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Depression and cardiovascular disease events among patients with type 2 diabetes: A systematic review and meta-analysis with bias analysis

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ABSTRACT

Aims: To provide updated systematic and quantitative summary of the association between depression and the risk of CVD events among individuals with type 2 diabetes. We also aimed to examine the sensitivity of the association to uncontrolled confounding.
Methods: Data sources included Medline, Embase, and PsycInfo through September 2019. Two independent reviewers selected cohort studies that evaluated the association between depression and fatal or non-fatal CVD events among individuals with type 2 diabetes. Bias analysis was performed using the bias formula approach.
Results: Of 2527 citations screened, 17 eligible studies with a total of 1,033,131 participants were identified. Based on random-effects meta-analysis, depression was associated with higher risks of non-fatal CVD events (relative risk 1.35, 95% confidence interval [CI] 1.20 to 1.53) and fatal CVD event (relative risk 1.47, 95% CI 1.21 to 1.77). Bias analysis indicated that unmeasured confounders alone may not explain the observed association between depression and CVD events among individuals with type 2 diabetes.
Conclusions: Depression was associated with a higher risk of non-fatal and fatal CVD events among individuals with type 2 diabetes. Our findings provide updated and robust evidence about the association between depression and CVD events among individuals with type 2 diabetes.

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1. Introduction

Cardiovascular disease (CVD) killed 17.9 million people globally in 2016, making it the most common cause of death (31%) among all causes.[1] Diabetes, one of the main risk factors for CVD, affects approximately 425 million adults and imposes substantial health and economic burden on the global population, resulting in 4 million deaths and $727 billion in health expenditure worldwide in 2017.[2] In response to these public health crises, as an essential part of the Sustainable Development Goals (SDGs), the United Nations has proposed to reduce morbidity and mortality for non-communicable diseases including CVD and diabetes, by one-third, by 2030.[3] Therefore, understanding the major risk factors for CVD among patients with diabetes and mitigating the risks of CVD events is imperative to achieving this challenging goal.

Depression is closely interrelated with CVD and diabetes.[4–6] According to the INTERHEART study, *psychosocial stress* accounts for approximately 30% of the attributable risk of acute myocardial infarction, ranking it third after lipids and smoking.[7] In addition, the prevalence of depression in patients with type 2 diabetes is approximately twice as high as for those without diabetes.[8] It is also known that diabetic patients suffer from distress related to chronic disease management, necessary lifestyle changes, and other long-term adverse health outcomes related to diabetes.[9] While a previous meta-analysis >7 years ago showed that depression increases the risk of cardiovascular mortality among patients with type 2 diabetes,[10] a comprehensive review that details the association between depression and incident non-fatal CVD events among diabetic patients is lacking. Given the large lifestyle and economic impacts of CVD events even without causing death,[1,11] clarifying the impact of depression on non-fatal CVD events with the most recent data is important.

Depression and CVD share many risk factors, including socioeconomic status or its components income, educational attainment, and occupational status.[4,12] While data for income and/or educational levels are often available to control for socioeconomic status in observational studies related to diabetes, mental health, and CVD, employment status has not been included in most of the previous studies. Recent studies have shown that unemployment is a risk factor of depression[13] and CVD events[14,15] independently of other socioeconomic factors (e.g., income, education, and marital status) indicating the importance of additionally controlling for employment status (prior to the onset of depression). Bias analysis for uncontrolled confounding is a standard strategy to mitigate and assess the magnitude of this limitation in studies with unmeasured confounding. While this approach allows to more validly estimate the risk of CVD among diabetic patients with depression compared to those without depression, few meta-analyses of observational studies have employed this method thus far.[16,17]

In the present systematic review and meta-analysis, we thus aimed to investigate the association between depression and the risk of CVD events among patients with type 2 diabetes. Given the potential for confounding bias due to unmeasured confounders such as employment status in observational studies, we also performed a bias analysis to evaluate the robustness of our findings to this common bias.

2. Methods

2.1. Data sources and searches

Literature searches were conducted through September 30, 2019, using the electronic databases MEDLINE, EMBASE, and PsycINFO for cohort studies investigating the association between depression and incidence and prevalence of CVD among individuals with type 2 diabetes. The following search terms in MEDLINE were applied: ("Diabetes mellitus, type 2"[MeSH Terms] OR "diabetes"[All Field]) AND ("Depression"[MeSH Terms] OR "depression"[All Field] OR "depressive disorder"[MeSH Term] OR "depressive"[All Field]) AND ("Cardiovascular Diseases"[MeSH Terms] or "cardiovascular"[All Fields]) AND ("longitudinal"[All field] or "cohort"[All Field] or "Cohort studies"[MeSH Terms]). We applied no language or study type restrictions. We also manually searched the references of relevant studies. The same search strategy was also applied for searches of EMBASE and PsycINFO (Supplementary Table 1). The present study followed the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group.[18]

2.2. Study selection

Two investigators (the first and second authors) independently evaluated the articles for eligibility. The inclusion criteria were: 1) a cohort study of people diagnosed with diabetes (defined clinically or by self-report) either as total sample or subgroup, 2) CVD events (see Table 1 for details in the assessment of CVD in each study) reported as the study outcome, and 3) the association between depression and CVD events during follow up was estimated in those with diabetes. Cohort studies were defined as those that prospectively identified a group of people, assessed exposures of interest, and followed them for the incidence of outcome events or those that used existing data records to retrospectively identify a group of people in whom exposure (i.e. depression) was assessed prior to the occurrence of outcome (i.e. CVD) events.[17] We restricted our analyses to cohort studies to assure the timing for the onset such that CVD events did not affect depression rather than the other way around among those with type 2 diabetes. We included studies that identified depression by applying standardized screening tools or clinical criteria or identified in medical records. We determined the eligibility of the candidate studies by retrieving and screening the full text. All discrepancies were resolved by consensus after discussion that also included co-authors.

2.3. Data extraction and quality assessment

We extracted the following information; study characteristics (first author name, publication year, country of study, length of follow-up, study design and sample size), participant characteristics (age, sex, diabetes assessment, CVD history), exposure assessment, outcome assessment, adjustment factors, analysis strategy, and multivariable-adjusted relative risks and variance. If the appropriate information was missing, we requested this from the investigators. Two investigators (the first and second authors) independently extracted data and all discrepancies were resolved by discussion with co-authors.

To assess study quality, we evaluated sources of participants, comparability between respondents and non-respondents, exposure assessment, outcome assessment, and statistical quality.[17] As the scoring itself submerges detail information of each study, we chose not to employ a scoring system to formally rate study quality.[19]

2.4. Data synthesis and analysis

Relative Risks (RRs) were estimated based on hazard ratios (HRs) reported in studies for CVD events among depressed and non-depressed study populations with diabetes since all cohort studies used Cox

Table 1
Characteristics of studies included in meta-analysis.

Study	Year	Country	Length of follow-up (years)	N of participants	Age (years)[a]	Male, %[a]	Diabetes assessment	Depression (exposure) assessment	CVD (outcome) assessment	Covariate adjustment
Black et al.[27]	2003	US	7.0	636	73.3	41.0	Self-report	CESD	Macrovascular complications: CVD, stroke, kidney disease (identified by self-report)	Age, sex, education, marital status
Egede et al.[28]	2005	US	7.0	715	63.2	38.0	Self-report	CESD	CHD mortality (identified by National Death Index)	Age, sex, race, poverty, education, marital status, smoking, physical activity, BMI, cancer, hypertension, heart disease, stroke, aspirin
Bruce et al.[38]	2005	Australia	7.8	1273	64.1	48.7	Clinical diagnosis	GHS	CVD mortality (identified by government register records)	Age, sex, race, smoking, duration of diabetes, HbA1c, CHD history, anti-hypertensive medication, albumin-creatinine-ratio, retinopathy, neuropathy
Katon et al.[29]	2008	US	2.0	10,704	75.6	56.3	Registry	ICD-9	CVD, CVA (identified by ICD-9)	Age, sex, race, Charlson comorbidity index, prior amputation, CVD history
Lin et al.[30]	2009	US	4.4	4184	64.0	51.5	Registry	PHQ-9	CVD mortality (identified by medical records, autopsy reports, or death certificates)	Age, sex, race, education, marital status, type of treatment, smoking, physical activity, BMI, duration of diabetes, HbA1c, hypertension, medical comorbidity,
Lin et al.[31]	2010	US	5.0	3723	64.3	52.1	Registry	PHQ-9	Macrovascular events: MI, stroke, CHD, cardiovascular procedures, revascularization of the lower extremity (identified by medical records, or ICD-9)[b]	Age, sex, race, education, marital status, duration of diabetes, smoking, physical activity, BMI, treatment, costs, hypertension, HbA1c, RxRisk score
Pan et al.[32]	2011	US	6.0	4873	67.6	0	Self-report	MHI-5	CVD mortality (identified by report from next of kin, postal authorities, or National Death Index)	Age, marital status, smoking and drinking status, BMI, physical activity level, hormone replacement therapy, aspirin and multivitamin use, family, history of cancer, parental history of MI, major comorbidities (hypertension, elevated cholesterol, heart disease, stroke and cancer)
Scherrer et al.,[33]	2011	US	7.0	53,632	55.6	88.3	ICD-9	ICD-9	MI (identified by ICD-9)	Age, sex, race, marital status, insurance
Bot et al.[39]	2012	Netherland	6.2	330	65.0	70.3	Self-report	BDI	CVD mortality (identified by Municipal Personal Records database)	Age, sex, smoking, hypertension, previous MI, Killip class, LVEF
Sullivan et al.[34]	2012	US	4.7	2053	62.2	60.4	Clinical diagnosis	PHQ-9	Composite outcome (major coronary artery disease events, nonfatal MI, and unstable angina)	Age, sex, race, education, smoking, alcohol, living alone, BMI, weight, waist circumference, duration of diabetes, blood pressure (systolic and diastolic), triglycerides, LDL and HDL cholesterol, serum creatinine, HbA1c, fasting glucose, presence of microvascular complications, antihypertensive medication, and antihypertensive medication, and lipid-lowering medications
Ting et al.[40]	2013	Hong Kong	7.4	7835	56.5	46.5	Registry	Medical record	CVD outcome: CHD, peripheral vascular disease (identified by hospital discharge records and ICD-9)[b]	Age, sex, smoking, BMI, systolic and diastolic blood pressure, duration of diabetes, HbA1c, lipids, eGFR, lipid drugs, antihypertensive medication, antidiabetic medication, insulin, urinary albumin.
Coleman et al.[35]	2013	US	10.0	4128	63.4	51.9	Self-report	PHQ-9	CVD mortality (identified by ICD-10)	Age, sex, race, education, marital status, treatment, smoking, physical activity, BMI, duration of diabetes, HbA1c, hypertension, comorbidity
Cummings et al.[36]	2016	US	6.0	4090	64.8	42.0	Self-report	CESD	Acute CHD, and CVD mortality (identified by self-report or medical records)	Age, sex, race, education, region, income, insurance, smoking, BMI, systolic blood pressure, cholesterol, heart disease, CRP, AF, LV hypertrophy, statin
Novak et al.[37]	2016	US	6.7	933,211	64.0	97.0	ICD-9	ICD-9	CHD (identified by ICD-9 or Current Procedural Terminology code)	Age, sex, race, marital status, BMI, eGFR, comorbidities at baseline (hypertension, CVD, Congestive heart failure, peripheral vascular disease, lung disease, dementia, rheumatic disease, malignancy,

(continued on next page)

Table 1 (*continued*)

Study	Year	Country	Length of follow-up (years)	N of participants	Age (years)[a]	Male, %[a]	Diabetes assessment	Depression (exposure) assessment	CVD (outcome) assessment	Covariate adjustment
										HIV/AIDs, and PTSD), statin, antihypertensive medication, serum albumin level.
Bruce et al.[41]	2016	Australia	3.7	1337	65.8	43.0	Clinical diagnosis	PHQ-9	CHD (identified by self-report or medical records) and CVD mortality (medical records)	Age, sex, aborigial, smoking, blood pressure, HbA1c, eGFR, prior CHD, Charlson comorbidity index, insulin use (covariates were selected based on statistical association with outcomes)
Wang et al.[42]	2018	Australia	1.5	274	71.0	54.7	Self-report	PHQ-9	Heart failure (identified by Framingham HF criteria)	Age, sex, obesity, HbA1c, LVH, E/e′
Hamieh et al.[43]	2018	France	20.0	133	47.8	74.5	Self-report	CESD	Angina pectoris, MI (identified by self-report)	Age, sex, smoking status, physical activity, obesity, hypertension, dyslipidemia, occupational grade, parental CHD history,

CESD, Center for Epidemiologic Studies Depression Scale; GHS, General Health Status Questionnaire; ICD, International Classification of Diseases; PHQ, Patient Health Questionnaire; MHI-5, five-item Mental Health Index; BDI, Beck Depression Inventory; CVD, cardiovascular disease; CHD, coronary heart disease; CVA, cerebrovascular accident; MI, myocardial infarction; BMI, body mass index; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

[a] Mean age and percent of male among diabetic patients were calculated based on tables in each paper if not presented.

[b] CVD as a cause of mortality was included in the definition of outcome assessment.

proportional hazard models. For studies that quantified HRs of CVD events using participants without diabetes and depression as a reference group, we calculated the HRs of CVD events for diabetic patients with depression relative to diabetic patients without depression using the method proposed by Altman and Bland.[20] For studies that reported multiple estimates, we selected the estimate which most closely adjusted for age, sex, race, socioeconomic status, and comorbidities. If studies presented the HRs according to the severity of depression, we used the estimates of the most severe depression group.[21]

The potential for publication bias was assessed using funnel plots, Begg's test,[22] and Egger's test.[23] We summarized the effect estimates using a random effects model.[24] The statistical heterogeneity of relative risks across studies was assessed using Cochrane's Q test and I^2 statistics.[25,26] Low, moderate, and high degree of heterogeneity was defined as $I^2 \leq 25\%$, 25–75%, and >75%, respectively. We additionally performed stratified analyses by study location (US[27–37] or Non-US[38–43]), length of follow-up (>6 years[27,28,33,35,37–40,43] vs. ≤6 years[29–32,34,36,41,42]), inclusion criteria (including previous CVD[28–32,34–39,41] vs not[27,33,40,42,43]), diabetes assessment (type 2[27,30–35,38,40–42] vs. type unclear[28,29,36,37,39,43]) and non-fatal CVD outcomes (including stroke[27,31,36,40] vs. not[28–30,32–39,41–43]). *P* values for comparisons between subgroups were computed using the method proposed by Altman and Bland.[20] An additional sensitivity analysis removing each study one at the time was also conducted to examine the magnitude of influence of each study on pooled estimates.

We performed a bias analysis to investigate the potential impact of uncontrolled confounding by an unmeasured confounder. Because none of the studies included in this meta-analysis controlled for employment status as an important confounders between depression and CVD events (Supplementary Fig. 1), we used employment status for assessing the potential influence due to unmeasured confounders on our results in this bias analysis. We assigned plausible prevalence estimates for the unmeasured unemployment among diabetic patients without depression (10%), and among diabetic patients with depression (10%, 15%, 20%, or 25%), and the relative risks relating the unmeasured employment status and cardiovascular disease (a wide range of relative risks from 1.0 to 5.0), based on prior studies.[14,15,44,45] Using these assigned values, we computed the adjusted relative risks, and 95% confidence intervals (CI), externally adjusted for the unmeasured employment status. In our bias analysis, we divided the observed relative risk of each study by a bias factor, which is the degree of bias due to failure to adjust for employment status. We assigned the same bias factor to all studies (except Hamieh et al.[43] because this study restricted participants to employees) and pooled the bias-adjusted relative risks using a random effects model. More details about the bias analysis methods are described in Supplementary Table 2 and elsewhere.[16,17] All statistical analysis was performed using STATA version 15.

3. Results

3.1. Study characteristics

After applying our inclusion and exclusion criteria, we identified 17 studies (1,033,131 participants) that met the inclusion criteria for our meta-analysis (Fig. 1).[27–43] The number of participants in each study ranged from 133 to 933,211, with a mean age range of 47.8–75.6 years (Table 1). The follow-up period ranged from 1.5 to 20 years. All studies included in the meta-analysis adjusted for age and sex, while other factors such as socioeconomic status and comorbidities were less consistently included in fully adjusted models. Further detail with a quality assessment of each study is shown in Supplementary Table 3.

3.2. Random effects meta-analysis

The random effects meta-analysis indicated that depression was associated with higher risk of non-fatal CVD event (relative risk = 1.35, 95% CI = 1.20 to 1.53) and fatal CVD event (relative risk = 1.47, 95% CI = 1.21 to 1.77) (Fig. 2). As Lin et al.,[31] Sullivan et al.,[34] and Ting et al.[40] included death in their definition of CVD, we removed them for the analysis of non-fatal CVD events but the results did not change substantially (relative risk = 1.31, 95% CI = 1.15 to 1.51). We found high and moderate heterogeneity for effect estimates in studies for non-fatal CVD events ($I^2 = 89.3\%$; $P < 0.01$ for heterogeneity) and for fatal CVD events ($I^2 = 28.7\%$; $P = 0.20$ for heterogeneity) respectively. Begg's *P* values were 0.35 and 0.54, and Egger's bias coefficients were 1.06 (95% CI = −0.91 to 3.04, *P*-value = 0.25) and 1.89 (95% CI = −1.11 to 4.89, P-value = 0.18) for non-fatal and fatal CVD events, respectively. The funnel plot for non-fatal CVD events appears asymmetrical (Supplementary Fig. 2) but the results did not substantially change after removing studies (Black et al.[27] and Wang et al.[42]) with relatively small sample size and stronger effect estimates (relative risk = 1.30, 95% CI = 1.16 to 1.47). The funnel plot for fatal CVD events appears to be symmetrical, indicating a lack of evidence for publication bias.

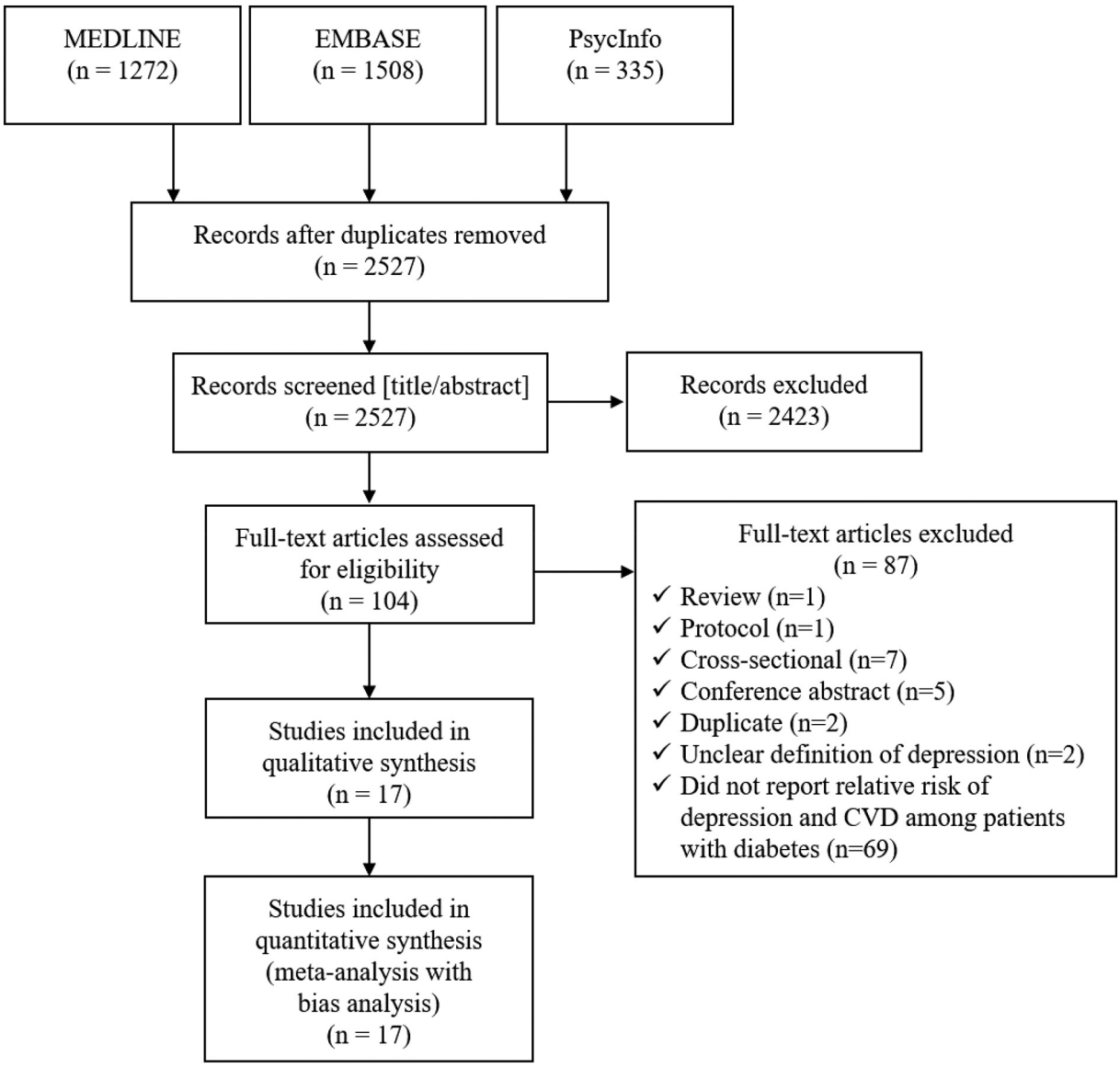


Fig. 1. Flow of studies through review.

3.3. Stratified analysis

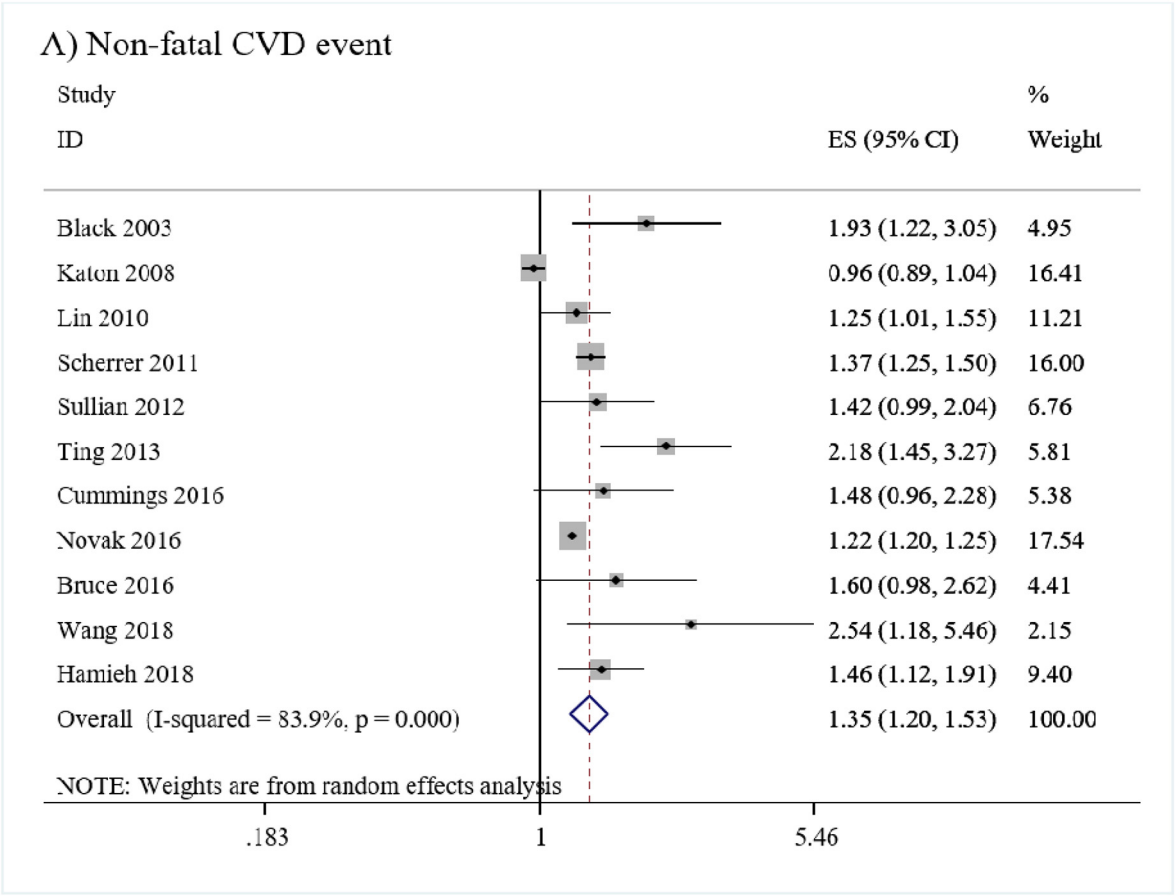
For non-fatal CVD events, we found evidence of heterogeneity in the results according to inclusion criteria (including previous CVD or not) (Table 2). On the other hand, stratifying by the length of follow-up (>6 years vs ≤6 years), diabetes assessment (type 2 vs type unclear), or CVD outcome definition (including stroke or not) did not result in more than minimal heterogeneity. For fatal CVD events, we did not find evidence of heterogeneity in the stratified analysis (i.e. study location, and length of follow-up) or the overall result. No particular study was identified as influential in leave-one-out sensitivity analysis (Supplementary Fig. 3).

3.4. Bias analysis

The bias analysis indicated that unmeasured unemployment alone is unlikely to explain the observed association between depression and CVD events among individuals with type 2 diabetes (Fig. 3, Supplementary Table 4). To explain the association between depression and non-fatal CVD events, unemployment (assuming a basic prevalence of unemployment among diabetic patients - without depression - of 10%) would have had to be much more prevalent in diabetic patients with depression (>25%) and also have a very strong association with non-fatal CVD events (RR > 5.0) among individuals with type 2 diabetes. Similarly, to account for the association between depression and fatal CVD events, unemployment status would have needed to be much more highly prevalent in diabetic patients with depression (>25%) and have a strong association with fatal CVD events (RR >5.0) among individuals with type 2 diabetes.

4. Discussion

In this meta-analysis of 1,033,131 patients with type 2 diabetes from 17 studies, we observed a higher risk of both non-fatal and fatal CVD events among those with depression compared with those without depression. Bias analysis indicated that the observed association between depression and CVD events among patients with type 2 diabetes is unlikely to be entirely due to confounding by an unmeasured (uncontrolled) co-factor such as unemployment. Given the high prevalence of depression in patients with type 2 diabetes, our findings



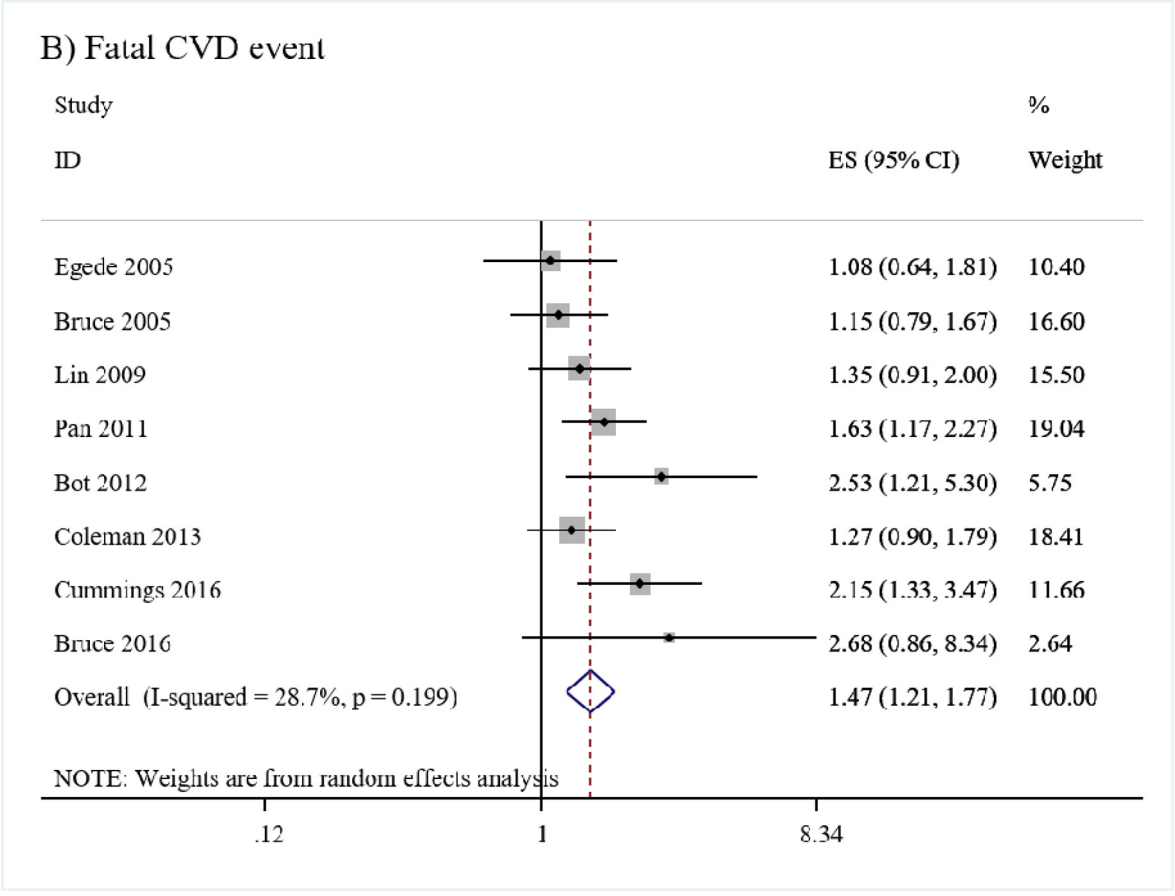


Fig. 2. Random effects meta-analysis of the association of depression with non-fatal and fatal CVD events among patients with type 2 diabetes.

Table 2
Stratified analysis of depression and the risk of non-fatal and fatal CVD events among individuals with type 2 diabetes.

	No of studies	RR (95% CI)	P for heterogeneity	I^2 (%)	P for interaction
Non-fatal CVD event					
Total	11	1.35 (1.20–1.53)	<0.001	89.3	
Study location					
US	7	1.25 (1.10–1.43)	<0.001	87.3	0.02
Non-US	4	1.73 (1.37–2.19)	0.29	20.9	
Follow-up					
>6 years	5	1.42 (1.23–1.63)	0.001	78.8	0.65
≤6 years	6	1.33 (1.04–1.69)	0.001	75.5	
Inclusion criteria					
Including previous CVD	6	1.21 (1.04–1.42)	<0.001	86.5	0.02
Excluding previous CVD	5	1.64 (1.33–2.02)	0.07	54.7	
Diabetes definition					
Type 2 diabetes	7	1.51 (1.30–1.76)	0.11	41.9	0.06
Type unclear	4	1.20 (0.99–1.44)	<0.001	91.9	
Outcome definition					
Including stroke	4	1.61 (1.22–2.13)	0.07	58.0	0.15
Without stroke	7	1.28 (1.11–1.46)	<0.001	87.8	
Fatal CVD event[a]					
Total	8	1.47 (1.21–1.77)	0.20	28.7	
Study location					
US	5	1.45 (1.19–1.78)	0.29	20.4	0.57
Non-US	3	1.75 (0.94–3.27)	0.09	58.2	
Follow-up					
>6 years	4	1.28 (0.99–1.66)	0.26	24.6	0.13
≤6 years	4	1.66 (1.33–2.07)	0.41	0.0	
Diabetes definition					
Type 2	4	1.45 (1.18–1.77)	0.51	0.0	0.81
Type unclear	4	1.53 (1.03–2.29)	0.06	60.1	

[a] All studies included and controlled for previous history of CVD at baseline.

highlight that mental health management for diabetic patients may reduce their risk of CVD events.

Our findings advance our current state of knowledge about the link between depression and CVD among patients with diabetes. A prior meta-analysis showed that depression was associated with fatal CVD events among patients with type 2 diabetes (HR 1.39, 95% CI = 1.11 to 1.73).[10] We have updated the results including 3 additional large cohort studies on this topic published between 2013 and 2019.[35,36,41] In addition, the risk of non-fatal CVD events due to depression in diabetic patients has not been adequately established. Although recent meta-analyses reported the association between depression and subsequent CVD events,[46,47] these studies have limited information involving 9–11 studies, requiring a more comprehensive systematic review and a meta-analysis on this topic. Furthermore, given that depression and CVD share many common causes,[4,12] it is critically important to assess the robustness of the summary estimates to uncontrolled confounding as this is one of the common and important potential biases in observational studies.[16] In this context, our meta-analytic findings are based on the most updated information through 2019, and along with our bias analysis, highlight that depression in patients with type 2 diabetes may need to be seriously considered as depression may increase the risks of not only mortality but also non-fatal CVD events which are a strong predictor of health-related quality of life and economic burden.[1,11]

There are several mechanisms that could explain why depression increases the risk of CVD events in patients with type 2 diabetes. Depression induces the following biological responses which are well-known risk factors of CVD events; including alterations of autonomic nervous system activity, decrease of heart-rate variability, the elevation of heart rate, catecholamine levels, and inflammatory activity, and the induction of endothelial and platelet dysfunction.[48–53] In addition, the hypothalamic-pituitary-adrenal axis, which is essential for regulating glucocorticoid production by the adrenal glands, is prone to dysregulation with low socioeconomic status and poor health behaviors in those with a genetic predisposition.[4] Such dysfunction may exacerbate the development of diabetes, metabolic syndrome, and insulin resistance, and increase the risk of having CVD events.[54] Depressive symptoms are also linked to behaviors such as failure to stop smoking, sedentariness,[55] low physical activities,[56] poor adherence to medication,[57] poor diets, self-neglect, and decreased self-esteem,[4] and all of these may also contribute to the incidence of CVD events.

We found between-study heterogeneity for non-fatal CVD events risk with depression by study location (US or Non-US). Given the variability of clinical guidelines for the treatment of depression[58] and the potential genetic vulnerability leading to comorbid depression and CVD,[59] we may need to consider race or country (culture)-specific risk factors for CVD when aggregating measures of association across regions. Our findings of a lower risk of non-fatal CVD events with depression in studies including subjects with a prior CVD history compared with studies excluding those with prior CVD events at baseline indicate that the risk of primary and secondary CVD events among diabetic patients might differ (i.e. larger effects of depression on primary CVD events compared with secondary CVD events). However, we cannot rule out the possibility that the history of CVD events in patients with depression might be so disabling that they cannot be enrolled in studies (i.e. bias towards the null). Pharmacological management of depression specific to patients with a prior CVD[59] and careful follow-up of such patients might also contribute to the observed difference. Further investigations would be needed to validate these hypotheses.

Using bias analysis, we also demonstrated that uncontrolled confounding alone is unlikely to sufficiently explain our findings. Given that depression and CVD share environmental and lifestyle risk factors such as socioeconomic status, social adversity, smoking, and physical inactivity,[6] uncontrolled confounding is one of the important issues in observational studies that prevents us from inferring a causal relationship between depression and CVD events. In the present study, we focused on unemployment because none of the included studies controlled for this variable (except one study that included only employed individuals) despite prior findings that unemployment is one of the major risk factors of depression[13] and CVD.[14] Our bias analysis indicated that unemployment status among diabetic patients would have needed to have a very strong association with both depression and CVD. According to the

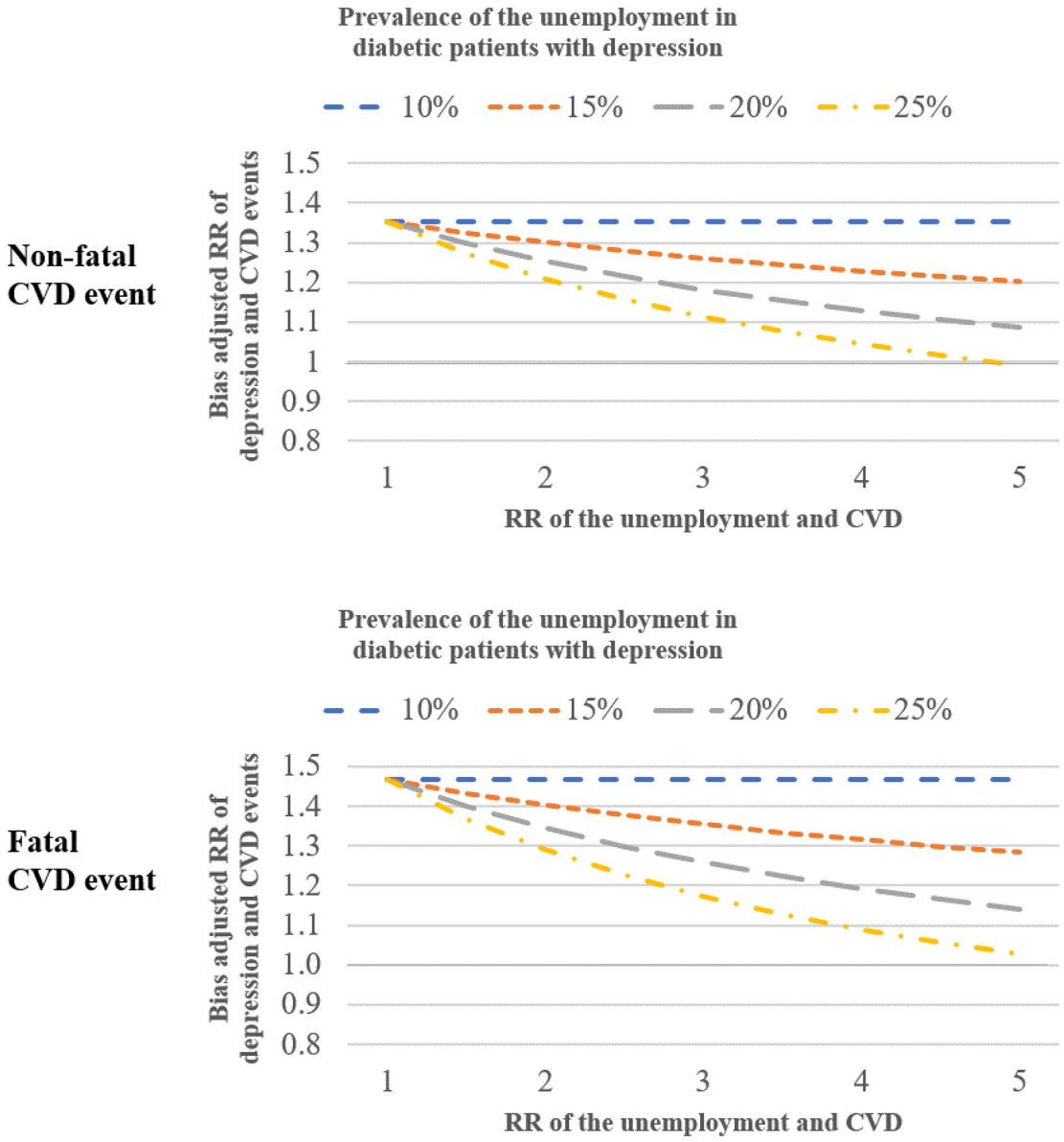


Fig. 3. Random effects meta-analysis of the association of depression with non-fatal and fatal CVD events among individuals with type 2 diabetes adjusting for bias due to unmeasured confounding (unemployment).[a] [a]Assuming the prevalence of unemployment in diabetic patients with depression is 10%.

previously reported association with an HR of 1.74 between unemployment and CVD events risk,[14] failing to control for unemployment may not fully explain the observed association between depression and CVD among patients with type 2 diabetes. Furthermore, given the current unemployment crisis due to the COVID-19 pandemic,[60] the potential role of employment status and its sequela such as access to health insurance and health care in diabetes epidemiology would require more attention than ever. Thus, our bias analysis emphasizes the importance of this factor as a potential confounder in future diabetes-related research.

Our study has several limitations. First, a bias analysis for uncontrolled confounding does not remove the possibility that the selected cohort studies may have suffered from other sources of bias such as measurement error and selection bias. Most cohort studies included in this meta-analysis rely on self-reports of diabetes, which may lead to misclassification. The bias from such misclassifications is most likely non-differential with respect to CVD outcome events, and thus would bias the measure of association towards the null, if at all. Selection bias could also be induced by a differential loss to follow up in each study given that some studies identified CVD events by self-report.[27,32,36,41] Second, manifestations of CVD events might be heterogeneous across the studies included in this meta-analysis. For example, the study by Scherrer et al.[33] defined myocardial infarction incidence as their primary outcome, while the study by Wang et al[42] estimated the risk of heart failure incidence. Third, depression and type 2 diabetes have bidirectional associations, but most studies included in this meta-analysis do not specify which condition developed first. When diabetes is a confounder of the association between depression and CVD outcomes, the stratification by diabetes status (described as [*Type 2 Diabetes*] in Supplementary Fig. 4) would remove the confounding bias due to diabetes. However, it is also possible that diabetes occurred after the development of depression. In this scenario, diabetes would be a mediator between depression and CVD outcomes, and conditioning on diabetes would not allow us to accurately estimate the total effects of depression on CVD outcomes. To overcome these limitations, further longitudinal studies with clear causal ordering and consistent definitions of depression, diabetes, and CVD will be necessary. Fourth, as type 1 diabetes has different biological and socio-behavioral mechanisms from type 2 diabetes, our result may not extend to patients

with type 1 diabetes. Finally, this meta-analysis cannot conclude whether treating depressive symptoms in diabetic patients will be effective in reducing CVD risks, while reducing depressive symptoms will certainly improve health-related quality of life.

5. Conclusions

In conclusion, the present meta-analysis found that depression is associated with an increased risk of non-fatal and fatal CVD events. Our bias analysis showed that the observed association between depression and CVD events may not be entirely explained by confounding due to uncontrolled factors such as unemployment. Further investigations are needed to understand whether and to what extent mental health management prevents fatal and non-fatal CVD events among patients with type 2 diabetes.

CRediT authorship contribution statement

All authors had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Inoue, Beekley, Goto, Jeon, Ritz.

Acquisition, analysis, or interpretation of data: Inoue, Beekley, Goto, Jeon, Ritz.

Drafting of the manuscript: Inoue, Beekley.

Critical revision of the manuscript for important intellectual content: Inoue, Beekley, Goto, Jeon, Ritz.

Statistical analysis: Inoue, Goto, Jeon.

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Declaration of competing interest

All authors state that they have no conflict of interest.

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Appendix A. Supplementary data

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