Review

Cardiovascular mortality and depression: A systematic review and meta-analysis of the association with antidepressant treatment and co-morbidity

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Abstract

Background: Depression is associated with increased mortality, with underlying causes unclear. We conducted a systematic review and meta-analysis of cardiovascular (CV) mortality in depression and how antidepressant treatments and comorbidities modify this.

Methods: We searched Medline, Embase, Scopus, Web of Science and Cochrane registers (inception to 31 December 2024) for randomised controlled trials (RCTs) and observational studies comparing CV mortality in adults with depression vs without, and receiving antidepressants vs controls. We excluded studies with <12 months follow-up, reporting only all-cause mortality or lacking control groups. Random-effects meta-analyses were conducted with CV mortality as the primary outcome. Risk of bias was assessed with RoB 2 and ROBINS-I. PROSPERO: CRD42020200812.

Results: We included 7 RCTs and 47 cohort studies (1,593,722 people). In multivariable-adjusted cohorts ($k=26$), depression was associated with a significantly higher CV mortality versus no-depression (hazard ratio (HR): 1.45, 95% CI: 1.25–1.69). Effects were similar in non-selected community-dwelling cohorts and those with CV disease or type 2 diabetes. Antidepressants overall were associated with increased CV mortality in cohorts but after adjustment only tricyclic antidepressants (TCAs) had significantly increased risk vs no antidepressant ($k=4$; HR: 1.27, 95% CI: 1.02–1.58). RCT findings were directionally consistent but underpowered.

Conclusions: Depression is associated with increased risk of CV mortality irrespective of comorbid group studied. Antidepressants do not appear to modify this risk, apart from TCAs, which may increase it. The antidepressant models in particular had high heterogeneity, reflecting a knowledge gap on the long-term effects of antidepressants in patients with depression on CV mortality.

Keywords
antidepressants, cardiovascular, depression, mortality, multimorbidity

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality globally, responsible for over 18 million deaths annually (Mensah et al., 2023). Depression, a common psychiatric disorder affecting 280 million people worldwide, is increasingly implicated as a potential risk factor for adverse CV outcomes (Global Burden of Disease Mental Disorders Collaborators, 2022). The most widely reported comorbidity in this context is that of depression post-acute myocardial infarction (AMI), as it is common and associated with poor clinical outcomes. The prevalence of major depressive disorder (MDD) post-AMI, when assessed systematically with structured interviews, is approximately 20% (Thombs et al., 2006). This is at least double the depression prevalence estimated from population-based samples of older adults (Sjöberg et al., 2017). In an individual patient data meta-analysis of post-AMI studies (for a total of 10,175 patients), depression was associated with a 23% increased risk in all-cause mortality compare to non-depressed post-AMI patients, corresponding to an hazard ratio (HR) of 1.23, with a 95% confidence interval (CI) of 1.15–1.31 adjusted for age, sex, diabetes, smoking, BMI and cardiac disease severity, including left ventricular ejection fraction, Killip class and history of previous myocardial infarction (Meijer et al.,

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2013). Similar findings were reported in the US multicentre prospective Translational Research Investigating Underlying Disparities in AMI Patients' Health Status (TRIUMPH) cohort study of 4062 adult patients during the index AMI admission, where 18.7% were diagnosed with depression using a validated rating scale (Smolderen et al., 2017). In this study, which aimed to determine whether the prognosis of patients with treated versus untreated depression differed, a diagnosis of depression post-AMI, compared to no-depression, was associated with a significantly higher risk of 1-year all-cause mortality (10.8% vs 6.1%; HR: 1.91, 95% CI: 1.39–2.62). In the double-blind, placebo-controlled Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), comparing the safety and antidepressant efficacy of sertraline vs placebo in 361 post-AMI patients with depression, long-term follow-up (median 6.7 years) showed that baseline MDD severity (HR: 2.30, 95% CI: 1.28–4.14) and lack of improvement in MDD in the first 6 months post-AMI (HR: 2.39, 95% CI: 1.39–2.44) were significantly associated with increased long-term all-cause mortality (Glassman et al., 2009).

Depression could therefore be associated with an increase in CV risk of similar magnitude to that attributed to well described and unquestionable factors such as smoking, which has been estimated to increase the risk of mortality for patients with coronary heart disease by 36%, when compared to those who quit smoking (relative risk (RR): 0.64, 95% CI: 0.58–0.71; Critchley and Capewell, 2003). As with depression, and for obvious reasons, the evidence regarding the risk of smoking comes mostly from observational studies. The challenge is that while the evidence to support smoking cessation is overwhelming, the benefits of treating depression on CV mortality remain uncertain (Centers for Disease Control and Prevention et al., 2010). While some meta-analyses of AMI studies suggest antidepressants may reduce rehospitalisation or recurrent MI (Sweda et al., 2020) others report little or no effect on all-cause mortality (Fernandes et al., 2021). The TRIUMPH US multicentre prospective cohort offered some insights into the effects of treating post-AMI depression: patients who were prescribed antidepressants or referred for counselling had similar 1-year all-cause mortality rates (6.7%) similar to those without depression (6.1%; Smolderen et al., 2017). However, this was not a controlled trial, and it did not address whether the depression had been successfully treated or not. The best randomised controlled trial (RCT) evidence for the effects of antidepressant therapy on long-term CV outcomes post-AMI perhaps comes from a 24-week double-blind, placebo-controlled trial of escitalopram in 300 post-AMI patients with depression, with a median follow-up period of 8.1 years (Kim et al., 2018). The group randomised to escitalopram (in flexible doses), had a significantly lower risk of major adverse cardiovascular events (MACE) compared to placebo (HR: 0.69, 95% CI: 0.49–0.96). It is not clear how generalisable these effects are, as the long-term data from the SADHART trial showed that treatment with sertraline did not significantly reduce long-term post-AMI all-cause mortality compared to placebo (HR: 0.99, 95% CI: 0.63–1.56), though as described above improvement in depression in the first 6 months post-AMI was associated with a lower all-cause mortality rate (Glassman et al., 2009). Therefore, even in patients post-AMI, where the additional clinical burden of depression is well known, there is uncertainty whether antidepressant treatment reduced CV mortality or not.

The first remaining uncertainty is whether depression independently increases the risk of CV mortality regardless of comorbidities. Much of the existing literature exploring the relationship between depression and CV mortality focuses on groups of patients assumed to have elevated CV risk, such as those post-AMI discussed above, or with established coronary disease (Fernandes et al., 2021), heart failure (Hedrick et al., 2020) or diabetes (Farooqi et al., 2019). Such studies focus on a primary physical condition, with depression being conceptualised as a 'risk marker'. This could be by way of depression 'biologically' changing risk (e.g. by modulating inflammatory function or the autonomic nervous system) or lead to 'behavioural' changes that consequently drive risk (e.g. poor adherence to rehabilitation programmes, diet or prescribed medication). Both can have a significant impact on functional capacity, including fatigue, which is associated with poor CV outcomes (Denu et al., 2025). Emerging biological evidence supports a potential causal mechanism. Kramer et al. (2023) applied the Genetic Depression Risk Score (GDRS; Howard et al., 2019) in a cohort of 3061 patients referred for coronary angiography in Germany, showing that a higher GDRS was significantly associated with increased CV mortality at 10-years (HR: 1.31, 95% CI: 1.11–1.55), even after adjusting for CV risk factors including age, sex, BMI, lipids, hypertension, smoking, and diabetes. Regardless, there is a knowledge gap on the independent effects of depression on CV mortality across comorbid groups and in the 'general population'. The latter seems particularly relevant to identify any putative direct effects of depression.

A second remaining uncertainty relates to the role of antidepressants as modifiers of CV mortality risk. Antidepressant treatments are often summarised in mortality reviews into a 'catch-all' category, despite the wide variety of antidepressant medication classes and neurostimulation therapies used with distinct and well-described mechanisms of action. There is some evidence that different antidepressant classes may have differing effects on all-cause mortality and other adverse events in community-based studies. In a UK 'general population' cohort of 238,963 patients aged 20–64 years with a diagnosis of depression based on GP records, tricyclic antidepressants (TCAs; HR: 1.39, 95% CI: 1.22–1.59) and mirtazapine (HR: 1.67, 95% CI: 1.33–2.09) were associated with significantly increased all-cause mortality when compared to SSRIs (Coupland et al., 2018). This study also highlights significant uncertainty in relation to indication bias for specific antidepressant prescription.

Given the high prevalence of depression and CVD, clarifying their association should be a public health priority. Despite significant research into this association, uncertainty remains about the independent effect of depression on CV mortality, the role of diagnostic heterogeneity, and the impact of antidepressant treatment. RCTs allow us to separate the effects of depression from those of antidepressant treatment. However, RCTs are often not feasible in those with multiple comorbidities (who tend to be excluded) or when the aim is to study long-term mortality (which raises obvious deliverability and ethical issues). Large-scale observational studies offer complementary 'real-world' evidence, include more diverse populations, and enable longer-term follow-up (Sarri et al., 2022). As linked digital registries grow, observational studies are increasingly seen not as 'second best' to RCTs but as complementary sources of

information by regulatory bodies (Frank et al., 2019) and patient groups (Oehrlein et al., 2019).

Accordingly, we performed a systematic review and meta-analysis, with separate models for RCTs and observational studies, to address two main questions: (1) Does depression, compared with no depression, increase CV mortality either in community-based cohorts or among higher-risk groups such as those with known CVD or diabetes? (2) Does antidepressant treatment modify the risk of CV mortality?

Methods

Search strategy and selection criteria

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009; Supplemental Appendix A) and followed the International Society for Pharmacoepidemiology recommendations on integrating randomised and non-randomised study data (Sarri et al., 2022). The protocol was preregistered with PROSPERO on 31 July 2020, and last updated on 20 May 2024 (Centre for Reviews and Dissemination, 2020; CRD42020200812). Ethical approval was obtained from the Newcastle University Ethics Committee (reference 34733/2023).

We searched MEDLINE, Embase, Scopus, the Web of Science Core Collection and the Cochrane databases from inception. The first search was conducted on 2 August 2020, with subsequent searches on 6 March 2022 and 31 December 2024 (Supplemental Appendix B for search syntax). No language restrictions were applied. Grey literature sources were consulted for reference checking but not included in the analyses. Systematic reviews were screened for primary studies. We contacted corresponding authors for unpublished data (Supplemental Appendix O).

We included: (1) RCTs or observational studies (cohort or case-control) with ⩾12 months follow-up; (2) adult populations (⩾18 years); (3) reporting CV mortality; (4) comparing either (a) individuals with depression (unipolar or bipolar) versus those without or (b) individuals prescribed antidepressant treatment (pharmacotherapy or neurostimulation) versus placebo, no controlled intervention and/or treatment as usual.

Exclusion criteria were: (1) case reports, letters, abstracts, reviews, and animal studies; (2) mixed populations (e.g., paediatric and adult samples, or depression and bipolar disorder, grouped together) unless relevant data for adults with depression were separately reported; (3) missing control group; (4) outcomes reported only as combined morbidity/mortality endpoints (e.g. MACE) unless CV mortality could be isolated and (5) reports with exclusively aggregated data (e.g. census) where it was not possible to determine the exact numbers of deaths and people exposed.

Depression was defined broadly on inclusion (self-report, health records, rating scales or structured interviews), with details on diagnosis method extracted to allow for sensitivity analysis. We excluded non-physical antidepressant interventions (e.g. exercise, psychotherapy). For multiple reports from the same sample, the most comprehensive publication was used (Supplemental Appendix P).

Screening and data extraction

After removing duplicates in EndNote (Clarivate, 2020), two authors (TDSC, BH, SH, RT, ER, SA) independently screened titles and abstracts using Rayyan (Ouzzani et al., 2016). The same pairs reviewed full-texts, resolving discrepancies by discussion or referral to a third reviewer (IM, SW, AB, or RHM-W). We piloted data extraction forms adapted from Cochrane Collaboration templates (Cochrane, 2024) and subsequently extracted study design, trial name, country of origin, setting, time frame of data collection, primary study population, outcomes, the intervention (e.g. specific antidepressant class or neurostimulation modality), duration of randomised phase (for RCTs), *n* of cases and controls, % of females, mean age (and standard deviation (SD)), depression diagnosis instrument, proportion of sample diagnosed with depression, follow-up duration for mortality assessment, method to determine deaths, raw CV mortality and adjusted effect estimates (when reported). All extracted data were then cross-verified by a second reviewer, with a third resolving discrepancies. Data extraction started on 23 May 2022.

Risk of bias assessment

Risk of bias was assessed using the ROBINS-I (Sterne et al., 2016) for observational studies and the RoB 2 (Sterne et al., 2019) for RCTs (Supplemental Appendix N). One reviewer conducted the initial assessment, which was checked by a second. Disagreements were resolved by a third reviewer. We used the {robvis} package in Rto create 'traffic light' plots (McGuinnes and Higgins, 2021).

Statistical analysis

We conducted separate meta-analyses for RCTs and observational studies comparing: (1) CV mortality in depressed vs. non-depressed individuals; (2) CV mortality in people receiving antidepressant treatment versus placebo, no controlled intervention, and/or treatment as usual.

Data from observational studies were stratified post-hoc by population: community-based cohorts (e.g. UK Biobank), individuals with known CVD or individuals with known diabetes. Likewise, observational data were stratified by antidepressant treatment class: 'any antidepressant', selective serotonin reuptake inhibitors (SSRIs), TCAs, 'other' antidepressants, electroconvulsive therapy (ECT) and vagus nerve stimulation (VNS). Each stratification group was treated as a separate 'study' (*k*) in the meta-analysis models to accommodate different analyses: For example, a single observational study can provide separated outcome data for SSRIs and TCAs. This explains why meta-analytic models can include a higher number of 'studies' (*k*) than the total identified manuscripts. There was no duplication of cases in any of the stratified analyses.

For raw CV mortality counts, we used a random-effects Mantel–Haenszel method ({metabin} function in R), applying a 0.5 continuity correction for zero-event cells, reporting pooled RRs and 95% confidence intervals (CIs).

For maximally adjusted HRs, we applied an inverse-variance random-effects method ({metagen} in R), using log(HR) and standard errors derived from 95% CIs. We excluded studies that

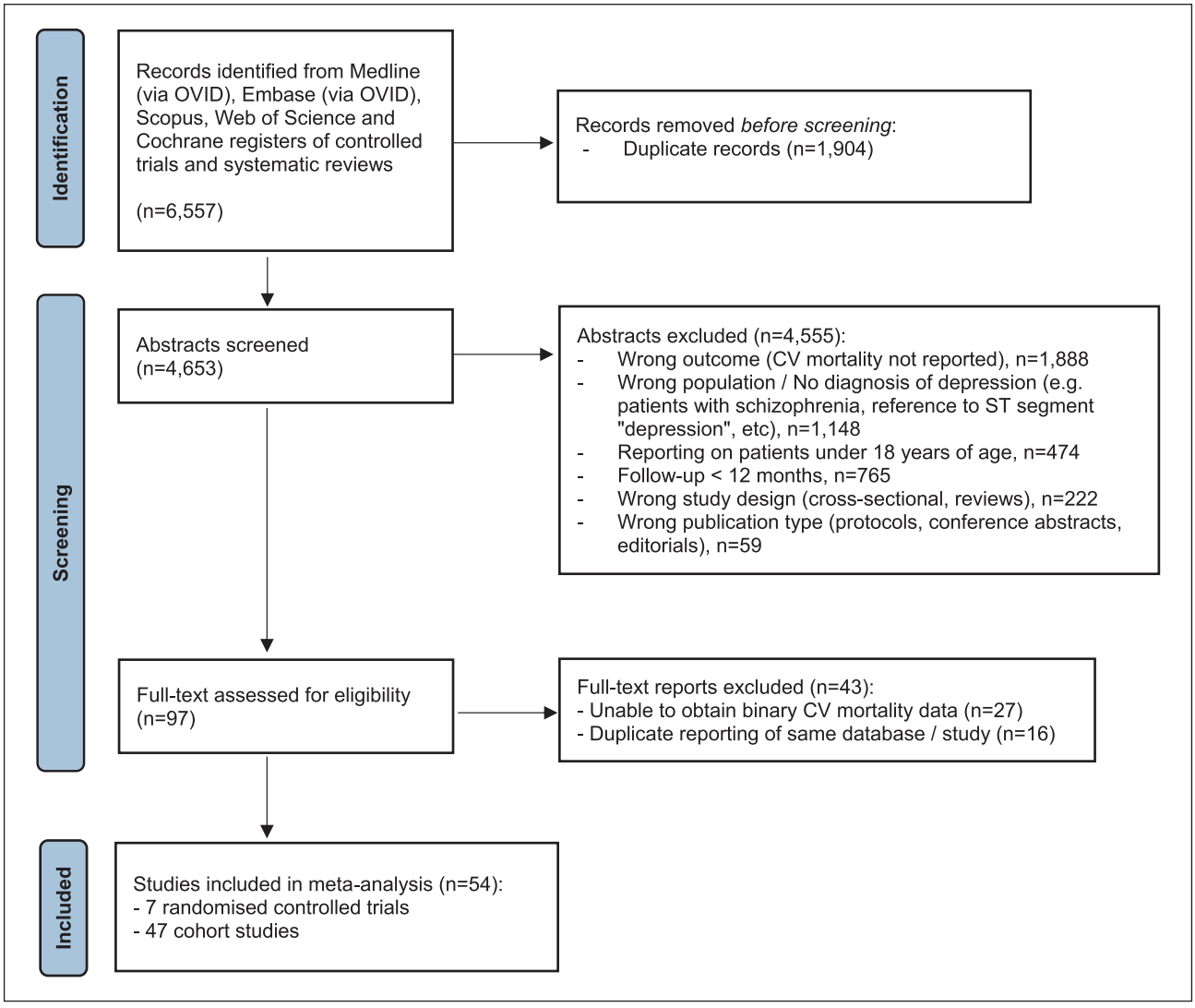

Figure 1. PRISMA flow diagram.
CV: cardiovascular; PRISMA: preferred reporting items for systematic reviews and meta-analyses.

only reported odds ratios or RRs without sufficient data to convert into HRs.

Between-study variance (τ^2) was estimated via the Paule–Mandel method, with heterogeneity assessed using I^2. Knapp–Hartung adjustments were used for CIs. Prediction intervals (PIs) are reported for all models.

Sensitivity analyses involved excluding statistical outliers (95% CI non-overlap) and 'leave-one-out' analyses. Additional subgroup sensitivity analyses examined overall risk of bias, population sampled, depression and mortality assessment methods, proportion of population with known depression diagnosis, treatment group and treatment group assessment measure.

We assessed publication bias with funnel plots and Egger's regression test ($p < 0.05$) when $\geqslant$10 studies were included.

The R code used for analysis and model input datasets is available in a GitHub repository (see section 'Analytic code availability').

Role of the funding source

The funders of this work had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication.

Results

Study selection overview

We identified 6557 records in the initial database search, which included 1904 duplicates (Figure 1). After screening 4653 titles and abstracts, 97 full-text articles were retrieved and assessed for eligibility, with 54 articles meeting the inclusion criteria. These comprised 7 RCTs and 47 cohort studies, collectively including 1,593,722 participants. Unpublished data were obtained for five studies (Supplemental Appendix O). Five studies contributed

data to both the depression diagnosis and antidepressant treatment analyses.

Six studies explicitly excluded bipolar depression. Only three cohort studies reported a substantial proportion of participants with bipolar disorder (Aaronson et al., 2017; Lemogne et al., 2013; Murray-Thomas et al., 2013). Data on bipolar-specific outcomes were insufficient for meta-analysis (Supplemental Appendix Q).

The characteristics of included RCTs and cohort studies are detailed in Tables 1 and 2, respectively, including the raw number of deaths and cases exposed for each study and analysis. The list of all papers included in the meta-analysis is available in Supplemental Appendix D, and Appendices R–X include further details on study characteristics.

Studies comparing CV mortality between people with and without depression ('depression vs no-depression')

RCTs ('depression vs no-depression'). Three RCTs (13,693 participants; 3116 with depression) reported on unadjusted CV mortality data (1261 deaths). All trials were multicentric. Sample sizes ranged from 2481 to 6083 patients. The mean age of the individuals was 63.2 years (SD: 6.2 years), and the mean proportion of female patients was 52.7% (SD: 5.4%). Mean duration of follow-up for ranged from 29 to 130 months. A variety of measures were used to assess depression: one RCT used a validated self-reported rating scale (Berkman et al., 2003), one used a validated instrument delivered during a structured interview (Hazuda et al., 2019), while another used primary care records of previous diagnosis and/or antidepressant use as proxy measure of depression (Chowdhury et al., 2019). Two of the included RCTs controlled for depression severity. In the ENRICHD trial (Berkman et al., 2003) of post-AMI patients, treatment-resistant depression (TRD) was an independent mortality predictor (HR: 1.99, 95% CI: 1.01–3.94; compared to non-TRD). In the Look AHEAD diabetes trial (Hazuda et al., 2019) higher depression scores on the Beck Depression Inventory (BDI) were associated with higher CV risk for males but appeared to be protective for females. Cause of death was assessed in all trials on a case-by-case basis by an independent panel. All RCTs received a risk of bias assessment with 'some concerns' related to risk of 'deviation from intended interventions', as none were double blind. Details from quality assessment are in Supplemental Appendix N.

Pooled estimates for CV mortality unadjusted data ($k=3$) suggested a non-significant increase in risk for participants with depression (RR: 1.13, 95% CI: 0.73–1.74; Figure 2). Two RCTs also provided adjusted HRs, yielding a non-significant association (HR: 1.39, 95% CI: 0.10–20.35; Figure 3). Both models controlled for age, smoking status and a diagnosis of co-morbid type 2 diabetes. Details of additional variables included in each model in Supplemental Appendix T. We did not proceed further with this meta-analysis due to the small number of available RCTs.

Cohort studies ('depression vs no-depression'). Thirty-five cohorts (1,885,437 individuals; 216,524 with depression) contributed data on 28,773 CV deaths (2895 among those with depression). Sample sizes ranged from 89 to 678,831 patients. The mean age of the participants was 62.9 years (SD: 6.3 years), and the mean proportion of female patients was 42% (SD: 25.4%). Two cohorts reported only on females (Pan et al., 2011; Whooley, 1998) and one only on males (Burg et al., 2003). All cohorts were prospective except for Murray-Thomas et al. (2013). The duration of follow-up varied markedly, ranging from 1 to 20 years. A wide variety of measures were used to assess depression and cause of death (Supplemental Appendix V). Risk of bias was 'low' in 14 (26%) cohorts, 'moderate' in 19 (40%), and 'serious' in 14 (30%), commonly due to issues with confounding (e.g. no multivariable adjusted model reported for CV mortality outcome) or lack of evidence of 'intervention balance between groups' (e.g. not controlling for antidepressant treatment). Details from quality assessment are in Supplemental Appendix N.

Pooled estimates for CV mortality unadjusted data ($k=43$) found a significantly higher risk of CV mortality in depressed versus non-depressed participants (RR: 1.53, 95% CI: 1.34–1.75; Figure 4). Removal of six outliers ($k=37$) attenuated heterogeneity (I^2 from 80.7% to 45%) and did not significant change the effect size (RR: 1.49, 95% CI: 1.36–1.63; Supplemental Appendix F). The method for cause of death assessment appeared to have a significant effect on CV mortality estimates. Studies using data from death registers ($k=21$), or a combination of death registers and health records ($k=18$), produced statistically significant pooled estimates of similar magnitude to the full meta-analytic model. The minority of studies which relied solely on health records ($k=2$) or had unclear methods ($k=2$) produced non-statistically significant models (Supplemental Appendix F). Four of these cohort studies (Bruce et al., 2005; Diez-Quevedo et al., 2013; Parker et al., 2011; Podolecki et al., 2017) also reported data for the antidepressant treatment analysis (described below): the pooled effect for these studies (RR: 1.20, 95% CI: 0.75–1.93) was not significantly different from the whole sample ($k=43$) but had lower heterogeneity (I^2 63%). See Supplemental Appendix F for details of sensitivity analysis.

In adjusted analyses ($k=26$ extracted from 20 cohort studies reporting HRs), depression remained associated with higher CV mortality (HR: 1.45, 95% CI: 1.25–1.69; Figure 5). All models controlled for age and sex, 18 (69%) for smoking status, 17 (65%) for a diagnosis of hypertension, 14 (54%) for BMI, 12 (16%) for educational level and marital status, and 11 (42%) for a history of MI, amongst other variables. Only one of the adjusted models (Bruce et al., 2005) controlled for antidepressant treatment, reporting an effect estimate with HR: 1.15 (95% CI: 0.79–1.67). Details of all variables included in each model are in Supplemental Appendix W–X. Removal of five outliers attenuated heterogeneity (I^2 from 83.5% to 57%) and did not significantly change the effect size (pooled RR: 1.45, 95% CI: 1.26–1.67; Supplemental Appendix H).

The pooled effects were of equal direction and magnitude when analysis was broken down into samples of community-dwelling adults without any selected diagnosis apart from depression ($k=10$; pooled HR: 1.29, 95% CI: 1.11–1.51), those with a known additional diagnosis of type 2 diabetes ($k=7$; pooled HR: 1.83, 95% CI: 1.28–2.61) and those with a known diagnosis of pre-existing CVD ($k=9$; pooled HR: 1.39, 95% CI: 0.95–2.05). More details of sensitivity analysis are in Figure 5 and Supplemental Appendix H. When analysis of the CVD cohorts was broken into diagnoses, the five studies with samples of post-AMI patients with comorbid depression (Bot et al., 2012; Dickens et al., 2008; Lauzon et al., 2003; Lespérance et al., 2002; Welin et al., 2000) produced significant pooled estimates of higher CV mortality when compared to no-depression (HR: 2.01, 95% CI: 1.25–3.25), with relatively low heterogeneity (I^2 28%). The four

Table 1. Summary description for included RCTs.

Author (year)	Trial name	Trial intervention	Data used for depression diagnosis meta-analysis (number of deaths and n of exposed)	Data used for antidepressant treatment meta-analysis (number of deaths and n of exposed)	Notes on RCT design/analysis in included paper	Country/region and setting	Study sample at a glance
Angermann et al. (2016)	Morbidity, mortality, and mood in depressed heart failure patients (MOOD-HF)	Escitalopram (10–20 mg OD) versus placebo	n/a	See Table 2 in source paper: Escitalopram group: 10 deaths (out of 185 cases). Placebo group: 9 deaths (out of 187 cases)	Double blind	Germany, multicentric	Cardiac, all outpatients with HF open to specialist clinic, all with depression
Berkman et al. (2003)	Enhancing recovery in coronary heart disease patients (ENRICHD)	CBT-based psychosocial intervention versus TAU	Additional unpublished data: Cases (major depression): 84 deaths (out of 955 cases); controls (including 'isolated', dysthymia and minor depression): 127 deaths (out of 1526 cases)	n/a	Randomised open-label with blinded assessors. Secondary data analysis	USA, multicentric	Cardiac, all post-AMI inpatients, all with depression
Chowdhury et al. (2019)	Second Australian National Blood Pressure Study (ANBP2)	Either angiotensin converting enzyme inhibitors or thiazide diuretic-based treatment versus TAU	See Table 2 in source paper: Cases ('all depression'): 227 deaths (out of 1229 cases); controls ('no depression'): 713 deaths (out of 4854 cases)	n/a	Randomised open-label with blinded assessors. Secondary data analysis	Australia, multicentric	Cardiac, community sample with hypertension
Eisenberg et al. (2013)	Zyban as an effective smoking cessation aid for patients following an acute coronary syndrome (ZESCA)	Bupropion SR (150 mg OD for 3 days, followed by 150 mg BD for the remainder of trial) versus placebo. Both arms with counselling	n/a	See Table 2 in source paper: Bupropion: 4 deaths (out of 192 cases); placebo: 2 deaths (out of 200 cases). All deaths during the 9-week treatment period. All events were deemed to not be related to study medication	Double blind	USA, Canada, Bangladesh, India, Iran, Pakistan and Tunisia	Cardiac, all post-AMI inpatient smokers
Hazuda et al. (2019)	Action for health in diabetes (look AHEAD)	(i) Intensive lifestyle intervention designed to achieve and maintain weight loss by decreased caloric intake and (ii) increased physical activity versus a control condition of diabetes support and education, versus TAU	Additional unpublished data: Cases (BDI $\geqslant$ 10): 17 deaths (out of 932 cases); controls (BDI $<$ 10): 93 deaths (out of 4197)	Additional unpublished data: Antidepressant use: 21 deaths (out of 848 cases); no antidepressant: 89 deaths (out of 4123 cases)	Randomised open-label with blinded assessors. Secondary data analysis	USA, multicentric. Outpatients in the community with type 2 diabetes	Diabetes type 2, community sample
Kim et al. (2018)	Escitalopram for depression in ACS (EsDEPACS)	Escitalopram (5–20 mg OD) versus placebo	n/a	See eTable 2 (supplementary) in source paper: Escitalopram: 16 deaths (out of 149 cases); placebo: 20 deaths (out of 151 cases)	Double blind. Secondary data analysis (per protocol)	South Korea (1 centre)	Cardiac, all post-AMI inpatients, all with depression
Rigotti et al. (2006)	n/a	Bupropion SR (150 mg OD for 3 days, then BD for remained of trial) versus placebo. Both arms with counselling	n/a	See Table 3 in source paper: Bupropion: 0 deaths (out of 124 cases); placebo: 1 death (out of 124 cases)	Double blind	USA, multicentric	Cardiac, all post-AMI inpatient smokers

ACS: acute coronary syndrome; AMI: acute myocardial infarction; BD: bi-daily; BDI: Beck Depression Inventory; CBT: cognitive behavioural therapy; HF: heart failure; OD: once daily; mg: milligrams; RCT: randomised controlled trial; TAU: treatment as usual; USA: United States of America.

Table 2. Summary description for included cohort studies.

Author (year)	Study/database	Cohort population at a glance	Study aims of relevance	Data used for depression diagnosis meta-analysis (no. of deaths and no. of exposed)	Data used for antidepressant treatment meta-analysis (no. of deaths and no. of exposed)	Country/region
Aaronson et al. (2017)	LivaNova D23 database	Patients with TRD	Assess mortality in a group of depressed patients treated with VNS or TAU	n/a	See page 4 of online supplement in source paper: VNS group: 0 deaths (out of 494 cases); TAU group: 2 deaths (out of 301 cases)	USA, multi-centre
Ahmadi et al. (2016)	n/a	Depressed patients	Explore the efficacy of ECT on long-term clinical outcome of comorbid MDD and PTSD	n/a	See Table 1 in source paper: ECT group: 4 deaths (out of 92 cases); no ECT group: 390 deaths (out of 3393 cases)	USA
Ahola et al. (2012)	Finnish diabetic nephropathy study (FinnDiane)	Community-dwelling adults with type 1 diabetes	Explore the effects of depression on cause-specific mortality in people with diabetes	n/a	See Table 3 in source paper: For those buying ADs at baseline or follow-up: 56 deaths (out of 175 cases); for those with no AD purchases: 126 deaths (out of 280 cases)	Finland, multi-centre
Ahto et al. (2007)	n/a	Community-dwelling elderly adults free of CHD at baseline	Describe associations between symptoms of depression and the risk of death from CHD or MI	See Table 2 in source paper: Non-depressed males: 47 deaths (out of 244 cases); depressed males: 14 deaths (out of 38 cases). Non-depressed females: 39 deaths (out of 316 cases); depressed females: 14 deaths (out of 62 cases)	n/a	Finland
Avery et al (1976)	n/a	Depressed inpatients	Assess mortality in a group of depressed inpatients treated with ECT, antidepressants or neither treatment	n/a	See Table 1 in source paper: ECT: 0 deaths (out of 135 cases); ADs: 0 deaths (out of 71 cases); ECT + ADs: 3 deaths (out of 122 cases). Controls: 3 deaths (70 cases)	USA
Baker et al. (2001)	n/a	Cardiac, all patients post-coronary bypass surgery	Determine if preoperative depressive symptoms result in an increased risk of late mortality following CABG surgery	See second paragraph of Results section in reference paper: Depressed: 1 death (out of 24 cases); non-depressed: 1 death (out of 134 cases)	n/a	Australia
Bansal et al. (2022)	UK Biobank	Community-dwelling adults	Investigate the association between antidepressant use and CVD mortality	n/a	For numerators (deaths) see 10-year mortality estimates on Table 3 from reference paper. For denominators (number of exposed) see Supplemental Appendix 2 from reference paper. Prescribed any AD: 65 deaths (out of 7240 cases) – of these, 50 deaths in those prescribed SSRIs (out of 5941 cases) and 15 deaths in those prescribed 'other' ADs (out of 1299 cases). Not prescribed any AD: 389 deaths (out of 96,327)	UK, multicentre
Barefoot et al. (1996)	n/a	Cardiac, all patients post first cardiac catheterisation	Explore the relationship between depression and long-term mortality in patients admitted for their first cardiac catheterisation	For numerators (deaths) see first paragraph of Results section in reference paper. For denominators (number of exposed) see Table 1 in reference paper. Non-depressed: 28 deaths (out of 785 cases); mild depression: 141 deaths (out of 333 cases); moderately to severely depressed: 73 deaths (out of 141 cases)	n/a	USA
Bingefors et al. (1996)	n/a	Community-dwelling adults	Assess long-term mortality in a group of individuals prescribed anti-depressants and controls	n/a	See Table 2 in reference paper: Treated with ADs ('All ADs'): 54 deaths (out of 456 cases); not treated with ADs: 98 deaths (out of 912 cases)	Sweden

(continued)

Table 2. (continued)

Author (year)	Study/database	Cohort population at a glance	Study aims of relevance	Data used for depression diagnosis meta-analysis (no. of deaths and no. of exposed)	Data used for antidepressant treatment meta-analysis (no. of deaths and no. of exposed)	Country/region
Bot et al. (2012)	Depression and myocardial infarction study (DepreMI) and the myocardial infarction and depression-intervention trial (MIND-IT)	Cardiac, all patients post-MI, some with diabetes type 2 others without	Examine the joint association of diabetes and depression with post-MI mortality	See Table 2 in reference paper: No depression, no diabetes: 84 deaths (out of 1673 cases); diabetes, no depression: 18 deaths (out of 210 cases); depression, no diabetes: 51 deaths (out of 544 cases); depression and diabetes: 22 deaths (out of 98 cases)	n/a	Netherlands, multicentre
Bruce et al. (2005)	Fremantle diabetes study	Community-dwelling adults with type 2 diabetes	Assess the impact of depression and antidepressants on cardiac mortality in people with diabetes	Additional unpublished data: Depressed group: 60 deaths (out of 400 cases); not depressed group: 92 deaths (out of 871 cases)	Additional unpublished data: Cardiac deaths among those depressed, by AD treatment status: Prescribed AD=6 deaths (out of 49 cases); not prescribed ADs=54 deaths (out of 351 cases)	Australia, multicentre
Burg et al. (2003)	n/a	Cardiac, all patients with non-urgent coronary artery bypass graft surgery	Determine the contribution of presurgical symptoms of depression to cardiac mortality after CABG	See first paragraph of Results section in reference paper: Depressed: 4 deaths (out of 25 cases); not depressed: 1 death (out of 64 cases)	n/a	USA
Cocchio et al. (2019)	n/a	Cardiac, all patients post-MI	Examine the relationship between antidepressant use prior to AMI and post-AMI mortality	n/a	See Table 2 in reference paper: AD users: 96 deaths (out of 281 case); non-users: 760 deaths (out of 3158 cases)	Italy, multicentre
Coleman et al. (2013)	Pathways epidemiologic study	Community-dwelling adults with type 2 diabetes	Examine the relationships between depression status and mortality in people with type 2 diabetes	For numerators (deaths) see Table 3 in reference paper. For denominators (number of exposed) see Table 1 in reference paper. Not depressed: 337 deaths (out of 3279 cases); minor depression: 42 deaths (out of 343 cases); major depression: 58 deaths (out of 495 cases)	n/a	USA, multicentre
Connerney et al. (2001)	n/a	Cardiac, all patients post-coronary bypass surgery	Assess the effect of depression on outcomes after CABG surgery	See fourth paragraph of Results section in reference paper: MDD group: 1 death (out of 63 cases); not depressed group: 7 deaths (out of 246 cases)	n/a	USA
Coupland et al. (2011)	QResearch database	Community-dwelling adults with depression	Determine the impact of antidepressants on the mortality of older people with depression	n/a	For numerators (deaths) see Table 26 in reference paper. For denominators (number of exposed or 'No. of patients who received at least one prescription') see Table 4 in reference paper. Prescribed SSRIs: 21 deaths (out of 42,575 cases); prescribed TCAs: 14 deaths (out of 29,085 cases); prescribed 'other' ADs: 8 deaths (out of 10,485 cases); not currently prescribed ADs: 40 deaths (out of 6708 cases)	UK
Cummings et al. (2016)	REasons for geographic and racial differences in stroke (REGARDS) study	Community-dwelling adults, some with type 2 diabetes, others without	Examine the association between the presence of depressive symptoms at baseline and risk of incident CV events	See Table 2 in reference paper: Depression and diabetes: 23 deaths (out of 416 cases); diabetes, no depression: 81 deaths (out of 2583 cases); depression, no diabetes: 23 deaths (out of 1118 cases); no depression and no diabetes: 237 deaths (out of 12,620 cases).	n/a	USA, multicentre

(continued)

Table 2. (continued)

Author (year)	Study/database	Cohort population at a glance	Study aims of relevance	Data used for depression diagnosis meta-analysis (no. of deaths and no. of exposed)	Data used for antidepressant treatment meta-analysis (no. of deaths and no. of exposed)	Country/region
Damen et al. (2013)	Rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry	Cardiac, all patients with coronary artery disease treated with stent	Examine the association of depression with mortality in patients treated with PCI	See last paragraph of Results section (point 3.2) in reference paper: Depressed: 15 deaths (out of 197 cases); not depressed: 31 deaths (out of 633 cases)	n/a	The Netherlands
Dickens et al. (2008)	n/a	Cardiac, all patients post-MI	Assess whether cardiac mortality is associated with depression that develops in the months post-MI compared with depression that predated the MI	See Table 2 in reference paper: Not depressed: 20 deaths (out of 273 cases); pre-MI depression: 2 deaths (out of 96 cases); new onset depression: 10 deaths (out of 71 cases)	n/a	UK
Diez-Quevedo et al. (2013)	n/a	Cardiac, all HF outpatients (any aetiology)	Assess the association of depression and the use of antidepressants with long-term mortality in people with heart failure	Additional unpublished data: Depressed: 108 deaths (out of 424 cases); non-depressed: 160 deaths (out of 593 cases)	Additional unpublished data: Any AD prescription: 83 deaths (out of 304 cases); any SSRI prescription: 78 deaths (out of 282 cases); any SNRI prescription: 4 deaths (out of 40 cases); any TCA prescription: 4 deaths (out of 9 cases); any mirtazapine prescription: 1 death (out of 12 cases)	Spain
Egede et al. (2005)	National Health and Nutrition Examination Survey I epidemiologic follow-up study (NHANES I)	Community-dwelling adults, some with type 2 diabetes, others without	Evaluate the effect of depression on coronary heart disease mortality in people with and without type 2 diabetes	See Table 2 in reference paper: No diabetes, not depressed: 301 deaths (out of 7032 cases); diabetes, not depressed: 55 deaths (out of 453 cases); depressed, no diabetes: 125 deaths (out of 2278 cases); depressed and diabetes: 41 deaths (out of 262 cases)	n/a	USA
Feng et al. (2023)	National health and nutrition examination survey (NHANES)	Community-dwelling adults with type 2 diabetes	Evaluate the impact of depression on CV mortality in people with type 2 diabetes	For numerators (deaths) see Table 3 in reference paper. For denominators (number of exposed) see Table 1 in reference paper. Total depression: 49 deaths (out of 722 cases); no depression: 274 deaths (out of 4973 cases)	n/a	USA
Frasure-Smith et al (1999)	Emotions and prognosis post-infarct (EPPI) study and Montreal heart attack readjustment trial (M-HART) trial	Cardiac, all patients post-MI	Examine whether there are gender differences in the prevalence and prognostic importance of depression during hospitalisation for an AMI	See Table 4 in reference paper. Depressed: 22 deaths (out of 290 cases); not depressed: 15 deaths (out of 606 cases)	n/a	Canada, multicentre
Hamer et al. (2011)	Scottish health survey	Community-dwelling adults without known CVD	Assess the association between antidepressant use and risk of CVD mortality	n/a	See Table 3 in reference paper: AD users: 27 deaths (out of 729 cases) – among these: SSRI=6 deaths (out of 299 cases); TCAs=18 deaths (out of 324 cases); other ADs=3 deaths (out of 106 cases). Non-users: 348 deaths (out of 14,055 cases)	UK, multicentre
Jeffery et al. (2024)	Clinical practice research datalink (CPRD)	Community-dwelling adults with type 2 diabetes and depression	Investigate the association between antidepressant prescribing and mortality in adults with comorbid depression and type 2 diabetes	n/a	See Table 2 in reference paper: total cases for each class is sum of 'cases' (those who died) and 'controls' (those who did not die). Any AD: 1152 deaths (out of 3943 cases); no AD: 483 deaths (out of 3566 cases)	UK, multicentre
Lane et al. (2001)	n/a	Cardiac, all patients post-MI	Examine the relationship between depression and mortality in patients hospitalised for AMI	See Table 3 in reference paper: Depressed: 9 deaths (out of 87 cases); not depressed: 18 deaths (out of 197 cases)	n/a	UK

(continued)

Table 2. (continued)

Author (year)	Study/database	Cohort population at a glance	Study aims of relevance	Data used for depression diagnosis meta-analysis (no. of deaths and no. of exposed)	Data used for antidepressant treatment meta-analysis (no. of deaths and no. of exposed)	Country/region
Lauzon et al. (2003)	n/a	Cardiac, all patients post-MI	Examine the relationship between depression and mortality in patients hospitalised for AMI	See Table 3 in reference paper: BDI $\geqslant$ 10: 13 deaths (out of 190 cases); BDI $<$ 10: 15 deaths (out of 375 cases)	n/a	Canada
Lemogne et al. (2013)	French GAZEL cohort	Community-dwelling adults	Examine the risk of mortality associated with depressive disorders, other SMD and controls with no SMD	See Table 2 in reference paper: Depressed: 53 deaths (out of 4212 cases); no SMD: 199 deaths (out of 16261 cases)	n/a	France, multicentre
Lespérance et al. (2002)	n/a	Cardiac, all patients post-MI	Examine the relationship between depression symptoms and long-term cardiac mortality post-MI	See Table 2 in reference paper: BDI $<$ 5: 24 deaths (out of 335 cases); BDI 5–9: 37 deaths (out of 271 cases); BDI 10–18: 39 deaths (out of 211 cases); BDI $\geqslant$ 19: 21 deaths (out of 79 cases)	n/a	USA
Meng et al. (2020)	Chinese Kadoorie biobank (CKB) and Dongfeng-Tongji (DFTJ) cohorts	Community-dwelling adults	Investigate whether depression is associated with CVD mortality in community-dwelling populations	For numerators (deaths) see Table 2 in reference paper. For denominators (number of exposed in respective cohort) see Table 1 in reference paper. CKB cohort: Depression: 147 deaths (out of 3280 cases); no depression: 17501 deaths (out of 509,432 cases). DFTJ cohort: Depression: 241 deaths (out of 4723 cases); no depression: 772 deaths (out of 21,575 cases)	n/a	China, multicentre
Murray-Thomas et al. (2013)	General practice research database (GPRD)	Community-dwelling adults	Assess cardiac mortality among antipsychotic users relative to nonusers	For numerators (deaths) see Table 4 in reference paper. For denominators (number of exposed) see Table 3 in reference paper. Major depression (non-AP users): 484 deaths (out of 134,105 cases); community-dwelling controls: 1363 deaths (out of 544,726 cases)	n/a	UK, multicentre
O'Connor et al. (2008)	n/a	Cardiac, all patients with HF with LVEF $<$35%	Evaluate the effect of depression and antidepressant use on survival of patients with HF	For numerators (deaths) see third paragraph of Results section (under 'Antidepressant use, depression, and other risk factors for mortality') in reference paper. For denominators (number of exposed) see second paragraph of Results section (under 'Baseline characteristics') in reference paper. Depressed: 161 deaths (out of 302 cases); not depressed: 268 deaths (out of 703 cases)	n/a	USA
Pan et al. (2011)	Nurses' Health Study (NHS)	Community-dwelling adults, some with type 2 diabetes, others without	Evaluate the individual and joint effects of depression and diabetes on CVD mortality rate	For numerators (deaths) see Table 2 in reference paper. For denominators (number of exposed) see Table 1 in reference paper. Depression: 265 deaths (out of 12,120 cases); no depression: 714 deaths (out of 66,162 cases)	n/a	USA

(continued)

Table 2. (continued)

Author (year)	Study/database	Cohort population at a glance	Study aims of relevance	Data used for depression diagnosis meta-analysis (no. of deaths and no. of exposed)	Data used for antidepressant treatment meta-analysis (no. of deaths and no. of exposed)	Country/region
Parker et al. (2011)	n/a	Cardiac, patients post-MI or with acute angina	Evaluate the relationship between the timing of a depression diagnosis, antidepressant prescription and CV mortality outcomes post-MI	See Table 1 in reference paper. No depression: 27 deaths (out of 265 cases); prior depression: 6 deaths (out of 77 cases); incident depression: 4 deaths (out of 24 cases); recurrent depression: 2 deaths (out of 20 cases); continuing depression: 3 deaths (out of 27 cases); non-continuing depression: 2 deaths (out of 23 cases)	See Table 3 in reference paper. Prescribed SSRI: 4 deaths (out of 15 cases); not prescribed SSRI: 40 deaths (out of 421 cases). Prescribed TCA/MAOI: 0 deaths (out of 12 cases); not prescribed TCA/MAOI: 44 deaths (out of 424 cases)	Australia
Penninx et al. (2001)	Longitudinal aging study Amsterdam (LASA)	One sub-sample with cardiac disease (includes coronary heart disease – angina or hx of MI – and heart failure), another sub-sample of community-dwelling adults	Examine and compare the effect of depression on cardiac mortality in community-dwelling person with and without cardiac disease	See Table 2 in reference paper. No cardiac disease: No depression = 69 deaths (out of 2072 cases); minor depression = 18 deaths (282 cases); major depression = 4 deaths (out of 43 cases). With cardiac disease: No depression = 67 deaths (out of 361 cases); minor depression = 21 deaths (out of 78 cases); major depression = 5 deaths (out of 11 cases)	n/a	The Netherlands, multicentre
Pequignot et al. (2013)	The Three City Study	Community-dwelling adults with no history of CHD, stroke or dementia	Investigate the association between baseline depressive symptoms and antidepressant use on CHD and stroke mortality	See Table 3 in reference paper. Depressed: 26 deaths (out of 1392 cases); non-depressed: 43 deaths (out of 5430 cases)	n/a	France, multicentre
Podolecki et al. (2024)	n/a	Cardiac, patients with degenerative aortic valve stenosis, AMI or chronic coronary artery disease	Assess the relationship between depression and CV outcomes, in patients who underwent CV intervention at a cardiac unit	See Table 3 in reference paper. Depressed (HAM-D $\geqslant$ 7): 4 deaths (out of 57 cases); non-depressed: 1 death (out of 76 cases)	n/a	Poland
Podolecki et al. (2017)	n/a	Cardiac resynchronisation therapy recipients (>60% with ischemic HF)	Assess the incidence and clinical impact of depression as well as the role of escitalopram in patients with HF	See Table 3 in reference paper. Depression: 28 deaths (out of 135 cases); no depression: 17 deaths (out of 150 cases)	See Table 4 in reference paper. Escitalopram: 12 deaths (out of 68 cases); no AD (with depression diagnosis): 16 deaths (out of 67 cases)	Poland
Prigge et al. (2022)	UK Biobank	Community-dwelling adults, some with type 2 diabetes, others without	Investigate the risks of all-cause and cause-specific mortality among people with diabetes and depression	See Table 1 in reference paper. No depression nor diabetes: 1947 deaths (out of 431,765 cases); depression (no diabetes): 277 deaths (out of 41,791 cases); diabetes (no depression): 499 deaths (out of 22,677 cases); depression and diabetes: 104 deaths (out of 3597 cases)	n/a	UK, multicentre
Rogal et al. (2013)	n/a	Post-liver transplant patients	Investigate the impact of early treatment of depression in post-transplant survival	See Table 3 in reference paper. Non-depressed: 7 deaths (out of 95 cases); treated depressed: 3 deaths (out of 31 cases); untreated depressed: 1 death (out of 41 cases)	n/a	USA
Shiotani et al. (2002)	Osaka acute coronary insufficiency study (OACIS) group	Cardiac, all patients post-AMI	Investigate the impact of the depressive symptoms on prognosis of patients with AMI	See Table 2 in reference paper. Depressed: 4 deaths (out of 438 cases); not depressed: 1 death (out of 604 cases)	n/a	Japan

(continued)

Table 2. (continued)

Author (year)	Study/database	Cohort population at a glance	Study aims of relevance	Data used for depression diagnosis meta-analysis (no. of deaths and no. of exposed)	Data used for antidepressant treatment meta-analysis (no. of deaths and no. of exposed)	Country/region
Smoller et al. (2009)	Women's Health Initiative (WHI)	Community-dwelling adults	Examine the prospective association between new antidepressant use and CV mortality in a cohort of postmenopausal women	n/a	See Table 2 in reference paper. SSRIs: 153 deaths (out of 2153 cases); TCAs: 69 deaths (out of 958 cases); other ADs: 47 deaths (out of 716 cases); controls: 3018 deaths (out of 70,497 cases)	USA, multicentre
Surtees et al. (2008)	European prospective investigation into cancer (EPIC-Norfolk)	Community-dwelling adults without known heart disease at baseline	Investigate the association between major depressive disorder and mortality from ischemic heart disease	n/a	For numerators (deaths) see Table 3 in reference paper. For denominators (number of exposed) see Table 1 in reference paper. AD users: 13 deaths (out of 201 cases); non-users: 261 deaths (out of 829 cases)	UK, multicentre
Tousoulis et al. (2008)	n/a	Cardiac, all patients with end-stage severe HF	Examine the impact of major depression on long-term survival of patients with end-stage severe heart failure	For numerators (deaths) see fourth paragraph of Results section (under 'Depression and Long-Term Survival in End-stage Heart Failure') in reference paper. For denominators (number of exposed) see Table 2 in reference paper. Depression: 106 deaths (out of 154 cases); no depression: 61 deaths (out of 96 cases)	n/a	Greece
Welin et al. (2000)	n/a	Cardiac, all patients post-MI	Examine if prognosis after a MI is related to psychological stress, lack of social support, anxiety and/or depression	See Table 1 in reference paper. Depressed: 26 deaths (out of 98 cases); non-depressed: 14 deaths (out of 169 cases)	n/a	Sweden
Wheeler et al. (2012)	Identifying depression as a comorbid condition (IDACC) database	Cardiac, all patients post-MI	Determine whether depression during hospitalisation for AMI predicts cardiac mortality	See Table 2 in reference paper. Not depressed: 12 deaths (out of 204 cases); mildly depressed: 2 deaths (out of 76 cases); moderately to severely depressed: 8 deaths (out of 56 cases)	n/a	Australia, multicentre
Whooley (1998)	n/a	Community-dwelling adults	Examine the association between depression symptoms and mortality from specific causes	For numerators (deaths) see Table 3 in reference paper. For denominators (number of exposed) see first paragraph in Results section. Depression: 52 deaths (out of 473 cases); no depression: 273 deaths (out of 7518 cases)	n/a	USA, multicentre

AD: antidepressants; AMI: acute myocardial infarction; BDI: Beck Depression Inventory; CABG: coronary artery bypass graft; CHD: coronary heart disease; CV: cardiovascular; CVD: cardiovascular disease; ECT: electroconvulsive therapy; HF: heart failure; LVEF: left ventricular ejection fraction; MAOI: monoamine oxidase inhibitors; MDD: major depressive disorder; MI: myocardial infarction; PCI: percutaneous coronary intervention; PTSD: post-traumatic stress disorder; SMD: severe mental disorders; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant; TRD: treatment resistant depression; VNS: vagus nerve stimulation; ZSDS: Zung Depression Scale.

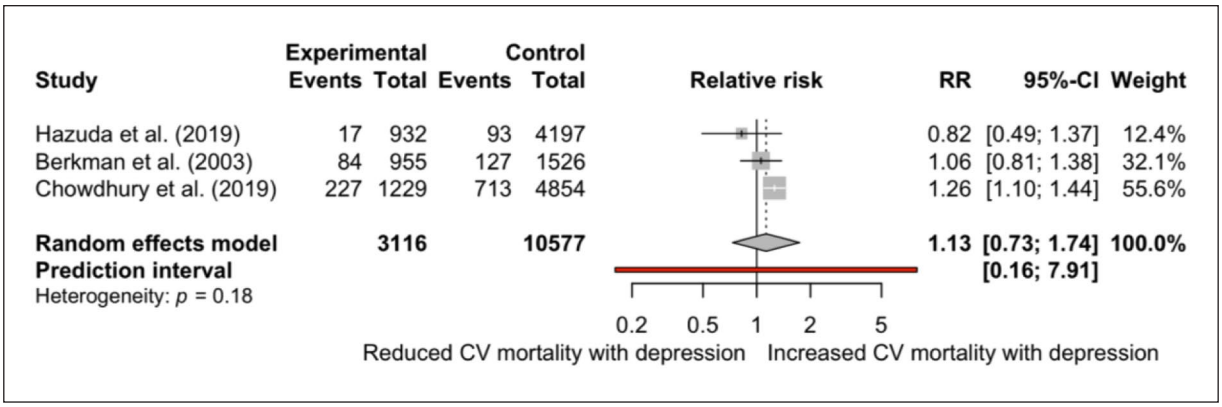

Figure 2. Forest plot of RCTs comparing unadjusted (raw) CV mortality between people with and without depression ($k=3$).
CI: confidence interval; CV: cardiovascular; RR: relative risk.

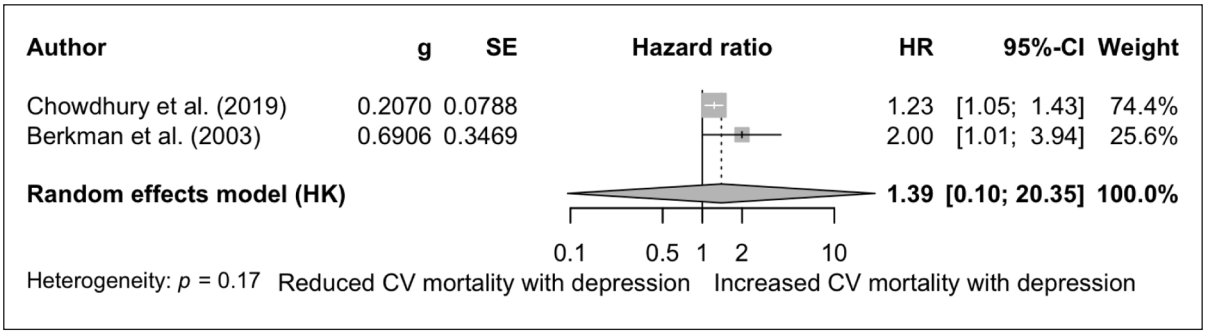

Figure 3. Forest plot of RCTs comparing multivariate CV mortality models between people with and without depression ($k=2$).
CI: confidence interval; CV: cardiovascular; HR: hazard ratio; SE: standard error.

studies (Burg et al., 2003; Diez-Quevedo et al., 2013; O'Connor et al., 2008; Tousoulis et al., 2008) reporting on patients with heart failure produced non-significant pooled estimates (HR: 1.01, 95% CI: 0.67–1.51), with high heterogeneity (I^2 72%). The publication bias assessment showed significant funnel plot asymmetry for adjusted models, suggesting that smaller studies showing lower (or non-significant) HRs may be missing or unpublished (Supplemental Appendix M).

Some of the cohort studies showed evidence to suggest a significant relation between severity of depression and mortality: Penninx et al. (2001), including multivariate models comparing those with and without known cardiac disease; Barefoot et al. (1996), of patients with coronary artery disease, including a multivariate model controlling for CV risk factors; Lesperance et al. (2002), of post-AMI patients; and Coleman et al. (2013), of patients with diabetes. However, the Wheeler et al. (2012) cohort of post-AMI patients did not find such an association between severity of depression and CV mortality. Some of the studies included in the systematic review, from samples of patients with known high blood pressure (Chowdhury et al., 2019) or post-AMI (Dickens et al., 2008; Parker et al., 2011), also distinguished between past and current depression, broadly showing that 'new onset' or 'incident' depression (vs know pre-existing depression) was associated with a higher risk of CV mortality.

Studies comparing CV mortality between people receiving antidepressant treatments and placebo, no controlled intervention, and/or treatment as usual ('antidepressant vs no-antidepressant')

RCTs ('antidepressant vs. no-antidepressant'). Five RCTs (6283 participants; 1498 receiving antidepressants) reported 172 CV deaths. All trials were multicentric apart from Kim et al. (2018). The included RCTs reported on bupropion (Eisenberg et al., 2013; Rigotti et al., 2006), escitalopram (Angermann et al., 2016; Kim et al., 2018) and several antidepressant classes within an intensive lifestyle intervention in the Look AHEAD type 2 diabetes trial (Hazuda et al., 2019). Sample sizes ranged from 248 to 4971 patients. This distribution is skewed by the large sample size of the Look AHEAD trial (Hazuda et al., 2019): if this is excluded, the mean sample size is 328, with a SD of 66.4. The mean age of patients was 58.1 years (SD: 2.9 years), and the mean proportion of females was 34.1% (SD: 14.9%). The duration of randomised phases ranged from 9 weeks to a median of 9.6 years. The mean duration of follow-up for mortality assessment ranged

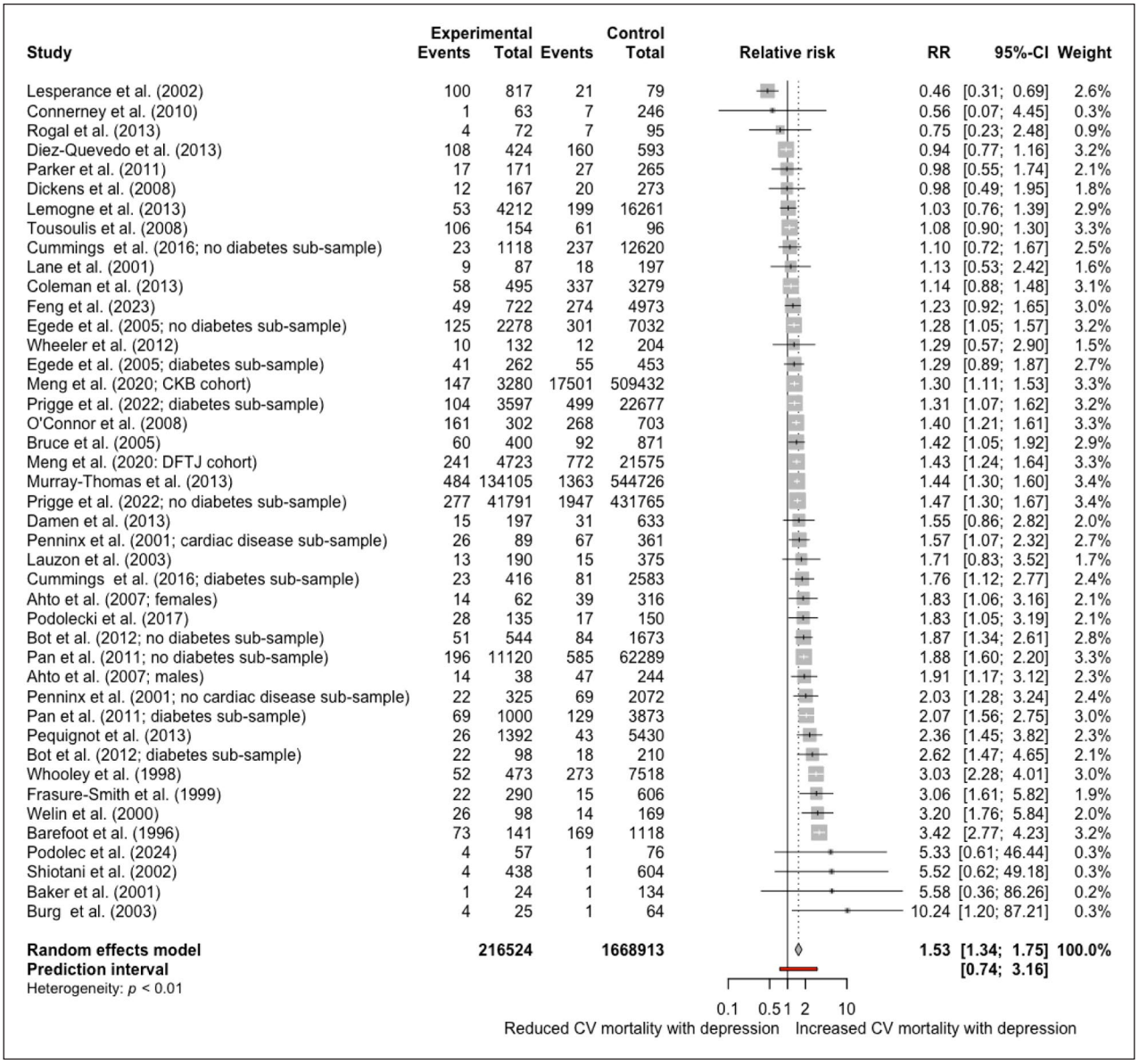

Figure 4. Forest plot of cohort studies comparing unadjusted (raw) CV mortality between people with and without depression ($k=43$).
CI: confidence interval; CV: cardiovascular; RR: relative risk.

from 1 to 9.6 years. A variety of validated instruments were used to assess depression: four of the trials used different versions of the BDI and one (Angermann et al., 2016) delivered the Structured Clinical Interview for DSM-IV together with a Patient Health Questionnaire 9-item version and Montgomery–Åsberg Depression Rating Scale. Cause of death was assessed in all trials on a case-by-case basis. Four RCTs were assessed as 'low' risk of bias. Only one (Hazuda et al., 2019) had 'some concerns', which, notably, was the only open trial (Supplemental Appendix N).

Pooled unadjusted data suggested no significant effect of antidepressant treatment on CV mortality (RR: 1.04, 95% CI: 0.75–1.45; Figure 6), with minimal heterogeneity ($I^2=0\%$). Only one RCT (Kim et al., 2018) reported a multivariate adjusted model (controlling for age, sex, BMI, blood pressure, lipids, smoking status and diabetes, amongst other variables; see Supplemental Appendix T for details) which estimated the HR of CV death in people with post-AMI depression treated with escitalopram (vs placebo) as 0.79 (95% CI: 0.41–1.52).

We did not proceed further with this meta-analysis due to the small number of available RCTs.

Cohort studies ('antidepressant vs no-antidepressant'). Sixteen cohorts ($N=582{,}128$; 100,346 receiving antidepressant treatments) reported 15,535 CV deaths, including 1886 among antidepressant users. Sample sizes ranged from 135 to 102,268. Mean age was 59.7 years (SD: 10.6); mean female proportion was 55.4% (SD: 21.6%). One cohort included only females (Smoller et al., 2009). All cohorts reporting on antidepressant

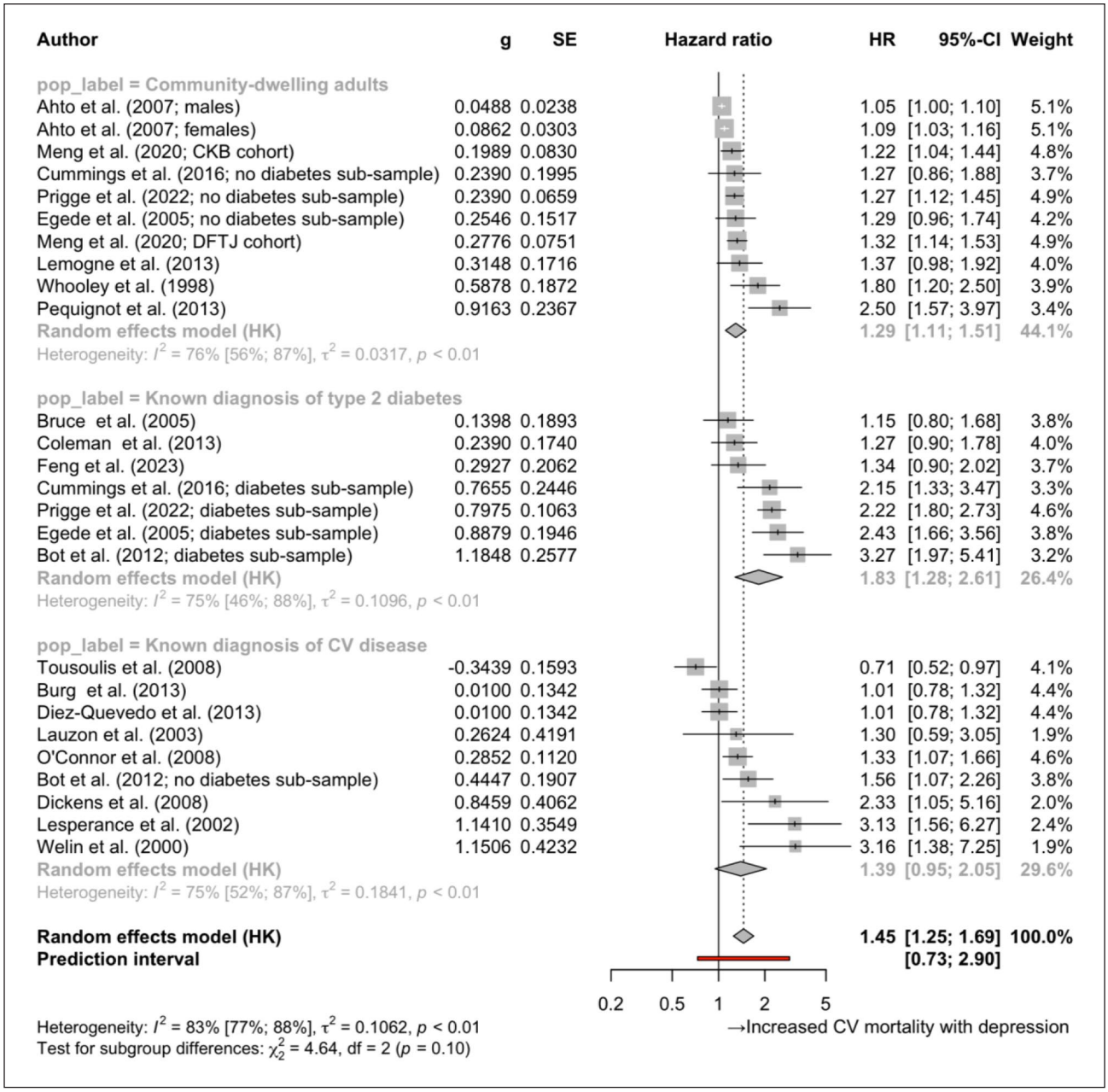

Figure 5. Forest plot of cohort studies comparing multivariate CV mortality models between people with and without depression (k=26).
CI: confidence interval; CV: cardiovascular; HR: hazard ratio; SE: standard error.

treatment were prospective except for two retrospective cohorts nested in a case-control design (Ahmadi et al., 2016; Jeffery et al., 2024), a retrospective review of health records (Cocchio et al., 2019) and one using the UK QResearch database (Coupland et al., 2011). Two studies were non-randomised prospective cohorts with comparator groups, where treatment was allocated by clinicians as part of usual care (Aaronson et al., 2017; Podolecki et al., 2017). Overall, the duration of follow-up varied significantly, ranging 3–10 years. A wide variety of methods were used to ascertain the depression diagnosis, antidepressant treatments and mortality (Supplemental Appendix V). All cohorts investigated the effects of antidepressant treatments but the proportion of the sample with a known diagnosis of depression was variable (mean 41% of the sample): in 7 studies it was 100% and in 3 studies it was ⩽50% of the sample. In the remaining six studies, there was no information on depression diagnosis, and the analysis was based on the use of an antidepressant irrespective of diagnosis: five studies (Ahola et al., 2012; Bansal et al., 2022; Bingefors et al., 1996; Cocchio et al., 2019; Smoller et al., 2009) relied on antidepressant purchase/prescription data including one study using UK Biobank data (Bansal et al., 2022) and one study on self-report of antidepressant use (Hamer et al., 2011). Selected treatment groups included: 7 (28%) samples prescribed 'any antidepressant,' 7 (28%) SSRIs, 4 (16%) TCAs, 5

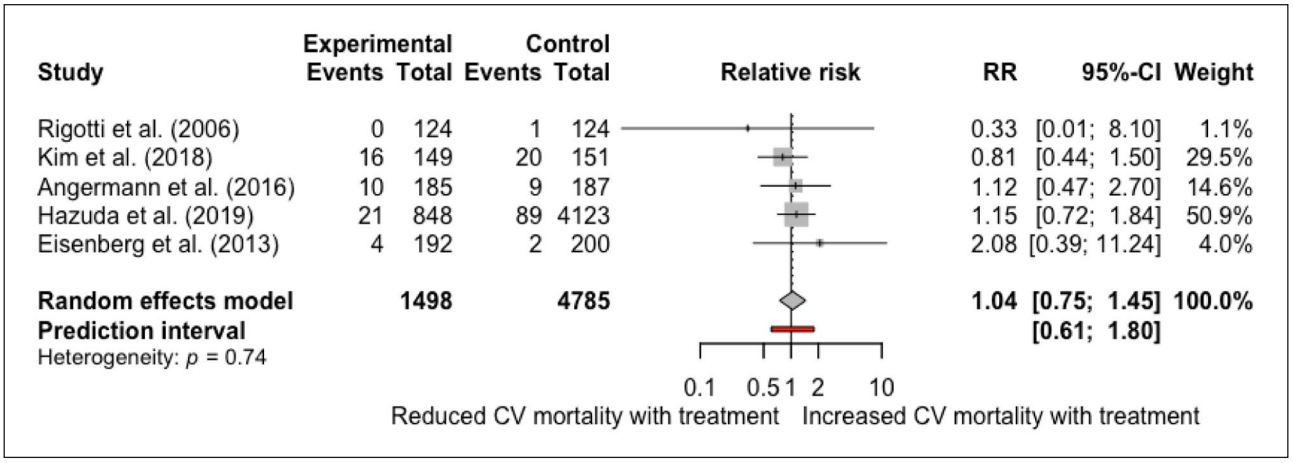

Figure 6. Forest plot of RCTs comparing unadjusted (raw) CV mortality between people receiving antidepressant treatments and placebo, no controlled intervention and/or treatment as usual ($k=5$).
CI: confidence interval; CV: cardiovascular; RR: relative risk.

(20%) 'other' classes of antidepressants, and 4 (16%) neurostimulation treatments (ECT and VNS). Risk of bias was classed as 'low' in 5 studies (31%), 'moderate' in 3 (19%) and 'serious' in 8 (50%). The most common reasons for 'moderate' or 'serious' risk of bias were confounders: for example, lack of control for depression diagnosis, use of proxy measures for antidepressant use such as purchase data, and no multi-variable adjusted model reported for CV mortality (Supplemental Appendix N).

Pooled estimates for unadjusted CV mortality data ($k=27$), suggest a non-significant reduction in CV mortality in individuals prescribed antidepressant treatments when compared to controls (RR: 0.77, 95% CI: 0.49–1.20; Figure 7), but heterogeneity was high (I^2 94.2%). Removing ten outliers reduced I^2 to 65.5% and yielded a RR of 0.99 (95% CI: 0.73–1.34; Supplemental Appendix J). When prescribed to patients with a known diagnosis of depression ($k=11$, out of 7 studies), antidepressant treatment (compared to no-treatment) appeared to significantly reduce the risk of CV death (RR: 0.26, 95% CI: 0.12–0.57; Figure 7 and Supplemental Appendix J) but heterogeneity was high (I^2 97.3%). See Supplemental Appendix J for details of sensitivity analysis.

Seven cohort studies reported adjusted HRs from multivariate models. Four were from the UK (Bansal et al., 2022; Coupland et al., 2011; Hamer et al., 2011; Surtees et al., 2008), with additional studies from Sweden (Bingefors et al., 1996), the USA (Smoller, 2009), and Spain (Diez-Quevedo et al., 2013). Most studied community-dwelling populations, with one focusing on heart failure outpatients (Diez-Quevedo et al., 2013). With exception of the studies by Bingefors et al. (1996) and Surtees et al. (2008), which only reported a model for 'all antidepressants', all studies reported different models for different antidepressant classes (SSRIs, TCAs or 'other' antidepressants) resulting in $k=15$ for the meta-analytic model (Figure 8). All models controlled for age and sex, 11 (73%) for a diabetes diagnosis, 10 (67%) for BMI, and 8 (53%) for levels of physical activity, smoking status and alcohol consumption, amongst other variables. Details of variables included in the models are in Supplemental Appendix W–X. The pooled effect was of a statistically significant increase in CV mortality for individuals prescribed antidepressants (HR: 1.28, 95% CI: 1.09–1.52). There were no outliers. Sensitivity analyses suggested that TCAs ($k=4$) might confer a risk compared with no-antidepressant (HR: 1.27, 95% CI: 1.02–1.58), while other antidepressant groups produced non-significant pooled estimates (SSRIs HR: 1.12, 95% CI: 0.72–1.73; Any antidepressants HR: 1.53, 95% CI: 0.89–2.65; 'Other' antidepressants HR: 1.51, 95% CI: 0.85–2.69; Supplemental Appendix L). Cohorts reporting from prescription and purchase data produced significant estimates of similar magnitude to the full meta-analytic model, while those relying on self-reported data produced non-significant estimates (Supplemental Appendix L). The method for assessment of mortality appears to have a significant effect on CV mortality estimates. Studies using data from established databases ($k=5$) produced statistically significant pooled estimates (HR: 1.71, 95% CI: 1.32–2.22), while others produced non-statistically significant models (Supplemental Appendix L). There was not enough data for a separate meta-analysis of ECT and VNS. The publication bias assessment does not suggest significant funnel plot asymmetry for adjusted models (Supplemental Appendix M).

Discussion

Our meta-analysis of 54 studies (7 RCTs, 47 cohort studies) addresses the two areas where there has been a lack of evidence outlined in the introduction.

Impact of a diagnosis of depression on CV mortality

Firstly, we show that depression is associated with elevated CV mortality, regardless of pre-existing comorbidities. Most of the evidence came from cohorts, with a pooled adjusted HR from maximally adjusted models of 1.45 (95% CI: 1.25–1.69). Our adjusted analyses suggest that depression contributes, independently and with similar magnitude, to worse CV mortality in both community-dwelling and high-risk cohorts, such as post-AMI patients and in those with type 2 diabetes. Although fewer trials

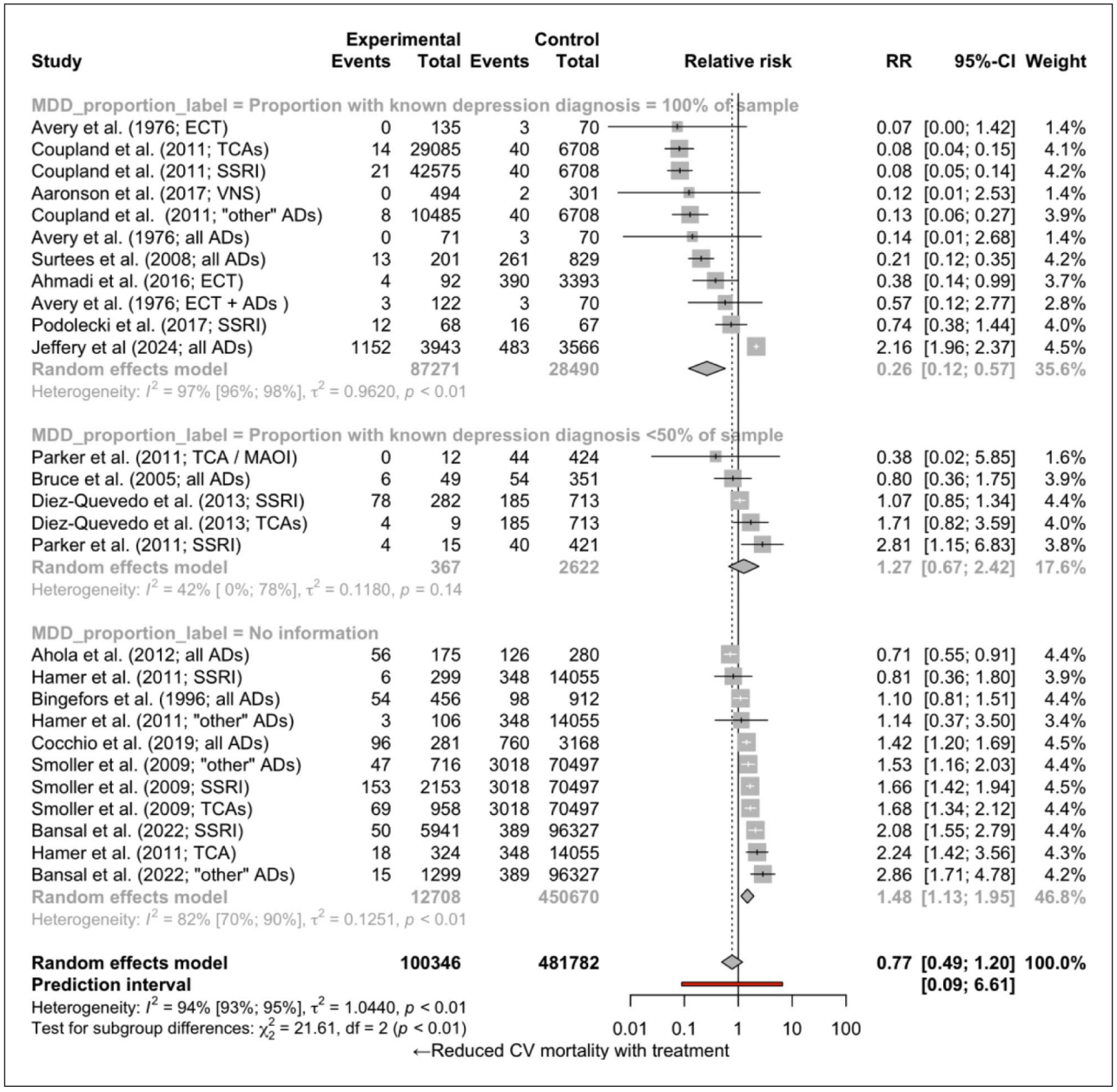

Figure 7. Forest plot of cohort studies comparing unadjusted (raw) CV mortality between people receiving antidepressant treatments and placebo, no controlled intervention, and/or treatment as usual (k=27).
CI: confidence interval; CV: cardiovascular; RR: relative risk.

were available, RCT findings align broadly with conclusions from cohorts, albeit with non-statistically significant models limited in power. These results expand on previous work and suggest that depression should not merely be regarded as a secondary risk modifier in high-risk groups, but as a primary target for CV prevention.

Our sensitivity analysis allowed us to explore the effects of different depression diagnosis methods on CV mortality estimates. Although the small number of studies available for each method limited the power of the sensitivity analysis, different diagnosis methods did produce significantly different mortality estimates in the antidepressant treatment analysis.

Depression severity and CV mortality

Across diverse populations, the studies including severity measures (e.g. rating scales) were consistent with a gradient in risk, supporting a 'dose–response' association between depression severity and CV mortality. However, we do not have enough data to quantify this in a meta-analytic model.

Sex differences

The Look AHEAD findings (Hazuda et al., 2019) raise the possibility of effect heterogeneity by sex. One plausible explanation

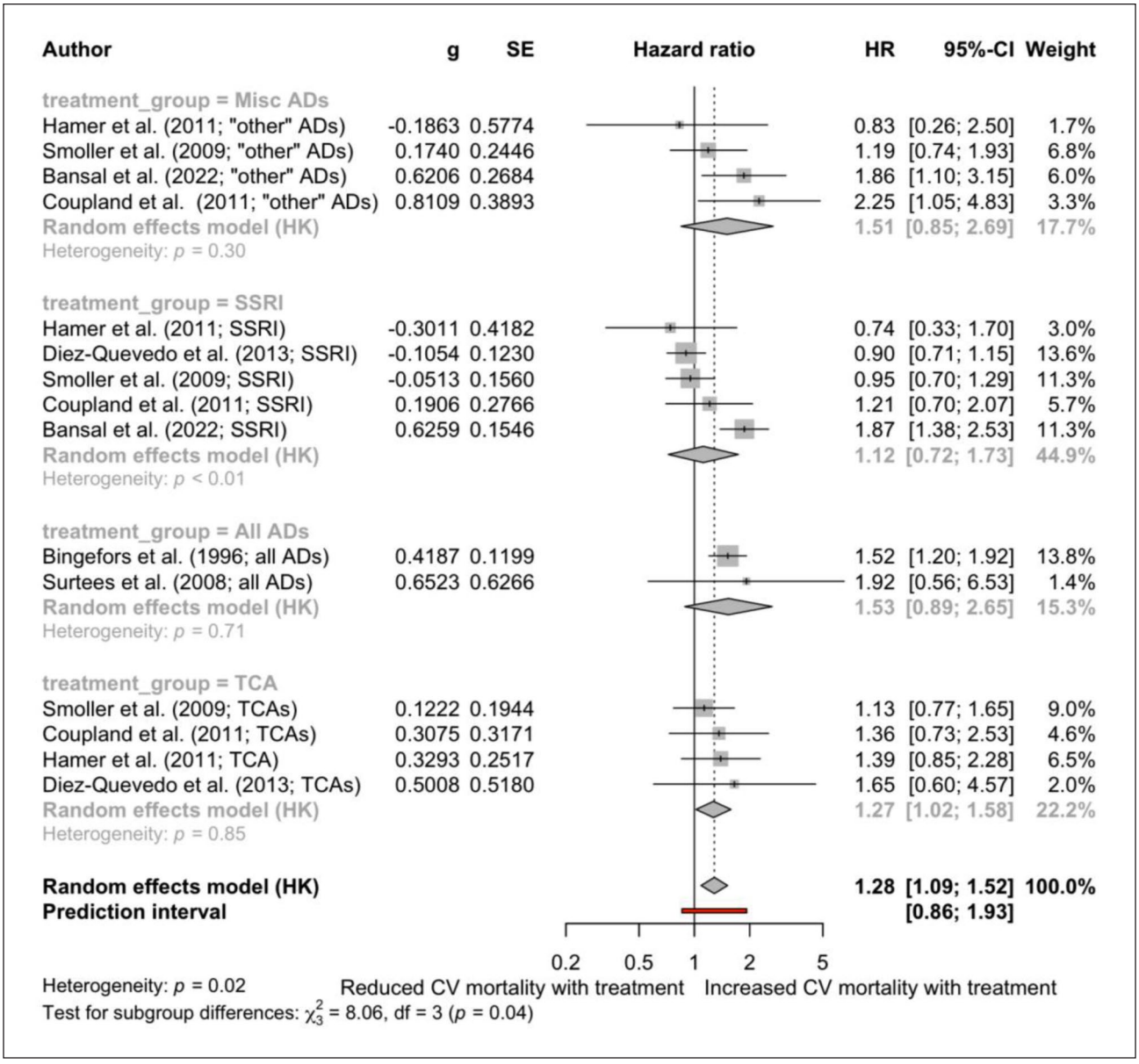

Figure 8. Forest plot of cohort studies comparing multivariate CV mortality models between people receiving antidepressant treatments and placebo, no controlled intervention, and/or treatment as usual (k=15).
AD: antidepressant; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; SE: standard error; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.

is differential help-seeking (Harris et al., 2016) and/or adherence to treatment in women (Pedrosa-Naudín et al., 2022), which could attenuate downstream risk. However, these are only hypotheses from observational data and should be interpreted cautiously.

Timing of depression onset

It is also not clear whether the negative effects of 'new onset' depression (vs know pre-existing depression) on long-term CV mortality relate to direct biological mechanisms, behavioural changes or even the effects of antidepressant treatment, which could be initiated after diagnosis. The available evidence does not allow these mechanisms to be disentangled.

All this evidence highlights the complex risk interactions between diagnosis and their treatment. Regardless, the evidence provides good arguments to support a causal hypothesis, and also, more practically, the delivery of good quality depression screening and severity rating scales, as this may substantially influence mortality effect estimates.

Impact of antidepressant treatment on CV mortality

Secondly, we assessed the effect of antidepressant use on CV mortality. In our meta-analysis, the overall effect of antidepressant use correlated with increased CV mortality in cohorts (HR: 1.28, 95% CI: 1.09–1.52). This could be confounded by indication, as the effect varied significantly according to antidepressant class and population studied. In our adjusted analysis, only those prescribed TCAs had significantly increased CV mortality when compared to no antidepressant treatment (HR: 1.27, 95% CI: 1.02–1.58), an effect not seen with, for example, SSRIs.

This class-specific higher risk for TCAs aligns well with prior all-cause mortality data (Coupland et al., 2018). One plausible explanation relates to direct drug side-effects, as TCAs are well known to be pro-arrhythmic, primarily via sodium channel blockade (Thanacoody and Thomas, 2005). However, in contemporaneous samples, there might be an important indication bias, as individuals prescribed TCAs will very likely have more severe or difficult-to-treat depression, concurrent physical conditions (e.g. neuropathic pain), or both – factors not necessarily captured in observational designs. It is possible that those prescribed TCAs due to severe or difficult-to-treat depression would have worse outcomes if untreated. In fact, other population-based cohorts in older people suggest that while the absolute risk of all-cause mortality at 1-year for people taking TCAs (8.1%) might be higher than that of people not taking antidepressants (7%), it might also be lower than that of people prescribed SSRIs (10.6%; with a HR compared to TCAs of 1.32, 95% CI: 1.26–1.39; Coupland et al., 2011). It should be noted that in that analysis (Coupland et al., 2011) trazodone was associated with the highest adjusted HR for all-cause mortality and classed as a TCA – a decision some experts might challenge. Coupland and colleagues also highlight that TCAs were prescribed at relatively lower doses than SSRIs and other antidepressants. This again suggests some TCAs were being prescribed for pain management, where target doses will usually be lower and risk profiles may differ. Comparative analysis with other samples is challenging, as even relatively large contemporaneous cohorts have very small numbers of patients prescribed TCAs (Diez-Quevedo et al., 2013).

The indication for use of antidepressants does seem relevant for CV mortality outcomes, as our sensitivity analysis shows that in those with a known depression diagnosis, antidepressants appeared to have a protective effect on CV mortality (RR: 0.26, 95% CI: 0.12–0.57) compared to cohorts in which the proportion of depression diagnosis is ⩽50% or not known, although the available data only allowed us to explore this in unadjusted models. In interpreting the divergent direction of association by diagnosis of depression, we consider indication bias and residual confounding as more plausible explanations than some paradoxical biological effect of antidepressants. Cohorts with a coded depression diagnosis can be reasonably expected to have a defined indication for antidepressant treatment. On the other hand, cohorts with unknown depression status likely represent a heterogeneous group in which antidepressants may be prescribed for uncoded depression, anxiety, chronic pain or other symptoms, and where exposure is therefore more strongly shaped by comorbidity, healthcare systems and variations in 'real world' clinical practice. This further amplifies confounding by indication. Such circumstances can generate directionally discordant estimates across groups defined by diagnostic classification. A useful parallel is aspirin: it has clear benefit in secondary prevention, which contrasts with attenuated or adverse net effects in primary prevention, reflecting differences in baseline risk and the greater influence of non-causal mechanisms when the indication is less clearly defined. Accordingly, results related to the 'diagnosis unknown' subgroup should be interpreted cautiously and not assumed to imply causality.

Finally, a relevant distinction should be made between antidepressant prescription and effective treatment of depression. Cohort studies can capture antidepressant exposure but rarely assess treatment response, meaning mortality risks in exposed groups may reflect difficult-to-treat depression rather than adverse pharmacological effects.

Future research directions

To better separate antidepressant-specific effects from mood-mediated effects and confounding by indication, future work should prioritise randomised designs allowing for causal inference. Pragmatically, this is more likely to be deliverable as active comparator designs between different antidepressant classes or antidepressants vs psychotherapy. In parallel, cohort data should be strengthened by capturing time-varying treatment, dose, duration, switching/augmentation, and adherence. This will also allow for better trial emulation.

A second priority is the harmonised phenotyping of depression across studies, including consistent definitions for diagnosis, severity, chronicity/recurrence, and timing relative to index events (pre-existing vs incident 'new-onset' depression). Such harmonisation would enable useful subgroup analyses and reduce misclassification that currently limits pooling of 'onset' effects.

Third, studies should incorporate competing risks when analysing CV mortality in depression, explicitly reporting suicide and deaths of undetermined intent alongside CV deaths. This would provide a more complete picture of excess mortality and mitigate bias from cause-of-death misclassification.

Finally, there is limited evidence on neuromodulation (e.g. ECT, Repetitive Transcranial Magnetic Stimulation (rTMS), VNS) in relation to CV mortality. In particular, given that ECT and VNS are typically reserved for patients with severe depression, adequately powered studies with robust covariate control (such as severity and comorbidities) and detailed treatment-trajectory assessment are needed to clarify whether their long-term CV outcomes differ from pharmacotherapy and psychotherapy.

Bipolar disorder merits specific attention. Only three of the included cohort studies had a substantial proportion of participants with bipolar disorder, and none provided bipolar-specific CV mortality outcomes suitable for meta-analysis. This is a very relevant gap. Large cause-specific mortality studies in bipolar disorder consistently demonstrate excess CV mortality (Lambert et al., 2022; Paljärvi et al., 2024; Westman et al., 2013). These data could not be included in our meta-analyses, as cases are typically defined as bipolar disorder diagnosis rather than depressive phase, amongst other practical issues. A future comparative analysis of CV mortality in MDD versus bipolar disorder seems like an obvious next step. Phenotyping bipolar illness would further address other key sources of heterogeneity related to prescription, as the clinical pharmacological management is distinct.

Strengths and limitations

This systematic review and meta-analysis is the largest synthesis of evidence on depression and CV mortality that we are aware of, including over 1.5 million participants and previously unpublished data from five studies. We provide the first systematic evidence that depression independently increases CV mortality regardless of baseline comorbidity and identify clinically relevant risk differences by antidepressant class.

However, there are inevitable limitations with meta-analytic methods. High levels of heterogeneity in our models from cohort data likely reflect the wide variation in methods used to define depression, ascertain mortality, and adjust for confounding. This is in practice inevitable when meta-analysing 'real-world' data. We reported I^2 statistics for comparability with other meta-analyses, recognising that in large population cohorts with smaller sampling error, even modest between-study differences yield high I^2 values. These should not be over-interpreted as evidence of poor study quality. We also reported τ^2 (between-study variance using the Paule–Mandel estimator), an absolute measure that revealed modest heterogeneity even when I^2 was high (as illustrated in Supplemental Appendices H and L), indicating that statistical heterogeneity did not necessarily reflect large dispersion of effect sizes.

CV mortality is relatively rare in RCTs and in some of the cohort sub-groups, particularly those reporting on the effects of antidepressant medication. Consequently, estimates pooled from these studies can be imprecise. This is reflected in wide CIs and PIs for some models. Accordingly, null findings or absence of statistical significance should be interpreted as inconclusive, rather than evidence of no association. All statements, particularly those comparing one antidepressant class with another, must be cautiously viewed in the light of these limitations of the methodology.

While over half of the included RCTs included assessment of mortality in their main outcome, interventional trials are likely to exclude frail individuals or those suffering with multimorbidity, where the risk of CV mortality might be higher. The proportion of females in the included RCTs varies between 16% and 59%, which is low when compared with a review of 115 trials in TRD, where the average proportion of females was 65% (Demyttenaere et al., 2024). A higher proportion of males in our aggregate sample of RCTs might increase raw CV mortality rates, although all adjusted models reported controlled for gender (except ENRICHD). The mean age of samples in the included RCTs varied between 55 and 62 years. So, on average, these are samples of relatively young working age adults. Still, they are older than the average patient included in TRD trials, where the mean age is 44 years (Demyttenaere et al., 2024). All adjusted models reported controlled for age.

Most cohort studies included were designed to capture mortality data but there will be geographical variations in death certification and recording practices, which go beyond our scope here. Sex and gender are reported in heterogeneous ways in the cohorts, which makes summary statements challenging and limits our methods. Despite this, the vast majority of adjusted models reported for cohorts controlled for age and sex. These limitations related to the demographic characteristics of the aggregate sample should be considered when interpreting results.

Publication bias was varied, and quality appraisal unsurprisingly indicated observational studies were especially prone to poor adjustment to confounds, including unmeasured differences in depression severity, adherence to prescribed medication, choice of dose or treatment settings, non-accounted for comorbidities and other factors in complex patient populations.

Most studies of the impact of a depression diagnosis on CV mortality do not control for antidepressant use. There is likely a low rate of depression in control groups not prescribed antidepressants, and there is therefore a risk that in treatment cohorts we are comparing depression to no-depression, even accepting that 'antidepressants' have other indications. Evidence is relatively scarce and heterogeneous, producing a complex picture.

Data for our meta-analysis derive mostly from prospective cohorts, not controlled studies. Particularly in relation to the effects of treatment, most evidence derives from 'general population' samples or disease-specific registries with narrow focus, limiting our ability to disentangle synergistic risks as we were able to do to a certain extent with the 'depression versus no-depression' models. This is not surprising given the methodological challenges already discussed. Still, our results from prospective cohorts demonstrate the need for properly powered, prospective, randomised trials to determine whether antidepressant treatments can modify long-term CV mortality.

Few of the included studies provide detailed temporal antidepressant exposure data. Jeffery et al. (2024), using primary care data from the UK Clinical Practice Research Datalink, analysed timing, duration, and number of antidepressant prescriptions in 23,897 people with comorbid depression and diabetes. Overall, those prescribed antidepressants had significantly higher all-cause, CV, respiratory and cancer mortality rates, compared to no-prescription. But given the likely different mechanisms for these diverse causes of death, it seems implausible to support a direct effect of antidepressants.

Finally, under-reporting of suicides is a well-described phenomenon, which may bias cause-specific mortality analysis (Tøllefsen et al., 2012). Unaccounted for suicides are believed to be mostly coded in error as events of undetermined intent, accidental deaths by poisoning, falls or other injuries, or unknown causes of death (Snowdon, 2025). While CV codes are not usual confounds for suicide misclassification, the data we aggregated do not allow us to control for suicide mortality, and this is a limitation of our methods.

Conclusion

Our findings have important clinical and public health implications. Depression is common, modifiable, and often underdiagnosed in patients at risk of CVD. Our review provides robust evidence that depression confers a higher risk of CV mortality and that antidepressant effects on mortality are likely complex and context-dependent. Our findings provide abundant evidence to justify integrated depression-CV care pathways that consider mental health, the management of comorbidities, and CV risk together. Careful diagnostic assessments for depression and appropriate treatment selection could improve outcomes for many, though more research in this area is urgently needed to allow for more informed treatment choices. This is essential for reducing the global burden of depression-related CV deaths.

Author note

We confirm that this work is original, all authors have approved this article, it has not previously been published, nor is it currently under consideration for publication elsewhere.

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BH, SH, RT, ER, SA and TDSC completed screening and data extraction, as well as risk of bias assessments. TDSC did the statistical analysis with support from RK and RHM-W. TDSC wrote the first draft with support from AB and RHM-W. Figures and tables were designed by TDSC and RHM-W. The manuscript was revised in several cycles with input from all authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Declaration of conflicting interests

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Data availability statement

The raw data used to run the meta-analytic models, with limitations, can be shared upon reasonable request to the corresponding author, TC. The limitations on data availability relate to restrictions from NHLBI on how the ENRICHD dataset can be shared.

Analytic code availability

Example code and model input datasets are available on a GitHub repository (https://github.com/tiagodscosta/Depression_CVMortality_Meta-analysis), available for academic use under a GPL license. The code used followed the methodological framework described by Harrer et al. (2021).

Supplemental material

Supplemental material for this article is available online.

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