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Comorbid depression and risk of cardiac events and cardiac mortality in people with diabetes: A systematic review and meta-analysis

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Abstract

Objective: To examine the association of comorbid occurrence of diabetes and depression with risk of cardiovascular endpoints including cardiovascular mortality, coronary heart disease and stroke.

Research Design and Methods: A systematic review and metaanalysis. We searched PUBMED/MEDLINE, Medscape, Cochrane Library, CINAHL, EMBASE and Scopus databases assessing cardiac events and mortality associated with depression in diabetes up until 1 December 2018. Pooled hazard ratios were calculated using random- effects models.

Results: Nine studies met the inclusion criteria. The combined pooled hazard ratios showed a significant association of cardiac events in people with depression and type 2 diabetes, compared to those with type 2 diabetes alone. For cardiovascular mortality the pooled hazard ratio was 1.48 (95% CI: 1.185, 1.845), p=0.001, for coronary heart disease 1.37 (1.165, 1.605), p<0.001 and for stroke 1.33 (1.291, 1.369), p<0.001. Heterogeneity was high in the meta-analysis for stroke events (I-squared = 84.7%) but was lower for coronary heart disease and cardiovascular mortality (15% and 43.4% respectively). Meta-regression analyses showed that depression was not significantly associated with the study level covariates mean age, duration of diabetes, length of follow-up, BMI, sex and ethnicity (p<0.05 for all models). Only three studies were found that examined the association of depression in type 1 diabetes, there was a high degree of heterogeneity and data synthesis was not conducted for these studies.

Conclusions: We have demonstrated a 47.9% increase in cardiovascular mortality, 36.8% increase in coronary heart disease and 32.9% increase in stroke in people with diabetes and comorbid depression. The presence of depression in a person with diabetes should trigger the consideration of evidence-based therapies for cardiovascular disease prevention irrespective of the baseline risk of cardiovascular disease or duration of diabetes.

Introduction

Diabetes is a major health challenge, affecting nearly 415 million people globally. This is expected to increase to 642 million by 2040 (1), predominately due to the prevalence of sedentary life styles and increasing rates of obesity (2).

Diabetes can have significant impact on quality of life and increases social isolation, negatively impacting mental health and long-term management of diabetes (3). Current research suggests that people with type 2 diabetes are more likely to be depressed, compared to those without, and people with depression are more likely to develop diabetes (4-7).

A number of studies have shown that those with diabetes and coexisting depression have higher rates of all- cause mortality and cardiovascular (CV) mortality (7-14) relative to those with no depression. In addition, diabetic patients are even more likely to be depressed following major cardiac events, which independently results in increased recurrent CHD risk (Milani et al., 1996). In a meta-analysis (8) a 39% increased risk of cardiovascular mortality was found with the presence of depression in people with diabetes. The study however assessed only five studies from 2005-2012. In this present study, we aim to update the review and further the nature of the relationship between diabetes and co-morbid depression with cardiovascular morbidity and mortality.

Methods

Data sources and search strategy

We conducted this literature-based review using a protocol registered in the PROSPERO International prospective register of systematic reviews (accessed at www.crd.york.ac.uk/ PROSPERO/display_record.asp?ID=CRD42017083968) and in accordance with guidelines of PRISMA. We searched PUBMED/MEDLINE, Medscape, Cochrane Library, CINAHL, EMBASE and Scopus databases, for all articles containing the keywords "diabetes" or "diabetes mellitus" in combination with "depression" or "depressive disorder", combined with "cardiac mortality" or "cardiovascular disease" or "macrovascular complications" or "stroke" (titles and abstract). Stroke was included as a cardiovascular outcome, and any papers including type 1 diabetes, depression and mortality associated with cardiovascular events were also included.

The computer-based searches combined free text and medical subject headings and combination of key words related to depression and diabetes, with results restricted to English language publications. We also searched reference lists of selected studies and relevant reviews for additional publications. No separate ethical approval was required for the conduct of this study, as any necessary ethical approval was obtained for each of the individual studies contributing data to the meta-analysis.

Study selection and eligibility criteria

We included only observational studies that enrolled adults with diabetes mellitus (either exclusively or as a subgroup) and a clinical history of depression that reported data on cardiovascular endpoints, all-cause mortality. Observational studies were chosen as these enable the strength of relationships between exposures and outcomes to be determined (15). Studies published from 1 January 1985 to

1 December 2018 were included to ensure a relatively consistent diabetes diagnostic criteria was used and avoid the earlier WHO 1985 guidelines definition.

Data extraction and quality assessment

The titles and abstracts of all articles identified by the broad literature search were assessed independently by two reviewers (SS and AF). Studies that did not meet the inclusion criteria were discarded. Full text of selected articles were retrieved and assessed to determine if they met the inclusion criteria. Of the studies that met the inclusion criteria, one author (AF) initially conducted the data extraction using a standardized data collection form and a second author (SS) independently checked the extracted data with that in the original articles. The quality of the studies were assessed independently by both reviewers. Data were extracted on the following characteristics: study title, journal name, first author, year, study design and population, length of follow up, sample size, assessment method of diabetes, depression and CVD, how outcomes were measured, antidepressants treatment and dose, statistical analysis used, and hazard ratio with corresponding 95% CI and multivariable adjustment.

For cohort and case-control studies, study quality was assessed based on the nine-star Newcastle–Ottawa Scale (NOS) (16) three pre-defined domains: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality. For cross-sectional studies, quality was evaluated using the NOS modified for cross-sectional studies (17).

Data synthesis and statistical analysis

Data was extracted from studies identified through the selection process. Most studies reported the associations of depression on cardiac events in terms of hazard ratios, although a few studies reported odds ratios. As hazard ratios represent instantaneous risk and odds ratios cumulative risk, they should not be combined directly in a meta-analysis (18) so only studies reporting hazard ratios were included in the data synthesis. Additionally, only hazard ratios comparing patients with type 2 diabetes and depression against type 2 diabetes alone were included, whilst studies comparing patients with type 2 diabetes and depression, against those with neither condition, were excluded. Only three studies were found that examined the association of depression in type 1 diabetes, and there was a high degree of heterogeneity and therefore data synthesis was not conducted for these studies.

9 studies reported relevant outcomes to be included in meta-analyses. Three random effects meta-analyses were run to combine study estimates on cardiovascular mortality, coronary heart disease and stroke. Heterogeneity between studies was assessed using the I-squared statistics (19), and explored through meta-regression models using study level estimates for mean age, mean duration of diabetes, mean follow-up, mean BMI, percent female, and percent white. For all meta-analyses models fitted, funnel plots and Egger's tests were carried out to assess for publication bias (20). All tests were two-tailed and p-values of 0.05 or less were considered significant. STATA release 14 (21) was used for all statistical analyses.

Results

A total of 1700 potentially relevant citations were retrieved from electronic database searches. From these, 178 abstracts were assessed for eligibility, and 25 articles were selected for full text review. Of these, 16 full texts were excluded (figure 1).

<figure 1>

Descriptive data synthesis

Overall 9 prospective cohort studies reported relevant outcomes to be included in meta-analyses (table 1). In total there were 346,037 people with diabetes and depression, and 614,574 with diabetes only. For these studies the follow up periods ranged from 4-20.8 years, with a mean follow up of 8.3 years. The mean age at baseline was 60.4 years, ranging from 41.3 - 64.3 years.

Studies used different assessment measures for depression. Six studies used self-report measures, including the Patient Health Questionnaire-9 (PHQ-9) (22), four-item Center for Epidemiologic Studies Depression (CES-D) questionnaire (23), or the General Health Status Questionnaire (GHS) (24). One study used the National Institute of Mental Health Diagnostic Interview Schedule- v3 (DIS) (25). Two studies defined depression based on administration records of the medical diagnosis of depression. No studies reported the effects of antidepressant treatment.

<table 1>

Data was extracted from studies identified through the selection process. Four studies, comprising 13,739 individuals with diabetes and including 3,592 (26%) with comorbid depression reported on **cardiovascular mortality** as an outcome.

Five studies, comprising 11,264 individuals with diabetes and including 3,390 (30%) with comorbid depression reported on **coronary heart disease** as an outcome. Two studies reported on cardiovascular or coronary heart disease events, such as myocardial infarction, or typical angina. One study reported on incident coronary heart disease, defined as the first hospitalisation for/with CHD. Two studies reported on macrovascular complications; one study included congestive heart failure and coronary artery bypass grafting, and the other study include composite macrovascular outcomes such as major coronary artery disease events such as unstable angina.

Three studies, comprising of 945,136 individuals with diabetes and including 342,466 (36%) with comorbid depression reported on **stroke** as an outcome. One study reported stroke events including events with symptoms lasting 24 hours with neuroimaging consistent with acute ischemia or haemorrhage.

NOS quality scores ranged from 6-9, with six studies (11, 26-30) receiving a score of 8 or higher. 8 studies reported type 2 diabetes, however one study (27) reported that in their sample, 34 participants (44.7%) had type 1 diabetes, and 42 (55.3%) had type 2 diabetes. They did not examine type 1 and type 2 patient samples separately.

Quantitative data synthesis

The combined pooled hazard ratios all showed a significant risk of cardiac events in people with depression and type 2 diabetes, compared to those with type 2 diabetes alone. For cardiovascular mortality the pooled hazard ratio was 1.48 (95% CI: 1.185, 1.845), p=0.001, for coronary heart disease 1.37 (1.165, 1.605), p<0.001 and for stroke 1.33 (1.291, 1.369), p<0.001 (figure 2). Heterogeneity was high in the meta-analysis for stroke events (I-squared = 84.7%) but was lower for coronary heart disease and cardiovascular mortality (15% and 43.4% respectively). Meta-regression analyses showed the impact of depression was not significantly associated with the study level covariates mean age, duration of diabetes, length of follow-up, BMI, sex and ethnicity (p<0.05 for all models). The Egger's test and funnel plot indicated no issues with publication bias for both stroke and cardiovascular mortality, but was significant for coronary heart disease (p=0.002), although this result appears to be influenced by one small statistically significant study. For all three meta-analyses the number of studies was small, making the presence of publication bias difficult to assess.

<figure 2>

Only two studies reported hazard ratios over a 10 year follow up period. One study (27) found that depression significantly accelerated the presentation of CHD over the 10 year period, p <0.01. However, another study (11) found there was no significant difference between hazard ratios, associated with cardiovascular mortality, between 5 and 10 year follow up periods.

Sensitivity analysis

Although self-report instruments such as the PHQ-9 are well-validated, one study (31) looked at the association of depression with long-term mortality in a prospective follow up study, and found a large discrepancy in the rates of depression defined by the PHQ-9 and the clinical interview (using specific modules from Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*). Another study (32) demonstrated a higher all-cause mortality risk when depression was measured by self-reports in people with diabetes, compared to when measured by clinical interviews. Self-reported measures such as the PHQ-9 may measure somatic symptoms of other physical health problems or substance misuse, rather than depression, and may therefore inflate the relationship between depression and mortality (31).

Two studies (29, 30) reported depression based on administrative records of the medical diagnosis of depression, and another study (27) reported depression based on the National Institute of Mental Health Diagnostic Interview Schedule- version 3. The clinical opinion of a psychiatrist was recorded as equivalent to a standardised psychiatric interview so these studies can be seen as gold standard and merged.

We ran a sensitivity analyses comparing studies which reported a more restricted measure of depression (clinically diagnosed depression) compared to those who used a self-reported measure. For the four studies reporting cardiovascular disease as an outcome, no studies used a self-reported measure, so no comparison could be made. For coronary heart disease, 4 studies reported a more restricted measure, whilst one study used a self-reported measure. A meta-regression analysis comparing effect size by type of depression measure found no statistical difference (p=0.155) (figure 3). For stroke, two out of the three available studies used a self-reported depressions score, but again no difference in the study hazard ratios was found by type of depression measure (p=0.823) (figure 4).

Discussion

Summary of findings

In this systematic and meta-analysis of cohort studies we have summarised all available observational studies that have assessed the association of the comorbid occurrence of diabetes and depression with clinical CVD endpoints. We have demonstrated a 47.9% increase in cardiovascular mortality, 36.8% increase in coronary heart disease and 32.9% increase in stroke in people with diabetes and comorbid depression. Our findings are consistent with previous reviews on this topic. A meta-analysis (8), which reviewed five studies from 2005-2012, found that depression was associated with an increased risk of all-cause mortality (HR = 1.46, 95% CI = 1.29-1.66), and cardiovascular mortality (HR = 1.39, 95% CI = 1.11-1.73) in people with diabetes. Another study (32) also demonstrated an increased all-cause mortality risk (HR = 1.76, 95% CI=1.45-2.14,) when depression was measured by self-reports in people with diabetes and HR = 1.49, 95% CI=1.15-1.93 when measured by clinical interviews. In addition to being an update of the previous reviews, our study focused on cardiovascular outcomes which are the leading cause of morbidity and mortality in people with diabetes, demonstrating the added burden of depression on mortality on these outcomes.

Interpretation of findings

The current evidence suggests an associated increased risk of cardiovascular mortality and stroke in people with comorbid depression and diabetes. This may be explained by several behavioural and physiological mechanisms. Depressive symptoms, associated with diabetes, are linked to an increase in counter regulatory hormones (such as cortisol and catecholamines), affecting insulin resistance and susceptibility to obesity (10). An increased risk of cardiovascular mortality is linked to biological alterations caused by depression, such as activation of the hypothalamic-pituitary-adrenal axis and proinflammatory cytokines, and dysregulation of the sympathic nervous system (8). Depressive symptoms are also related to unhealthy behaviours, such as a poor diet sedentary lifestyle, and poor adherence to medical treatment, resulting in higher rates of mortality (33).

Implications of findings

The current findings provide further insight on the increased risk of cardiovascular outcomes in people with diabetes and depression. It is therefore imperative that there is an increased focus on cardiovascular disease prevention in this group of patients.

Cardiac rehabilitation and exercise training may also reduce depression, and associated mortality rates, in diabetic CHD patients (Milani and Lavie, 1996). However, patients should also be screened for psychological risk factors, such as anxiety and hostility. These are involved in the pathogenesis and progression of CVD (Lavie et al. 2016), and may influence mortality rates after cardiac rehabilitation (Kachur et al., 2016), possibly mediated through depression (De Schutter et al. 2015). Additional interventions, such as stress management training, may enhance the benefits of cardiac rehabilitation (Lavie et al., 2016).

In most patients with diabetes of longer duration of more than 10 years, where the condition is considered a cardiovascular risk equivalent, and in people with diabetes and high cardiovascular risk, guidelines recommend starting statins for cardiovascular disease preventions. In these patients,

whether or not they have depression, they would already be getting the best available evidence for prevention of any extra cardiovascular risk confirmed by the depression. However, from our findings, it could be argued, that the presence of depression in a person with diabetes should trigger the consideration of evidence-based therapies for cardiovascular disease prevention irrespective of the baseline risk of cardiovascular disease or duration of diabetes.

Additionally, for clinicians managing depression, the most significant cause of mortally will be suicide and rightly, there is usually a focus in addressing suicide risk in these patient. Our findings open up and channel of consideration of reducing death in people with comorbid diabetes and depression. Clinicians managing depression therefore need to be aware of the presence of diabetes and recommend cardiovascular risk prevention to the patients family doctors.

Strengths and limitations

The main strength of analysis is the comprehensive search strategy which yielded several published studies on the topic. Overall, this review involved 346,037 participants with both diabetes and depression and evaluated a wide-range of CVD outcomes and their relationships with the diabetes and depression. Formal tests demonstrated no evidence of publication bias.

Our analysis was a limited by lack of data to assess the impact of baseline cardiovascular risk with people with diabetes and depression on subsequent cardiovascular outcomes. This makes our suggestions for clinical implications less generalizable. Additionally, as the studies included were observational, study level confounding factors, not corrected for, could all have affected the results and conclusions we are drawing from this meta-analysis.

No data was available on the effects of antidepressant treatment. A number of studies have found that different antidepressant drugs are associated with several potential adverse outcomes, including myocardial infarction (34-37), and stroke/ transient ischaemic attack (38). We therefore acknowledge possible confounding by antidepressants as a limitation, and associated implications for managing or preventing cardiovascular disease.

Combining data from studies with differing measures of depression is another limitation that should be considered, although we ran a sensitivity analysis comparing studies which reported clinically diagnosed depression compared to those who used a self-reported measure. It is important to acknowledge that in large data sets clinical interviews are prohibitively expensive, and may therefore be a limitation in future studies.

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Conflicts of Interest/Disclosures

None relevant to declare

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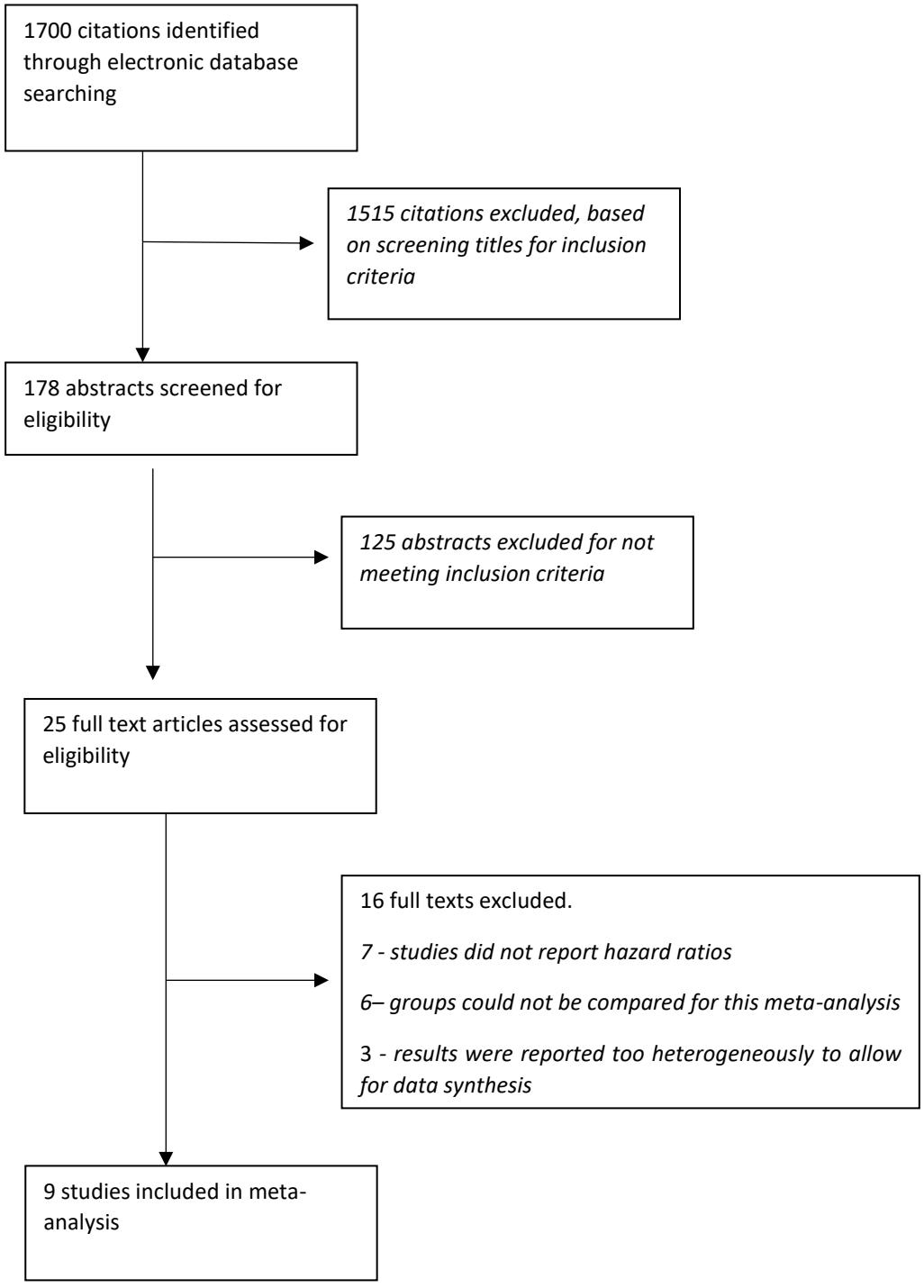

Figure 1. Flow chart summarising studies selected for review

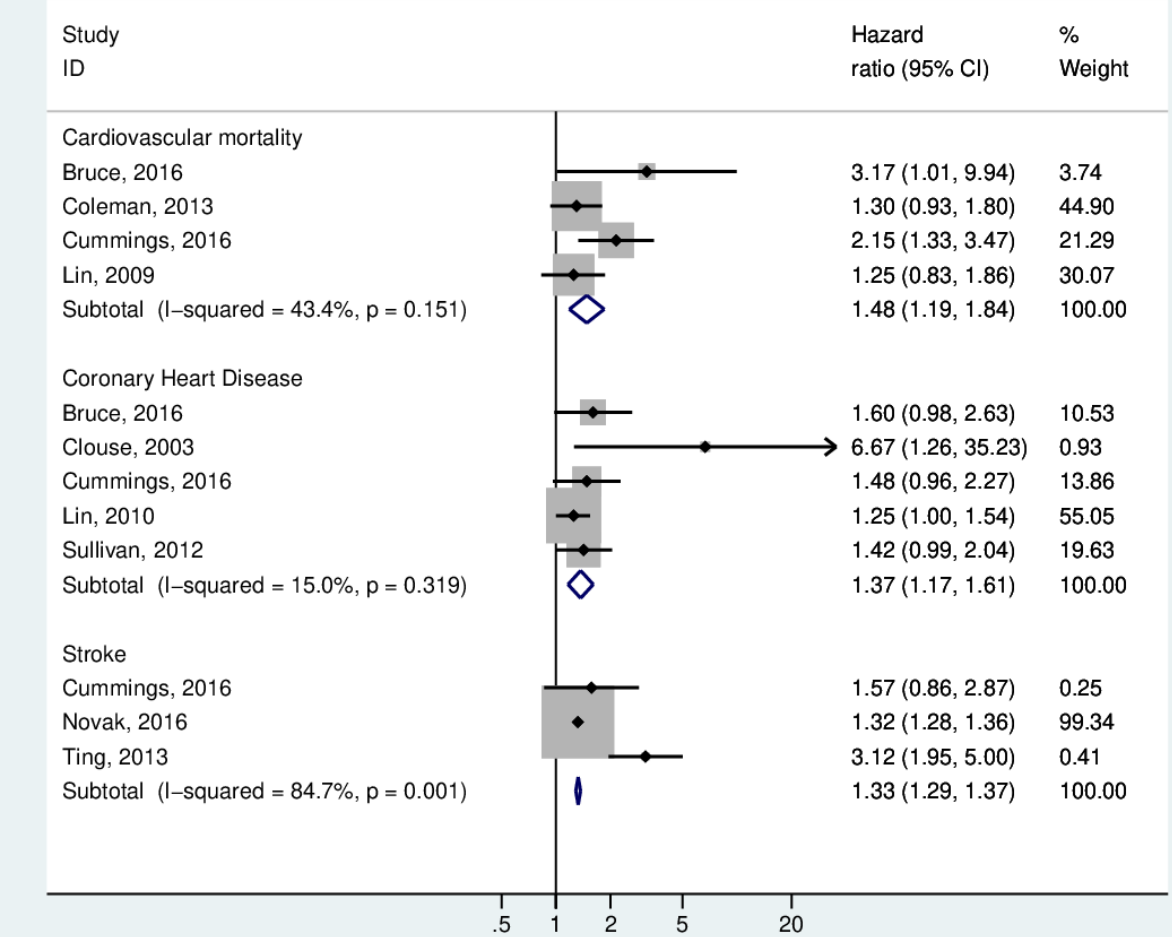

Figure 2. Depression as a risk factor for cardiac events and cardiovascular mortality in patients with type 2 diabetes

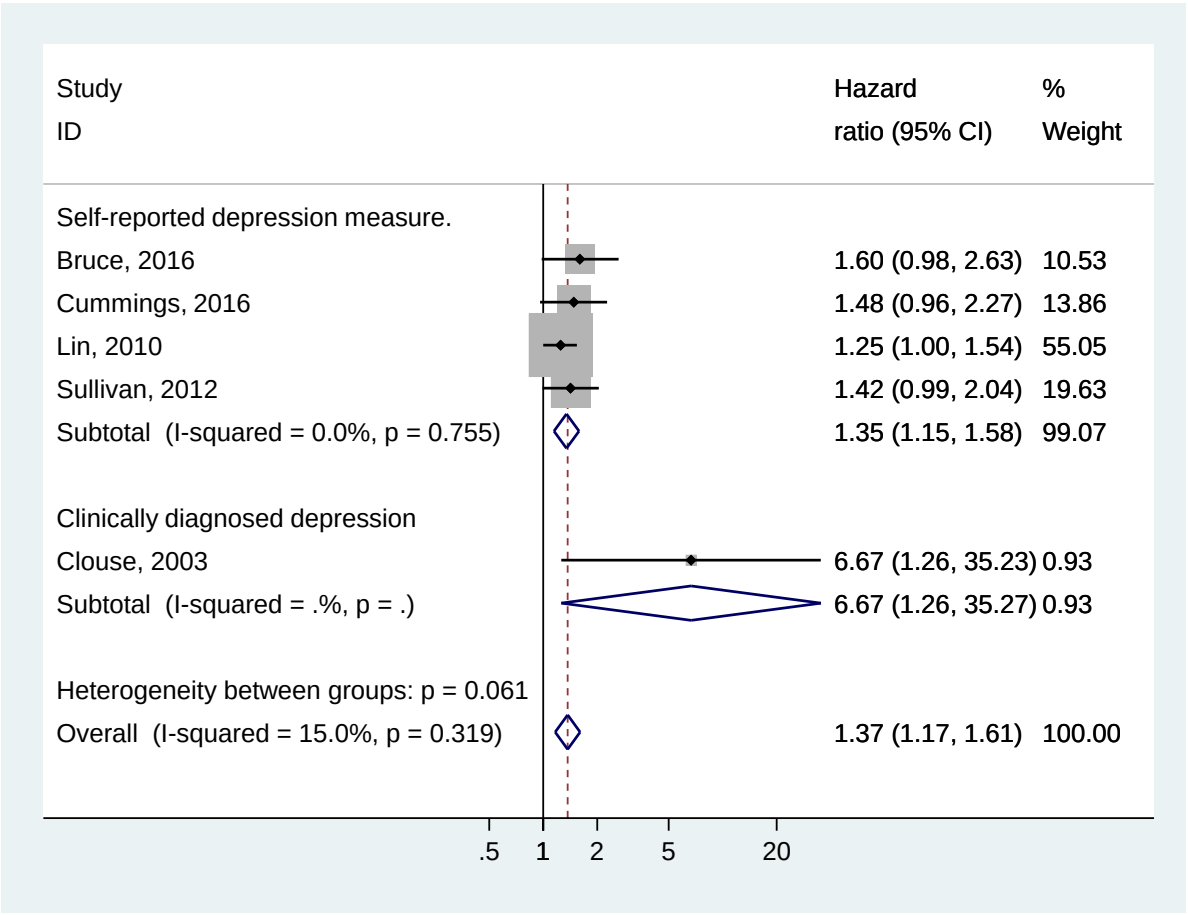

Figure 3. Meta-regression comparison of the pooled effect sizes between the two groups was not statistically significant for coronary heart disease, *p*=0.155.

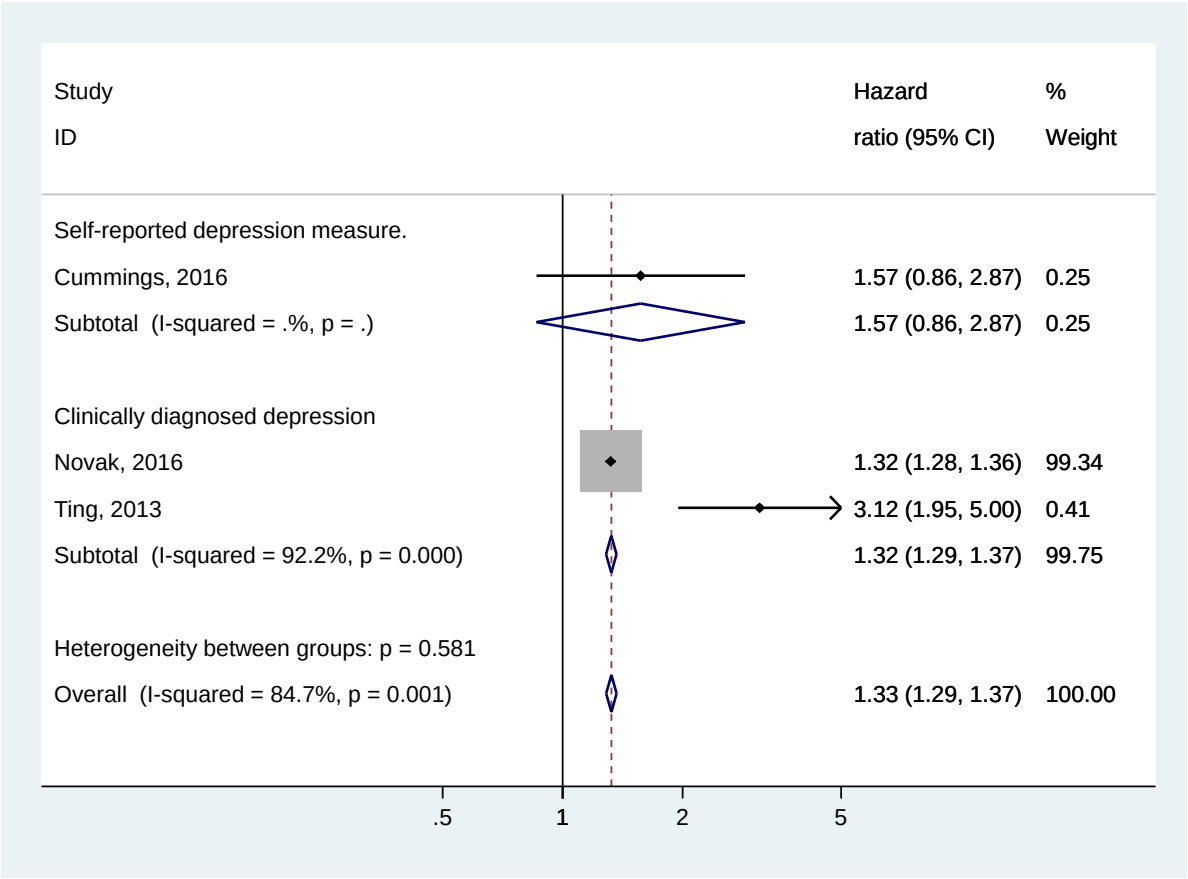

Figure 4. Meta-regression comparison of the pooled effect sizes between the two groups was not statistically significant for stroke, *p*=0.823.

Table 1. Summary of studies included in the meta-analysis

Study/year	Country	Sample size	Mean age/ years (SD)	Length of follow up (SD)	Adjustment for covariates
Bruce, 2016	Australia	1,337	64.9 (14.4)	4 years	N/A
Coleman, 2013	USA	4,128	63.4 (13.4)	10 years	Demographic and clinical characteristics (including diabetes duration, treatment intensity, medical co-morbidity and hypertension diagnosis)
Cummings, 2016	USA	22,003	64	5.95 years	Depressive symptom and stress category, demographic factors, social and economic factors and risk factors
Lin, 2009	USA	4,184	64 (12.5)	5 years (1.5)	Demographic, clinical characteristics, health habits and disease control measures
Clouse, 2003	USA	76	41.3 (15.7)	Up to 10 years	Demographic information, tobacco use, presence of hypertension or hyperlipidemia, BMI and glycosylated haemoglobin
Lin, 2010	USA	3,723	64.3 (12.5)	20.8 years	Demographic characteristics, clinical characteristics, health habits or self-care behaviours that may be affected by depression
Sullivan, 2012	USA	2,053	62.2 (6.7)	4.67 (1.45) years	Demographic, trial and clinical variables
Novak, 2016	USA	933,211	64 (11)	7 years	Demographic, race/ethnicity, baseline eGFR, comorbidities at baseline, use of statins and antihypertensive medications, BMI and serum albumin level
Ting, 2013	Hong Kong	7,835	51.6	7.4 years	Demographic and clinical characteristics