96.75
Gastrointestinal diseases	5	326,166/4,017,223	1.10 (0.92-1.31)	98.82
Liver diseases	4	11,266/22,584	1.03 (0.83-1.28)	96.41
Dementia	2	12,540/3,127	1.01 (0.89-1.14)	93.67
Other conditions	6	60,710/520,134	1.26 (0.84-1.89)	98.01

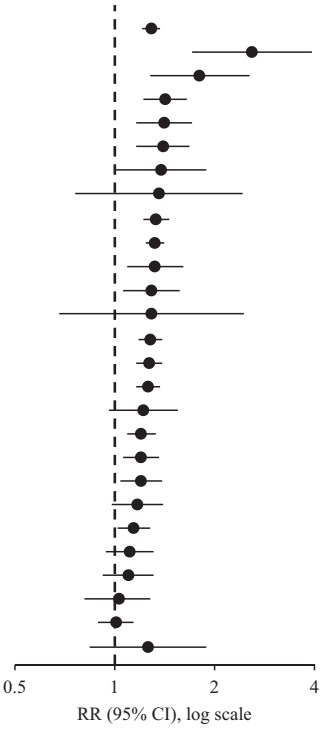


Figure 3 All-cause mortality risk in people with depression versus without depression matched for specific comorbid conditions. RR – relative risk, AIDS/HIV – acquired immunodeficiency syndrome / human immunodeficiency virus infection, COVID-19 – coronavirus 2019 disease. Significant values are highlighted in bold prints.

diseases (RR=1.47, 95% CI: 1.35-1.60, I^2=98.9%, n=36); genitourinary diseases (RR=1.45, 95% CI: 1.19-1.76, I^2=94.0%, n=6); cancers (RR=1.35, 95% CI: 1.20-1.52, I^2=98.8%, n=25); and cerebrovascular diseases (RR=1.27, 95% CI: 1.10-1.47, I^2=95.3%, n=10) (see Figure 2).

Subgroup and meta-regression analyses

Among individuals with depression (with or without any comorbid conditions), those treated with any antidepressant had a reduced risk of all-cause mortality (RR=0.79, 95% CI: 0.68-0.93, I^2=99.2%, n=16) compared to those without antidepressant use (see Figure 5). Moreover, while all-cause mortality risk was still increased in people with antidepressant-treated depression relative to no depression (RR=1.22, 95% CI: 1.10-1.37, I^2=98.9%, n=12), its magnitude in these people was significantly lower (p<0.001) than the all-cause mortality risk observed in the overall analysis for depression versus no depression (RR=2.01, 95% CI: 1.80-2.24, I^2=99.7%, n=92). Regarding antidepressant drug classes, use of serotonin and noradrenaline reuptake inhibitors (SNRIs) was associated with a decreased risk of all-cause mortality (versus no antidepressant use: RR=0.81, 95% CI: 0.65-0.99, I^2=96.7%, n=6), whereas the mortality risk was not decreased significantly with use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) (see Figure 5).

In individuals with depression and any comorbid physical conditions, use of any antidepressant (RR=0.69, 95% CI: 0.59-0.81, I^2=98.4%, n=9), of SSRIs (RR=0.75, 95% CI: 0.61-0.92, I^2=98.4%, n=4), of SNRIs (RR=0.74, 95% CI: 0.57-0.96, I^2=94.6%, n=4), and of TCAs (RR=0.78, 95% CI: 0.69-0.87, I^2=82.6%, n=4) was associated with reduced risk of all-cause mortality compared to no antidepressant use (see Figure 5). Individuals using SNRIs had an increased risk of suicide than those using SSRIs (RR=1.55, 95% CI: 1.08-2.22, I^2=5.9%, n=3) (see supplementary information).

Among individuals with depression (with or without any comorbid conditions), use of ECT (versus no ECT use) was associated with reduced mortality risk due to all causes (RR=0.73, 95% CI: 0.66-0.82, I^2=0%, n=6), natural causes (RR=0.76, 95% CI: 0.59-0.97, I^2=12.0%, n=4), and suicide (RR=0.67, 95% CI: 0.53-0.85, I^2=32.3%, n=4) (see Figure 5).

Subgroup analyses by sex did not show a significant difference in depression-associated all-cause mortality risk between men (RR=2.37, 95% CI: 2.06-2.71, I^2=99.9%, n=65) and women (RR=2.27, 95% CI: 1.90-2.71, I^2=99.9%, n=58) (between-group p=0.615). No significant difference in mortality risk for depression versus no depression/general population was detected for age categories (between-group p=0.139) (see Table 1). Subgroup analyses stratified by age and sex revealed a greatly increased mortality risk associated with depres-

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Comparison	n	Sample size for depression group/comparison group	RR (95% CI)
All-cause mortality			
MDD vs. no depression/general population	36	869,555/487,657,309	**2.17 (1.69-2.79)**
Dysthymia vs. no depression	3	2,366/253,209	**1.40 (1.30-1.51)**
0-180 days after depression diagnosis	2	NA/NA	**10.80 (6.21-18.77)**
180-365 days after depression diagnosis	2	NA/NA	**3.29 (1.51-7.17)**
1-5 years after depression diagnosis	4	NA/NA	**4.23 (2.25-7.97)**
Late-life depression vs. no depression	3	394/45,200	**2.11 (1.11-4.00)**
Early-life depression vs. no depression	2	819/43,872	**1.73 (1.38-2.17)**
Psychotic depression vs. non-psychotic depression	2	19,174/92,587	**1.61 (1.45-1.78)**
TRD vs. non-TRD	9	127,981/1,025,266	**1.27 (1.16-1.39)**
Unnatural-cause mortality			
MDD vs. no depression/general population	13	381,162/468,337,155	**7.71 (4.72-12.59)**
Depression vs. bipolar disorder (reference: depression)	3	48,854/5,196	0.71 (0.37-1.37)
TRD vs. non-TRD	4	72,284/573,484	**2.30 (1.68-3.14)**
Suicide			
MDD vs. no depression/general population	10	327,886/301,755,306	**12.01 (7.18-20.10)**
Depression vs. bipolar disorder (reference: depression)	3	48,854/5,196	0.64 (0.28-1.50)

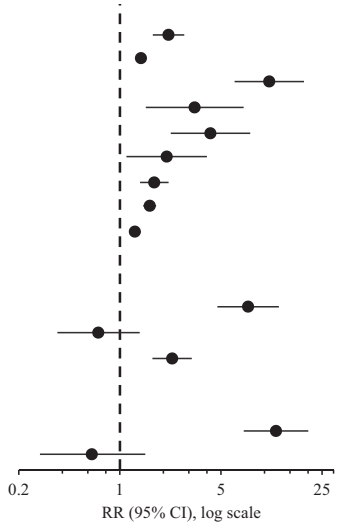


Figure 4 Other characteristics of depression associated with mortality. Regarding natural-cause mortality, no comparison pairs had sufficient number of studies for analyses. RR – relative risk, NA – not available, MDD – major depressive disorder, TRD – treatment-resistant depression. Significant values are highlighted in bold prints.

sion (versus no depression) in females aged <25 years (RR=6.15, 95% CI: 1.89-20.00, I^2=95.0%, n=2), and a substantially increased suicide risk associated with depression (versus no depression) in people aged <25 years (RR=9.91, 95% CI: 6.68-14.69, I^2=90.3%, n=3) and >60 years (RR=13.07, 95% CI: 7.87-21.71, I^2=95.8%, n=5) (see supplementary information).

Mortality risk associated with depression (versus no depression/general population) was higher when the source of study samples was health-system case registers (RR=2.23, 95% CI: 1.94-2.56, I^2=99.9%, n=55) (p for difference with community surveys = 0.036), or health-insurance databases (RR=2.80, 95% CI: 1.65-4.75, I^2=100%, n=15) (p for difference with community surveys = 0.041) (see Table 1).

All-cause mortality risk for depression versus no depression/general population was significantly higher (p<0.001) when people with depression were identified from inpatient settings (RR=2.95, 95% CI: 2.31-3.76, I^2=99.8%, n=29) than in the community (RR=1.57, 95% CI: 1.34-1.85, I^2=91.1%, n=28). Based on data from six continents, there was no significant regional difference in depression-associated mortality risk (versus no depression/general population; between-group p=0.278) (see Table 1).

In meta-regression analyses, depression-associated excess all-cause mortality (versus no depression/general population) decreased with increasing number of adjusted covariates (beta=–0.03, 95% CI: –0.05 to –0.01, p=0.001) and higher Newcastle Ottawa Scale scores (beta=–0.19, 95% CI: –0.35 to –0.02, p=0.026) (see Table 2). In comparisons between depression versus general population, the magnitude of excess all-cause mortality associated with depression increased with higher country/region human development index (beta=11.15, 95% CI: 1.14-21.17, p=0.029) (see supplementary information).

Depression-associated all-cause mortality risk (versus no depression matched for any comorbid condition) increased with higher socio-demographic index (beta=3.21, 95% CI: 1.20-5.22, p=0.002) (see Table 2). Excess natural-cause mortality associated with depression (versus no depression/general population, and versus stratified comparison groups) generally increased with more recent median year of observation period, higher human development index, and larger depression sample size, and decreased with longer observation period, greater number of adjusted covariates, and higher Newcastle Ottawa Scale score (see supplementary information).

DISCUSSION

This large-scale meta-analysis of 268 cohort studies, comparing 10.8 million people with depression versus about 2.8 billion controls, comprehensively quantifies the risk of excess mortality associated with depression. Specifically, we observed a two-fold increased all-cause mortality risk in people with depression versus no depression/general population controls (and in individuals with major depressive disorder versus no depression/general population), and a lower but still significantly 1.3-fold increased all-cause mortality risk versus comorbid condition-matched (mostly physical diseases) non-depression controls. People with depression displayed elevated risk of natural-cause (1.6-fold) and unnatural-cause (5.8-fold) mortality, as well as a 9.9-fold increased risk of suicide, relative to no

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Comparison	n	Sample size for treatment group/comparison group	RR (95% CI)
All-cause mortality			
Any AD vs. no AD	16	636,340/688,746	**0.79 (0.68-0.93)**
SSRIs vs. no AD	11	495,609/299,141	0.94 (0.79-1.12)
SNRIs vs. no AD	6	212,573/376,193	**0.81 (0.65-0.99)**
TCAs vs. no AD	9	90,002/386,376	1.03 (0.81-1.31)
ECT vs. no ECT	6	25,841/51,876	**0.73 (0.66-0.82)**
All-cause mortality (samples matched for comorbid conditions)			
Any AD vs. no AD	9	271,358/287,621	**0.69 (0.59-0.81)**
SSRIs vs. no AD	4	90,504/80,173	**0.75 (0.61-0.92)**
SNRIs vs. no AD	4	29,428/184,232	**0.74 (0.57-0.96)**
TCAs vs. no AD	4	27,058/194,879	**0.78 (0.69-0.87)**
Natural-cause mortality			
Any AD vs. no AD	3	26,823/131,053	1.09 (0.99-1.20)
SSRIs vs. no AD	2	10,814/21,842	1.04 (0.90-1.20)
SNRIs vs. no AD	2	1,417/23,957	0.98 (0.86-1.13)
TCAs vs. no AD	2	12,024/22,121	0.92 (0.69-1.22)
ECT vs. no ECT	4	15,558/34,467	**0.76 (0.59-0.97)**
Suicide			
Any AD vs. no AD	3	330,772/211,728	1.13 (0.78-1.64)
ECT vs. no ECT	4	5,393/15,498	**0.67 (0.53-0.85)**

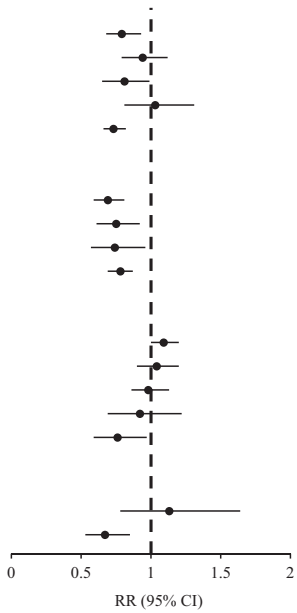


Figure 5 Risk of mortality associated with antidepressant (AD) treatment and electroconvulsive therapy (ECT) in patients with depression. RR – relative risk, SSRIs – selective serotonin reuptake inhibitors, SNRIs – serotonin and noradrenaline reuptake inhibitors, TCAs – tricyclic antidepressants. Significant values are highlighted in bold prints.

depression/general population controls. Dysthymia was also associated with excess mortality, while depression with psychotic symptoms and treatment-resistant depression conferred an incremental mortality risk. Antidepressant-treated patients exhibited decreased all-cause mortality risk versus untreated patients, both in the overall population and, especially, in the sub-populations of patients with depression matched for comorbidities. ECT was associated with a reduced mortality from all causes, natural causes and suicide in patients with depression.

Compared with previous meta-analyses[12,15] dating back to one decade ago, our review included a larger proportion of studies utilizing health-record databases (i.e., case registers, health-insurance databases, or clinic/hospital records), which identify people with depression who have received psychiatric outpatient and/or inpatient care, and who are generally more severely ill than those recruited in community surveys. Moreover, we only included studies defining depression according to ICD or DSM based on diagnostic interviews or a clinician-assigned coded diagnosis derived from health-record databases. This allowed us to avoid misclassification bias due to self-report screening measures, which tend to identify a significant proportion of people with milder or subthreshold symptoms who do not fulfill the clinical diagnosis of depression, resulting in an underestimation of the mortality risk associated with depression.

Our subgroup analyses found no significant differences in mortality risk in men versus women and across age categories. However, subgroup analyses further stratified by age and sex revealed a greatly increased depression-associated all-cause mortality risk in females aged <25 years, and a substantially increased suicide-specific mortality risk in people aged <25 years and >60 years. These represent specific groups requiring multi-component prevention and intervention strategies.

We observed excess depression-associated mortality risk across a broad spectrum of physical comorbidities, with a similar magnitude of risk estimates (RR range: 1.14-1.80). This similar degree of mortality risk may suggest that the association of depression with raised natural-cause deaths in the context of physical comorbidities is mostly attributable to general rather than disease-specific mechanisms, such as inflammatory processes, lifestyle risk factors (e.g., smoking, physical inactivity, unhealthy diet, alcohol use) and depression-related behavioral factors (e.g., poor self-management of health conditions, treatment non-adherence)[1]. Intriguingly, the magnitude of risk estimates associated with incident and prevalent depression was comparable in individuals with physical comorbidities, indicating that depression which occurs prior to the onset of physical diseases and depression emerging after the onset of these diseases may confer similar premature mortality risk, although the involved mechanisms may be different[315,316].

Notably, the risk of excess mortality was most pronounced within 180 days following depression diagnosis (10.8-fold increased risk), as compared to other post-depression time intervals (i.e., 180-365 days and 1-5 years). This finding indicates that the initial few months after depression diagnosis represent a critical period warranting comprehensive assessment, close monitoring and intensive

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Table 2 Meta-regression analyses on risk of all-cause mortality in patients with depression

Moderators	Depression vs. no depression/general population			Depression vs. no depression (with comorbid conditions)		
	n	Sample size for depression group/comparison group	Beta (95% CI)	n	Sample size for depression group/comparison group	Beta (95% CI)
Characteristics of overall sample						
Median year of observation period	125	7,407,473/2,737,228,741	0.00 (–0.01 to 0.01)	98	5,881,116/40,284,386	–0.01 (–0.02 to 0.00)
Number of years of observation period	128	7,410,593/2,797,649,150	0.00 (–0.01 to 0.01)	98	5,881,116/40,284,386	0.00 (0.00-0.01)
Mean follow-up duration	71	3,005,306/1,725,191,966	–0.01 (–0.04 to 0.02)	75	3,589,033/28,728,634	**0.01 (0.00-0.02)**
Number of adjusted covariates	128	7,410,593/2,797,649,150	**–0.03 (–0.05** to **–0.01)**	98	5,881,116/40,284,386	0.00 (–0.01 to 0.00)
Human development index	111	7,364,768/1,275,537,198	0.29 (–1.19 to 1.76)	98	5,881,116/40,284,386	2.73 (–0.32 to 5.77)
Socio-demographic index	128	7,410,593/2,797,649,150	0.04 (–1.17 to 1.25)	98	5,881,116/40,284,386	**3.21 (1.20-5.22)**
Newcastle-Ottawa Scale score	128	7,410,593/2,797,649,150	**–0.19 (–0.35** to **–0.02)**	98	5,881,116/40,284,386	0.02 (–0.16 to 0.19)
Characteristics of depression sample						
Sample size	118	7,410,593/2,361,649,150	0.00 (0.00-0.00)	96	5,881,116/40,284,386	0.00 (0.00-0.00)
% with major depressive disorder	44	931,391/855,171,523	0.64 (–0.19 to 1.47)	31	697,579/979,804	0.05 (–0.26 to 0.35)
% with dysthymia	15	244,899/462,835,825	–0.65 (–1.45 to 0.16)	23	663,079/636,807	–0.15 (–0.60 to 0.30)
% with antidepressant exposure	11	967,816/15,846,099	0.04 (–0.27 to 0.34)	17	218,211/3,417,105	–0.18 (–0.45 to 0.10)
Difference between depression and non-depression samples						
% females	71	4,419,696/1,474,617,672	–0.32 (–0.74 to 0.09)	68	1,727,911/11,977,697	0.00 (0.00-0.00)
Mean age	46	3,161,286/934,272,763	0.01 (0.00-0.01)	60	1,065,200/11,009,157	0.00 (0.00-0.00)
% White ethnicity	18	1,930,793/650,325,201	–0.13 (–0.52 to 0.27)	31	800,646/5,758,516	–0.94 (–2.28 to 0.39)
Body mass index	5	45,789/437,289	-	15	523,662/3,391,730	0.01 (–0.07 to 0.09)
% with obesity	12	98,377/662,761	0.95 (–2.86 to 4.76)	14	354,947/4,818,722	0.15 (–0.26 to 0.56)
% with current smoker status	25	1,092,009/5,462,422	–0.21 (–1.54 to 1.11)	25	209,272/2,970,839	–0.2 (–1.02 to 0.62)
% with married status	14	67,153/77,637,512	0.07 (–0.53 to 0.67)	12	552,089/1,263,174	–0.28 (–2.22 to 1.67)
% with alcohol use disorder	24	2,111,327/128,710,342	–0.27 (–0.95 to 0.42)	18	1,008,032/5,892,071	–0.29 (–0.87 to 0.29)
% with substance use disorder	15	2,233,456/153,465,672	–1.57 (–6.49 to 3.36)	11	460,289/6,325,928	–0.3 (–1.37 to 0.77)
% with diabetes	27	2,047,125/73,283,440	–0.46 (–1.94 to 1.01)	45	1,528,503/9,203,064	**1.21 (0.08-2.33)**
% with cancers	14	1,135,834/71,005,967	2.35 (–0.84 to 5.54)	17	1,068,797/5,269,880	**2.49 (0.35-4.63)**
% with renal diseases	7	1,822,787/71,983,909	-	17	758,904/3,662,367	1.88 (–1.04 to 4.80)

Significant values are highlighted in bold prints

treatment to optimize illness outcome and reduce mortality risk, in particular from suicide.

We found that the presence of psychotic symptoms conferred an incremental mortality risk associated with depression. As these symptoms might not be readily identified in depression[317,318], careful evaluation is required to facilitate their early detection and effective management. Moreover, treatment-resistant depression, which affects at least 30% of depressed people[319], was associated with 27% higher risk for all-cause mortality and a 2.3-fold increased risk for unnatural deaths relative to non-treatment-resistant depression. Previous research suggested that this increased mortality risk is driven largely by suicide and other external causes[203,252]. However, common chronic physical comorbidities such as cardiovascular diseases and diabetes mellitus are also over-represented in patients with this condition[319,320]. Early identification of treatment-refractory status followed by provision of adequate management is therefore needed to reduce the disproportionate morbidity and mortality associated with this subtype of depression.

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To our knowledge, this is the first meta-analysis comprehensively assessing mortality risk associated with antidepressant treatment in people with depression. In the overall analyses (i.e., including depression with and without comorbid conditions), we observed a significant mortality-reducing effect of any antidepressant and of SNRIs, relative to non-use of antidepressants. These data were reinforced by the observation that the magnitude of increased mortality in people with antidepressant-treated depression versus no depression was significantly lower (RR=1.22) than in the overall primary analysis of depression versus no depression (RR=2.01). Depressive symptom alleviation by antidepressant treatment might contribute to better physical health outcomes via enhanced self-management of physical conditions, improved treatment adherence, and increased engagement in healthy lifestyle behaviors[321]. Moreover, the observed protective effect of antidepressant treatment might also be due to factors such as improved glycemic control[322], reduction of pro-inflammatory state[323-325], and enhanced motor function[326].

Our analyses generally revealed comparable mortality risk between antidepressant drug classes. Nonetheless, SNRI use was associated with a higher suicide risk compared to SSRI use. A recent network meta-analysis based on randomized controlled trials (RCTs) reported venlafaxine as the only antidepressant linked to significantly increased risk of suicidal behavior or ideation compared to placebo and other antidepressants in children and adolescents[28]. However, our comparison analyses between venlafaxine and fluoxetine, which were based on only two studies, revealed no significant difference in suicide risk.

The US Food and Drug Administration issued a black-box warning in 2004 that antidepressants might have a differential effect on suicide risk across age groups, with an elevated risk in young people, no association in middle age, and a protective effect in the elderly[327]. Limited available research comparing the effect of antidepressant versus no antidepressant use on suicide risk in people with depression precluded us from investigating age-specific associations between suicide and antidepressant treatment.

Our pooled analyses demonstrated that use of ECT was associated with a reduced risk of all-cause, natural-cause and suicide-related deaths in people with depression, further supporting its critical role as an effective treatment for severe depression.

Large-scale research utilizing health-record databases with long observation periods would be required to better clarify the effect of antidepressant treatment and ECT on suicide risk in people with depression, which otherwise could unlikely be adequately captured (as a rare outcome event) and investigated in the context of RCTs.

None of the included studies compared mortality risk in people with depression who had received versus those who had not received psychotherapies or neuromodulation therapies, thereby precluding us from performing subgroup analyses to explore the associations between these treatment modalities and mortality risk associated with depression.

In line with a prior meta-analysis[12], our meta-regression models showed that an increasing number of adjusted covariates and higher study quality decreased the magnitude of elevated mortality risk in people with depression, suggesting that residual confounding might contribute to the reported excess mortality. This potential bias was partly addressed by our selection of the reported risk estimates adjusted for the most comprehensive set of covariates per included study into the pooled analyses. We also found that more recent median study year of investigation accentuated the excess natural-cause mortality risk in depression (versus no depression), indicating that people with depression have not benefited equally from recent enhancement of health care and life expectancy improvement compared to the general population.

Our results suggest that a higher human development index, which measures levels of social and economic development in a specific country/region[55], increases the risk of premature mortality in people with depression versus the general population. Despite better access to health services, it is recognized that individuals from regions with high social and economic development may be more likely to experience an escalated stress in relation to social exclusion, unemployment, working conditions, lack of family and social support, and violence, which are closely associated with suicidal behaviors and other non-communicable diseases[328]. One alternative explanation is that depression is more likely to be underdiagnosed and under-reported in less developed countries, resulting in apparently lower mortality risk in regions with low human development index.

Some limitations warrant consideration in interpreting our results. First, there was significant heterogeneity across studies regarding the mortality risk associated with depression. We attempted to assess the sources of heterogeneity via subgroup and meta-regression analyses. However, as data for other potentially relevant variables, such as socio-economic status and lifestyle risk factors, were not adequately captured in most included studies, sources of heterogeneity could not be further explored. Second, the included studies were observational in nature, and thus causality cannot be inferred regarding the moderating or aggravating factors that we identified. Third, although 268 studies were included in the meta-analysis, findings of some subgroup analyses (e.g., several specific physical comorbidities, some characteristics of depression, use of antidepressants and ECT) were based on few studies, and should be re-evaluated when more studies have been conducted in this respect.

Notwithstanding these limitations, this study is the most comprehensive meta-analysis to date quantifying the mortality risk associated with depression, encompassing a wide range of comorbid conditions, taking into account an array of potential aggravating and attenuating factors, and evaluating the protective effect of antidepressant treatment and ECT against excess mortality. The study findings thus facilitate formulation of relevant and actionable targets for clinicians and allied health professionals, researchers, health system administrators, policy makers, patients and caregivers, that can be leveraged to effectively reduce the avoidable mortality gap associated with depression.

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