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Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. — Source link

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a systematic review and meta-analysis

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Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis

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What's new?

- Numerous studies have examined the longitudinal relationship between depression and diabetes complications but comprehensive evidence about the magnitude and direction is unavailable.
- The current study shows that the relationship between depression and diabetes complications appears bi-directional with depression being associated with an increased risk of developing incident macrovascular and microvascular complications, and diabetes complications increasing the risk of subsequent depression.
- The increase in risk of developing diabetes complications in depressed people (by 38 and 33% for macrovascular and microvascular complications, respectively) is higher than the increase in risk of developing depression (by 9 and 24% for macrovascular and microvascular complications, respectively) in people with diabetes complications.

Abstract

Aims To conduct a systematic review and meta-analysis of longitudinal studies assessing the bi-directional association between depression and diabetes macrovascular and microvascular complications.

Methods Embase, Medline and PsycINFO databases were searched from inception through 27 November 2017. A total of 4592 abstracts were screened for eligibility. Meta-analyses used multilevel random/mixed-effects models. Quality was assessed using the Newcastle-Ottawa scale.

Results Twenty-two studies were included in the systematic review. Sixteen studies examined the relationship between baseline depression and incident diabetes complications, of which nine studies involving over one million participants were suitable for meta-analysis. Depression was associated with an increased risk of incident macrovascular (HR = 1.38; 95% CI: 1.30–1.47) and microvascular disease (HR = 1.33; 95% CI: 1.25–1.41). Six studies examined the association between baseline diabetes complications and subsequent depression, of which two studies involving over 230 000 participants were suitable for meta-analysis. The results showed that diabetes complications increased the risk of incident depressive disorder (HR = 1.14; 95% CI: 1.07–1.21). The quality analysis showed increased risk of bias notably in the representativeness of selected cohorts and ascertainment of exposure and outcome.

Conclusions Depression in people with diabetes is associated with an increased risk of incident macrovascular and microvascular complications. The relationship between depression and diabetes complications appears bi-directional. However, the risk of developing diabetes complications in depressed people is higher than the risk of developing depression in people with diabetes complications. The underlying mechanisms warrant further research.

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<H1>Introduction

Diabetes is associated with long-term complications including microvascular and macrovascular disease. Prospective studies have also shown a significant bi-directional relationship between Type 2 diabetes and depression.[1,2] Meta-analytical evidence of longitudinal studies indicates that diabetes increases the risk of developing depression by approximately 25%,[3,4] and that depression increases the risk of incident Type 2 diabetes by 40–60%.[2,3]

Depression not only increases emotional suffering in people with diabetes, it is also associated with elevated prevalence of diabetes complications.[5,6] More specifically, a meta-analysis of 27 studies focusing on the associations of depression with macrovascular complications (such as coronary artery disease), microvascular complications (diabetic retinopathy, neuropathy, nephropathy or end stage renal disease) and sexual dysfunction found a significant and consistently positive relationship.[7] Effect sizes (correlations) were small to moderate, ranging from 0.17 to 0.32 (overall effect size of 0.25) and were similar across Type 1 and Type 2 diabetes study samples. However, all of the included studies had a cross-sectional design, precluding the identification of directions and pathways. For example, similar to the longitudinal relationship between depression and diabetes, depression and diabetes complications may be related either bi-directionally (depression may increase the risk of incident diabetes complications and vice versa) or only uni-directionally.

Since the publication of that meta-analysis, a number of prospective population-based studies have examined the longitudinal relationships between depression and diabetes complications. However, comprehensive analysis of the magnitude and direction of these relationships is unavailable. Therefore, the aim was to examine the directional relationships between depression and diabetes macrovascular and microvascular complications by conducting a systematic review of longitudinal epidemiological studies. Where possible, meta-analyses were carried out to quantify the sizes of the associations.

<H1>METHODS

<H2>Data sources and searches

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[8] Literature searches were conducted using Embase, Medline and PsycInfo from inception through 27 November 2017, including references of eligible articles. Databases were searched using Medical Subject Headings (MeSH) and Boolean operators.

The search terms (for Embase see the supporting information) were adapted to meet the requirements of each database.

<H2>Study selection

The results of the searches were divided into batches of 500, and for each batch two authors independently screened the titles and abstracts. Selected papers were retrieved and two other authors independently scrutinized the full text papers for inclusion. Disagreements were resolved by discussion between the authors and the first author (AN).

Articles meeting the following study criteria were included: (i) involving adults (>18 years old) at the time of follow-up with Type 1 or Type 2 diabetes; (ii) published in peer-reviewed, English language journals; and (iii) examining the longitudinal relationship between depression and at least one long-term complication of Type 1 or Type 2 diabetes. Diabetes complications included microvascular diseases (retinopathy, neuropathy, nephropathy, sexual dysfunction, diabetic foot) and macrovascular diseases (angina, stroke, coronary artery disease, myocardial infarction, peripheral vascular disease). Studies solely focusing on amputations related to diabetes complications (n = 7) and studies examining the relationship between depression, diabetes and cardiovascular mortality were not included as these have been the topic of recent systematic review/meta-analyses.[9,10] Moreover, amputations reflect treatment decisions, which may confound their relationship with depression. Studies were also excluded if they focused on gestational diabetes, impaired glucose tolerance or pre-diabetes. Studies examining the relationship of diabetes complications with either lifetime or current depression were included.

<H2>Data extraction and quality assessment

One author (AN) performed data extraction, which was verified by two other authors (MA, MMI). Data of interest included: (i) name of first author; (ii) publication year; (iii) country; (iv) study design; (v) number of participants; (vi) mean age/age range; (vii) gender; (viii)

diabetes type; (ix) diabetes duration; (x) follow-up length; (xi) depression assessment method; (xii) diabetes assessment method; (xiii) diabetes complications assessment method; and (xiv) results regarding associations between depression and diabetes complication(s). Method of depression assessment could be either a diagnosis of depression assessed by a diagnostic psychiatric interview or assessment of depressive symptoms using a self-report questionnaire. Type of diabetes and diabetes complications could be assessed either via self-reporting or extracted from medical records. Diabetes complications could be assessed via self-reporting, with the use of diagnostic tests, or extracted from medical records.

Quality assessment of included studies was conducted by two authors (AN, KvD) based on the Newcastle-Ottawa scale[11] for cohort studies. Three domains were evaluated for each study: selection of the study groups, comparability of the groups and ascertainment of outcome of interest (Table 1). There were three levels of evidence: low risk of bias (a score of 7–9), moderate risk of bias (5–6) and a high risk of bias (score < 5).[12]

<H2>Data synthesis and analysis

The meta-analysis used multilevel random/mixed-effects models with random effects for studies and estimates within studies, which accounts for the dependency in the underlying true effects for studies supplying multiple estimates (in some studies, the same participants were assessed for multiple macrovascular and microvascular outcomes). Although correlation in the sampling errors is not automatically considered in this model, theoretical considerations and simulation studies[13] have shown that the multilevel model automatically subsumes this source of dependency into the correlation between the true effects and therefore provides valid inferences about the fixed effects. As a sensitivity analysis, we also used cluster-robust inference methods,[13-15] which yielded identical conclusions.

Criteria for meta-analysis were outcomes reported as proportional HRs and 95% CIs. For some studies, to obtain the estimate of interest (e.g. reference group people with diabetes and no depression vs. people with diabetes and depression) we recalculated HRs using the procedures described in Van Dooren *et al*.[9] For Black *et al*.[16] we combined the HRs for the group of participants with diabetes without any depressive symptoms (CES-D = 0) and those with diabetes with minimal depression (CES-D = 1–15) into the reference group. For Lin *et al*.[17] we combined the groups with probable minor depression (PHQ-9 algorithm) and no depression into the reference group and compared them with the group with probable major depression (PHQ-9 algorithm). For Scherrer *et al*.[18] we used the information from the four-group scenario (neither diabetes nor major depressive disorder, major depressive disorder alone, Type 2 diabetes alone, and co-morbid major depressive disorder and Type 2 diabetes) to obtain the HRs for the comparison of the two diabetes groups. For the meta-analyses, all outcome variables were dichotomized.

<H1>RESULTS

<H2>Search results

Figure 1 shows the results of the selection process. The searches yielded 7457 potential articles. After removing conference papers, books, dissertation abstracts and duplicates within or between the databases, 4591 abstracts remained. Twenty-nine eligible papers were selected, 24 from Embase and 5 additional papers from Medline (no additional papers from PsycInfo). One of the authors identified an additional paper[19] not included in the search results, bringing the total to 30 papers. Searches of the reference lists did not identify additional potential papers. The extracted data of the 30 studies are presented in Table S1A-C.

Where more than one study relied on the same cohort (six papers from the Epidemiological Diabetes Cohort study[20–25] and four from the Pathways Epidemiological study[17,26–28]), only the most recent or the most complete study[17,23] was selected for the review, resulting in 22 papers being included in the systematic review. Of those, 16 papers (including 1025 563 people with diabetes) examined the relationship of depression to incident diabetes complications (Table S1A,B) while 6 papers (including 239 519 people with diabetes) examined the relationship of diabetes complications to incident depression (Table S1C). Data came predominantly from the USA but also from Canada, China, Italy, Norway, Taiwan, Germany, the UK and The Netherlands.

Three of the 22 studies examined people with Type 1 diabetes,[23,29,30] 9 examined people with Type 2 diabetes,[16-19,32–36] and 6 examined people with either Type 1 or Type 2 diabetes.[31,37–41] Four studies did not specify the type of diabetes.[42–45]

Twelve studies quantified the results in terms of Cox proportional HRs,[16-19,31–34,38,41,42,45] while others used ORs,[29,30,36,40,43,44] RR[37], or provided regression coefficients.[39] Two papers briefly explained that depression did not increase incident diabetes complications but neither provided numerical data.[23,35] Of the 12 studies reporting Cox proportional HRs, 10 concerned depression as a risk factor for the onset of diabetes complications and 2 concerned the relationship from diabetes complications to incident depression.

<H2>Depression as a risk factor for diabetes complications

Finally, 9 of the 10 studies reporting HRs and 95% CI were suitable for meta-analysis; one study was not suitable for inclusion because a continuous depression measure was used rather than dichotomized depression.[41] Nine studies allowed for a meta-analysis testing depression as a risk factor for macrovascular disease. Four of the nine studies provided data on depression as a risk factor for microvascular complications, which could be used in an additional meta-analysis. Of the nine studies[16-19,31–33,38,45], most used a composite

macrovascular outcome including conditions such as myocardial infarction, coronary artery disease, congestive heart failure and stroke, but some also included cardiovascular procedures (e.g. percutaneous coronary artery intervention, coronary artery bypass grafting, abdominal aortic aneurysm repair and revascularization of the lower extremity[16]) or unstable angina[32] to obtain a single estimate of macrovascular disease. However, one study[31] reported separate outcomes for stroke and coronary heart disease for the same sample, which were included individually.

Of the four studies also analysing microvascular complications,[16,17,31,32] three included a composite microvascular outcome,[16,17,32] while Novak *et al*.[31] only used incident chronic kidney disease as an outcome.

To examine whether the HRs of developing complications in people with diabetes and depression differed according to the type of complication (macro/micro), we first carried out a moderator analysis. The results showed that the relationship between depression and complication development did not differ according to type of complication [$\chi^2(1) = 0.67$, $P = 0.41$], allowing us to analyse an overall measure of complications.

In this initial analysis, those with depression were on average 51% more likely to develop a complication than those without depression (HR = 1.51; 95% CI: 1.23–1.86). A forest plot of the HRs and 95% CI of each study, together with the estimated overall HR based on all estimates combined, is shown in Figure 2.

However, there was considerable heterogeneity between studies [Cochran's Q (13) = 92.30, $P < 0.001$; $I^2 = 86\%$]. Standardized residuals and Cook's distances showed that Black *et al*.[16] was an influential study and the source of the heterogeneity in these data (primarily due to a much larger effect size than other studies for microvascular disorders). This study was also the only one in the initial meta-analysis where complications were based on self-reporting;

therefore, we repeated the above analyses without its inclusion, and regard those secondary results as our study's primary findings.

Moderator analysis of complication type was significant for these 11 studies [χ^2 (1) = 18.82, $P < 0.001$]; therefore, results are reported separately for macrovascular and microvascular complications. Depression was associated with an increased risk of macrovascular (HR = 1.38; 95% CI: 1.30–1.47) and microvascular (HR = 1.33; 95% CI: 1.25–1.41) complications (Figure 2). Sensitivity analyses using the cluster-robust inference approach yielded identical conclusions in all of the analyses reported above.

A number of studies (n = 7) identified in the systematic review reported incompatible statistics and could not be included in the meta-analysis (e.g. ORs instead of HRs; for full details, see Table S1). In terms of macrovascular complications, the results of two studies supported the findings of the meta-analysis.[29,36] Another study[23] found a significantly increased risk only for angina (HR = 1.40; 95% CI: 1.06–1.84), but not for the objective, coronary artery disease (no statistics were provided for the latter). In terms of microvascular complications, results were mixed, with three studies supporting[30,41,43] and two failing to support the findings of the meta-analysis.[35,36] Regarding incident foot ulcers, one study found that there was a linear relationship between increased risk and the severity of depressive symptoms.[43]

<H2>Diabetes complications as a risk factor for depression

Six studies examined the hypothesis that diabetes complications increase the risk of incident depression.[34,37,39,40,42,44] For the two largest of these studies (combined N = 234 628), nine HRs of diagnosed depression were suitable for meta-analysis.[34,42] Therefore, we tested whether any diabetes complications increased the risk of incident depressive disorder, and analysis of the results using the cluster-robust approach confirmed this (HR = 1.14; 95% CI: 1.07–1.21). Because moderator analysis of complication type was significant [χ^2 (1) = 3.91, P

= 0.48], we report the results of the meta-analysis separately for macrovascular and microvascular complications. Both macrovascular (HR = 1.09; 95% CI: 1.02–1.17) and microvascular (HR = 1.24; 95% CI: 1.12–1.37) complications were associated with an increased risk of depressive disorder.

For a Forest plot of these results, see Figure 3.

The remaining four studies[37,39,40,44] reported statistics that were incompatible with their inclusion in the meta-analysis (e.g. ORs or RRs instead of HRs; for full details, see Table S1C). One study[44] found that diabetes complications (not specified) increased the odds of developing depressive symptoms (OR = 1.46; 95% CI 1.14–1.86). The results of the three studies that did examine specific diabetes complications mirrored those of the two studies in the meta-analyses. Regarding macrovascular complications, one study[37] found an increased risk of depressive symptoms with coronary artery disease, cerebral vascular disease and peripheral vascular disease, while another study[40] found this to be the case for macrovascular events or procedures, but not for stroke. Regarding microvascular complications, one study[40] found no significantly increased risk of depressive symptoms with either retinopathy or nephropathy. Two other studies[37,39] found an increased risk of depressive symptoms with neuropathy, but not with retinopathy or foot problems[37]. (For further details, see Table S1C).

<H2>Quality of evidence

Of the 22 included studies, 2 showed a high risk of bias, 8 showed a moderate risk of bias and 12 showed a low risk of bias (Table 1). Risk of bias was mainly due to the use of selected rather than representative cohorts (8 of 22 studies), use of self-reporting or failure to report the use of secure records or structured interviews to ascertain exposure (15 of 22 studies) or outcome (9 of 22 studies), and failure to demonstrate that the outcome of interest (diabetes complications/depression) was not present at baseline (10 of 22 studies, although all but 3 studies[36,38,45] statistically controlled for this).

<H1>DISCUSSION

This systematic review identified nine studies suitable for meta-analysis which showed that in people with diabetes, those with co-morbid depression have a 38 and 33% increased risk of developing macrovascular and microvascular complications, respectively, compared with controls without depression. Eight studies were identified as unsuitable for inclusion in the meta-analysis. For macrovascular complications, the results of these studies generally concurred with those obtained in the meta-analysis, except for one.[23] For microvascular complications, results were mixed, with three supporting[30,41,43] and two failing to support[35,36] the findings of the meta-analysis. Of the latter, one examined participants during their first two years of newly diagnosed diabetes,[36] and the other had cognitive function as the main predictor variable.[35]

Finally, six identified studies examined the relationship from diabetes complications to incident depression.[34,37,39,40,42,44] In the meta-analysis of the two largest studies[34,42] (total N = 234 628), diabetes complications increased the risk of developing depressive disorder by 14%. Although this increase in risk was found to be higher for microvascular than for macrovascular complications (by 24 vs. 9%, respectively), because of the small number of studies these results should be interpreted with caution. The results of the six studies not included in the meta-analyses (Table S1C) mimic those of the meta-analysis and suggest that having macrovascular and microvascular diabetes complications may increase the risk of developing depression. However, across the six studies examining the relationship of diabetes complication as a risk factor for depression, we did not find evidence of a systematic effect of specific complications.

Taken together, our results provide support for a bi-directional relationship between diabetes complications and depression. In other words, depression (both depressive symptoms and major depressive disorder) increases the risk of incident macrovascular and microvascular

diabetes complications, and the presence of diabetes complications increases the risk of significant depressive symptoms and/or possible depressive episode. However, the increase in risk of developing diabetes complications (by 38 and 33% for macrovascular and microvascular complications, respectively) in depressed people is higher than the increase in risk of developing depression (by 9 and 24% for macrovascular and microvascular complications, respectively) in people with diabetes complications. These findings parallel those found for the bi-directional longitudinal relationships between diabetes and depression with a modest increased relative risk (15%) of developing depression in people with diabetes and a higher relative risk (60%) for the development of diabetes in depressed people.[2] These findings may reflect different underlying mechanisms for the relationship from depression to diabetes or diabetes complications than for the relationship from diabetes or diabetes complications to depression. While the exact nature of these underlying mechanisms remains unknown, there are a number of common processes that may result in these negative outcomes. First, depression is often accompanied by behavioural changes, including reduced self-care and medication adherence,[46] increased smoking, reduced physical activity and increased sedentary behaviours, and increased intake of high-calorie food.[47] These behaviours may be particularly problematic in the context of diabetes and are likely to adversely affect glycaemic control, which, in turn, is associated with increased risk of complications[48]. Moreover, the UK Prospective Diabetes Study has shown that a 1% in reduction in HbA_{1c} may delay the onset of diabetes complications by 21%.[49] However, research found no evidence that depression delays insulin initiation.[50,51]

More recently, biological processes associated with obesity, insulin resistance and persistently poor glucose control, have been implicated in the development of diabetes complications in the context of depression. More specifically, inflammatory processes associated with both diabetes and depression[52] have been identified as possible

mechanisms.[53] Other studies have shown that depression and diabetes are associated with endothelial function, increasing the risk of macrovascular disease,[54] although the underlying mechanisms have yet to be elucidated.

The mechanisms underlying the increased risk of incident depression as a result of diabetes complications are likely to be similar to those hypothesized for diabetes as a risk for depression onset. Although inflammation and other biological factors may play a role,[52,54] the epidemiological evidence points to the role of diabetes burden and distress as contributing factors.[55,56] The results of our study, showing no systematic effect of specific diabetes complications, is consistent with the latter. It should be noted that only one study[39] examining the relationship of complications with incident depression controlled for pain as a possible contributor.

Overall, the results of the current study extend the findings of a previous systematic review/meta-analysis of cross-sectional studies[7] and shows that depression is associated with an increased risk of diabetes complications. Importantly, given that depression is a treatable condition, the clinical implication of this study is that depression could be a preventable risk factor for diabetes complications. Future studies are needed to examine whether intensive and successful treatment of depression in diabetes does indeed reduce the risk of future complications.[57]

The current study also adds to an increasing number of longitudinal studies showing that depression in diabetes, even when using self-report questionnaires, can have serious consequences, including reduced self-care,[39] increased cognitive decline,[58] dementia[59] and mortality.[9]

A number of limitations should be taken into consideration when interpreting the results of this study. First, despite the large number of participants upon which the meta-analyses were based, the relatively small number of studies available (n = 9 for the relationship from

depression to diabetes complications and $n = 2$ for the relationship from diabetes complications to depression) precluded examination of the contribution of factors such as specific diabetes complications, type of depression measurement, and type of diabetes. Moreover, although some studies included participants with Type 1 diabetes with paediatric onset, teasing out the effects of depression on diabetes complications in Type 1 vs. Type 2 diabetes remains a topic for future research.

Second, the quality assessment of the included studies found a high risk of bias in two studies due to, among other factors, the use of self-report measures to ascertain exposure or outcome. Self-reporting should be avoided when objective diagnostic tests are available, such as in the case of diabetes complications. However, as there are no known biomarkers for depression, its assessment remains based on symptomatology; although structured diagnostic interviews are considered the gold standard for identifying depression, self-report symptom questionnaires are commonly used. While the use of such questionnaires may be regarded as introducing bias, research suggests that symptom questionnaires and diagnostic interviews assess different constructs, with elevated depressive symptoms more reflective of general and diabetes-specific emotional distress than of clinical depression.[60] Furthermore, although most studies provided follow-up data, only a few studies provided information as to how many people had died from diabetes complications during the follow-up period. Because mortality is higher in people with depression, it is likely that the results from the meta-analysis are conservative. Third, the included studies did not provide information regarding the specific set of complications individuals developed during the study. It is therefore impossible to ascertain whether depression leads to the development of only single complications or a cluster of complications. Furthermore, some of the studies in the meta-analysis[17,31–33] included not only diabetes complications but also surgical interventions, which may or may not have resulted from the onset or worsening of diabetes complications and may have

confounded the observed relationships. Fourth, it is unclear how clinical management, access to medical care, disease management supplies and medications, financial burden of diabetes, and other socio-economic factors play into the development of depression or diabetes complications and the relationship between the two.

In summary, depression in people with diabetes is associated with an increased risk of incident macrovascular and microvascular complications. This relationship is likely to be bi-directional as diabetes complications were also found to increase the risk of incident depression. It remains to be determined whether effective treatment of depression reduces the risk of developing diabetes complications.

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<H2>Competing interests
No potential or existing conflicts of interest relevant to this article were reported.

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<H1>Supporting Information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Text S1 Search criteria Embase.
Text S2 Summary and scoring of the Newcastle-Ottawa scale.
Table S1A Depression to macrovascular complications (overview of all included studies sorted by publication date in ascending order).
Table S1B Depression to microvascular complications (overview of all included studies sorted by publication date in ascending order).
Table S1C Complications to depression (overview of all included studies sorted by publication date in ascending order).

Table 1 Results of quality assessment of studies identified in the systematic review, based on the Newcastle-Ottawa scale

	Selection				Comparability		Outcome			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure (predictor - depression/complication)	Demonstration that outcome of interest was not present at start of study	Controlled for minimum: Complications/depression at baseline or excluded	Controlled for anything else	Assessment of outcome	Was follow-up long enough for outcome to occur?	Adequacy of follow up of cohorts	Total score
Acceptable	a, b	a, b	a, b	a	a	a	a, b	a	a, b	9
Depression to diabetes complications										
Black *et al*., 2003[16]	b	a	c	b	a	a	c	a	b	6
Clouse *et al*., 2003[38]	c	a	b	b	b	a	b	a	b	6
Orchard 2003[23]§	c	a	c	a	a	a	d	a	b	6
Roy *et al*, 2007a[29]♯	b	a	c	a	a	a	b	a	b	8
Lin *et al*., 2010[17]¶	b	a	c	b	a	a	b	a	b	7
Scherrer *et al*., 2011[18]	c	a	a	a	a	a	b	a	-	7
Sullivan *et al*., 2012[32]	d	a	c	b	a	a	d	b	d	3
Ting *et al*., 2013[33]	c	a	a	a	a	a	b	a	b	8
Nefs *et al*., 2015[19]	b	a	c	b	a	a	b	a	d	6
Novak *et al*, 2016[31]	c	a	a	a	a	a	b	a	b	8
Roy *et al*., 2007b[30]♯	b	a	c	a	a	a	a	a	b	8
Gonzalez *et al*., 2010[41]*	c	a	c	a	a	a	c	a	a	6
Iversen *et al*., 2015[43]	a	a	c	a	a	a	c	a	b	7
Jani *et al*., 2016[45]	b	a	c	b	b	a	b	b	-	4
Ismail *et al*., 2017[36]	b	a	c	b	b	a	b	b	b	5
Trento *et al*., 2017[35]	b	a	c	b	a	a	a	a	b	7
Diabetes complications to depression										
Katon *et al*., 2009[40]¶	b	a	a	b	a	a	c	a	b	7
Vileikyte *et al*., 2009[39]*	c	a	c	b	a	a	c	a	b	5
Pan *et al*., 2012[42]	b	a	a	a	a	a	a	a	d	8
Jacob and Kostev, 2016[34]	a	a	a	a	a	a	b	a	-	8
Bell *et al*., 2017[44]	b	a	c	a	a	a	c	a	b	7
Deschênes *et al*., 2017[37]	a	a	c	a	a	a	c	a	c	6

♯EPESE cohort
§ EDC cohort
¶ Pathways cohort
*Baltimore, State College and Manchester Hospital cohorts
- Retrospective analyses
For a summary and scoring of the Newcastle-Ottawa scales, see the supporting information.

<Figure legends>

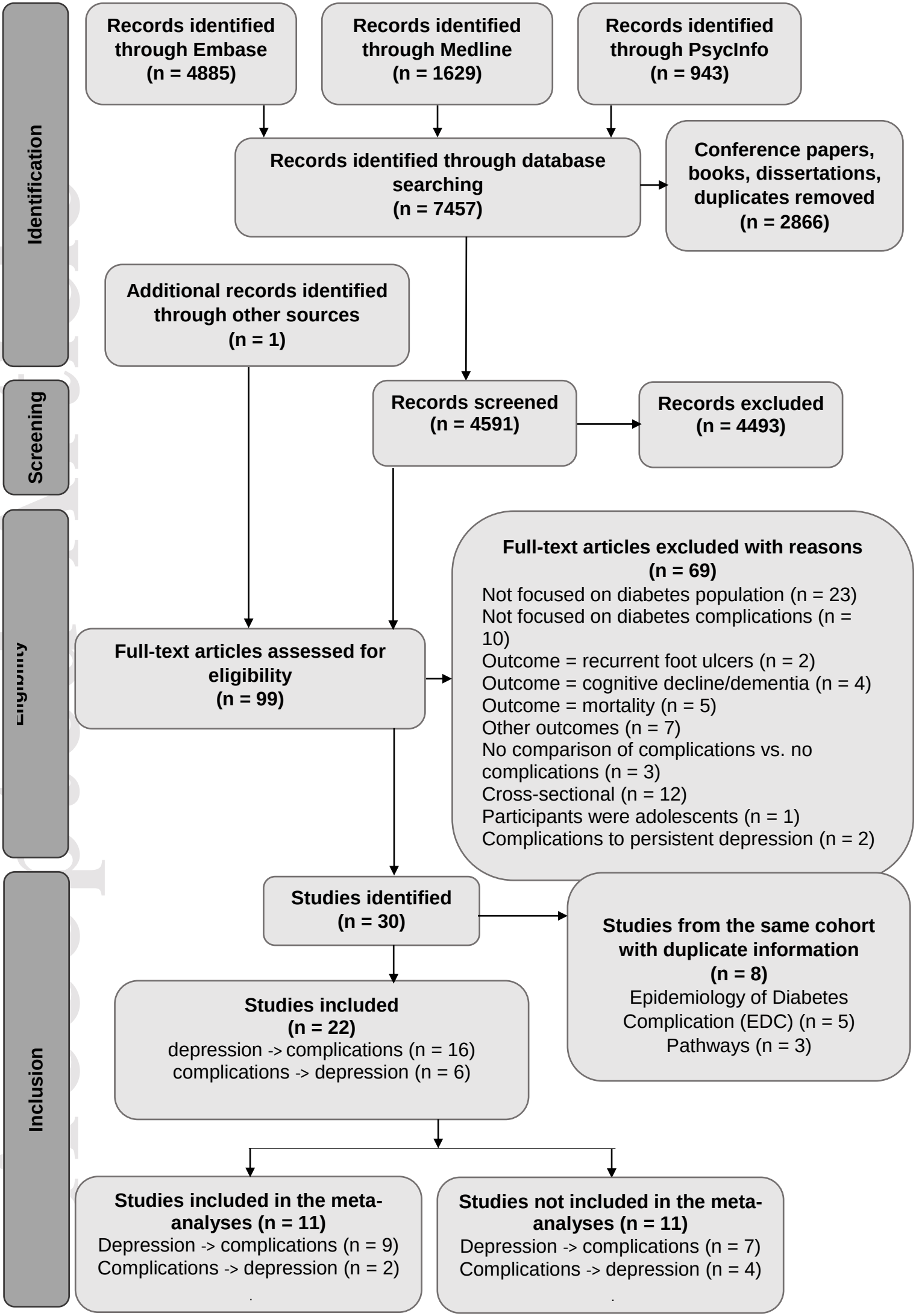
FIGURE 1 Flowchart of study selection process.

FIGURE 2 Forest plot of HRs of longitudinal studies included in the meta-analysis examining associations from baseline depression to incident diabetes complications, grouped by macrovascular complications and microvascular complications.

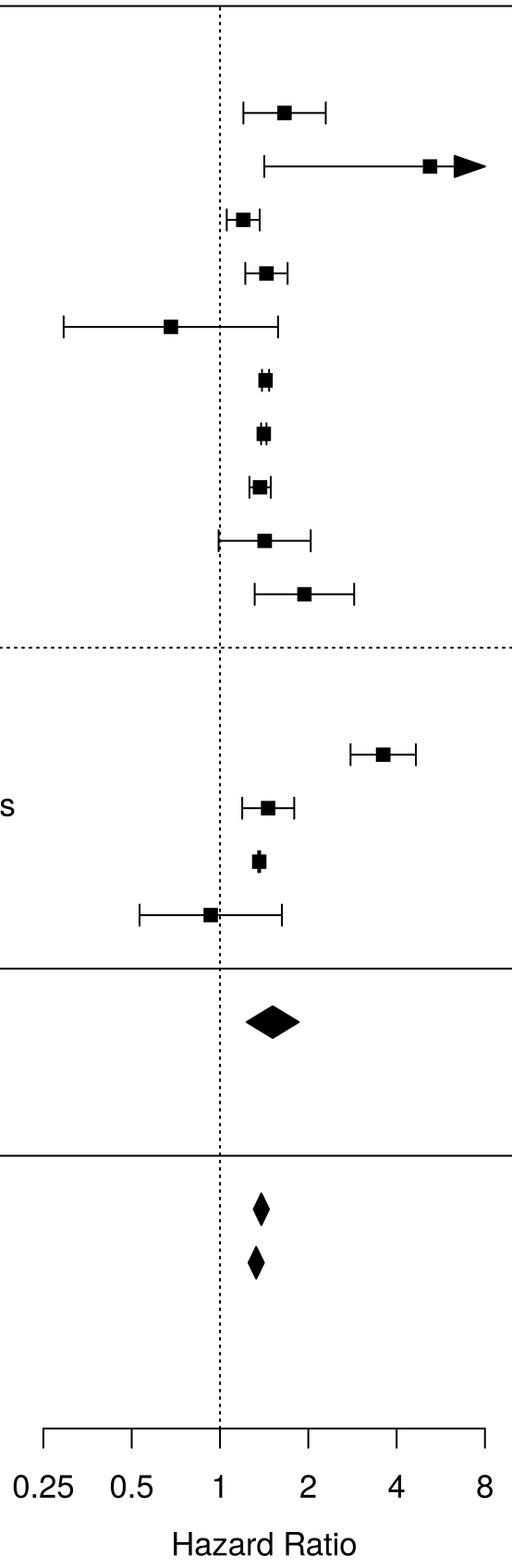
Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; CVD, cerebrovascular disease; MI, myocardial infarction; PVD, peripheral vascular disease.

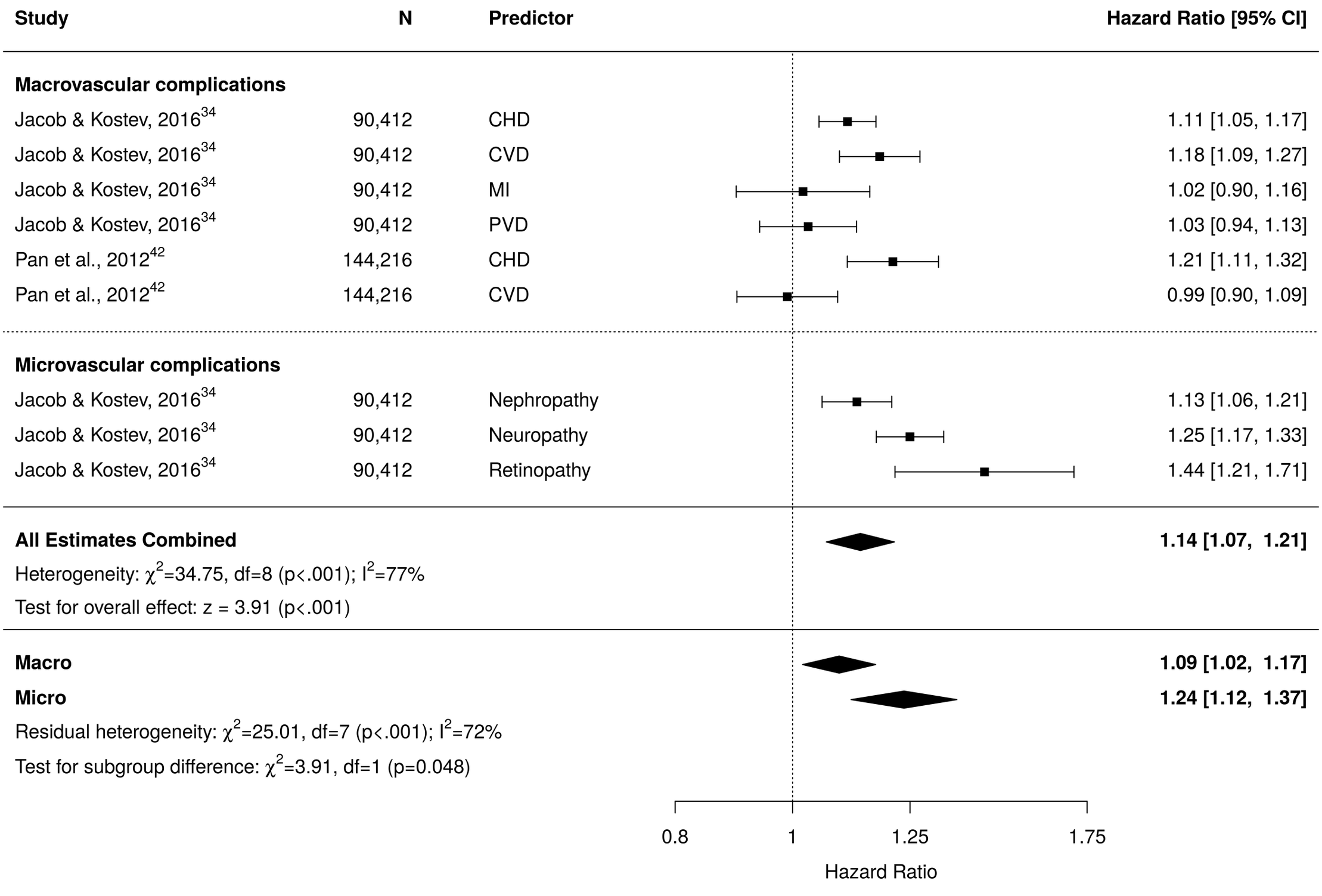
FIGURE 3 Forest plot of HRs of longitudinal studies included in the meta-analysis examining associations from baseline diabetes complications, grouped by macrovascular and microvascular complications, to incident depression.

Abbreviations: CHD, coronary heart disease; CVD, cerebrovascular disease; MI, myocardial infarction; PVD, peripheral vascular disease.


Identification
Records identified through Embase (n = 4885)
Records identified through Medline (n = 1629)
Records identified through PsycInfo (n = 943)
Records identified through database searching (n = 7457)
Conference papers, books, dissertations, duplicates removed (n = 2866)
Additional records identified through other sources (n = 1)
Screening
Records screened (n = 4591)
Records excluded (n = 4493)
Eligibility
Full-text articles assessed for eligibility (n = 99)
Full-text articles excluded with reasons (n = 69)
Not focused on diabetes population (n = 23)
Not focused on diabetes complications (n = 10)
Outcome = recurrent foot ulcers (n = 2)
Outcome = cognitive decline/dementia (n = 4)
Outcome = mortality (n = 5)
Other outcomes (n = 7)
No comparison of complications vs. no complications (n = 3)
Cross-sectional (n = 12)
Participants were adolescents (n = 1)
Complications to persistent depression (n = 2)
Inclusion
Studies identified (n = 30)
Studies from the same cohort with duplicate information (n = 8)
Epidemiology of Diabetes Complication (EDC) (n = 5)
Pathways (n = 3)
Studies included (n = 22)
depression -> complications (n = 16)
complications -> depression (n = 6)
Studies included in the meta-analyses (n = 11)
Depression -> complications (n = 9)
Complications -> depression (n = 2)
Studies not included in the meta-analyses (n = 11)
Depression -> complications (n = 7)
Complications -> depression (n = 4)

Study	N	Outcome	Hazard Ratio [95% CI]
Macrovascular complications			
Black et al., 2003[16]	636	CAD, CVD, Kidney Disease	1.66 [1.20, 2.29]
Clouse et al., 2003[38]	76	CHD, CVD, PVD	5.20 [1.42, 19.11]
Jani et al., 2016[45]	18,453	CHD, CVD	1.20 [1.05, 1.37]
Lin et al., 2010[17]	3,723	CHD, CVD, PVD	1.44 [1.22, 1.70]
Nefs et al., 2015[19]	961	CHD	0.68 [0.29, 1.58]
Novak et al., 2016[31]	933,211	CHD	1.43 [1.39, 1.47]
Novak et al., 2016[31]	933,211	CVD	1.41 [1.38, 1.44]
Scherrer et al., 2011[18]	53,632	CHD	1.37 [1.26, 1.49]
Sullivan et al., 2012[32]	2,053	CHD	1.42 [0.99, 2.04]
Ting et al., 2013[33]	7,835	CHD, CVD, PVD	1.94 [1.31, 2.87]
Microvascular complications			
Black et al., 2003[16]	636	Nephropathy, Retinopathy, Neuropathy	3.60 [2.79, 4.65]
Lin et al., 2010[17]	3,723	Nephropathy, Retinopathy, Diabetic Foot Ulcers	1.46 [1.19, 1.79]
Novak et al., 2016[31]	933,211	Nephropathy	1.36 [1.35, 1.37]
Sullivan et al., 2012[32]	2,053	Nephropathy, Retinopathy	0.93 [0.53, 1.63]
All Estimates Combined			**1.51 [1.23, 1.86]**
Heterogeneity: χ^2=92.30, df=13 (p<.001); I^2=86%			
Test for overall effect: z = 3.96 (p<.001)			
Macro (without Black et al, 2003)			**1.38 [1.30, 1.47]**
Micro (without Black et al, 2003)			**1.33 [1.25, 1.41]**
Residual heterogeneity: χ^2=18.97, df=10 (p=0.041); I^2=47%			
Test for subgroup difference: χ^2=18.82, df=1 (p<.001)			




Study
N
Predictor
Hazard Ratio [95% CI]
Macrovascular complications
Jacob & Kostev, 2016[34] 90,412 CHD 1.11 [1.05, 1.17]
Jacob & Kostev, 2016[34] 90,412 CVD 1.18 [1.09, 1.27]
Jacob & Kostev, 2016[34] 90,412 MI 1.02 [0.90, 1.16]
Jacob & Kostev, 2016[34] 90,412 PVD 1.03 [0.94, 1.13]
Pan et al., 2012[42] 144,216 CHD 1.21 [1.11, 1.32]
Pan et al., 2012[42] 144,216 CVD 0.99 [0.90, 1.09]
Microvascular complications
Jacob & Kostev, 2016[34] 90,412 Nephropathy 1.13 [1.06, 1.21]
Jacob & Kostev, 2016[34] 90,412 Neuropathy 1.25 [1.17, 1.33]
Jacob & Kostev, 2016[34] 90,412 Retinopathy 1.44 [1.21, 1.71]
All Estimates Combined 1.14 [1.07, 1.21]
Heterogeneity: χ^2=34.75, df=8 (p<.001); I^2=77%
Test for overall effect: z = 3.91 (p<.001)
Macro 1.09 [1.02, 1.17]
Micro 1.24 [1.12, 1.37]
Residual heterogeneity: χ^2=25.01, df=7 (p<.001); I^2=72%
Test for subgroup difference: χ^2=3.91, df=1 (p=0.048)
0.8
1
1.25
1.75
Hazard Ratio