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## Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis

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**Abstract** *Aims/hypothesis:* Evidence strongly suggests that depression and type 2 diabetes are associated, but the direction of the association is still unclear. Depression may occur as a consequence of having diabetes, but may also be a risk factor for the onset of type 2 diabetes. This study examined the latter association by reviewing the literature and conducting a meta-analysis of longitudinal studies on this topic. *Methods:* Medline and PsycInfo were searched for articles published up to January 2005. All studies that examined the relationship between depression and the onset of type 2 diabetes were included. Pooled relative risks were calculated using fixed and random effects models. To explore sources of heterogeneity between studies, subgroup analyses and meta-regression analyses were performed. *Results:* Nine studies met our inclusion criteria for this meta-analysis. The pooled relative risk was 1.26 (1.13–1.39) using the fixed effects model and 1.37

(1.14–1.63) using the random effects model. Heterogeneity between studies could not be explained by (1) whether studies controlled for undetected diabetes at baseline; (2) the method of diabetes assessment at follow-up; (3) the baseline overall risk of diabetes in the study population; and (4) follow-up duration. *Conclusions/interpretation:* Depressed adults have a 37% increased risk of developing type 2 diabetes mellitus. The pathophysiological mechanisms underlying this relationship are still unclear and warrant further research. A randomised controlled study is needed to test whether effective prevention or treatment of depression can reduce the incidence of type 2 diabetes and its health consequences.

**Keywords** Depression · Diabetes · Longitudinal · Meta-analysis · Observational studies · Risk factor

**Abbreviations** BRIDGE: Behavioral research in diabetes group exchange · HPA: Hypothalamic-pituitary-adrenocortical · PSAD: Psychosocial aspects of diabetes · PUFA: Polyunsaturated fatty acids

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### Introduction

Diabetes and depression are both common conditions in today's society. There are currently about 200 million people with diabetes worldwide. If nothing is done to slow down the epidemic, the number will exceed 333 million by the year 2025 [1]. Moreover, an estimated 121 million people currently suffer from depression: 6% of men and 10% of women will experience a depressive episode in any given year [2].

There is ample evidence that diabetes and depression are associated. According to a recent meta-analysis, the prevalence of depression is doubled in individuals with type 2 diabetes compared with those without diabetes [3]. However, the temporal or causal relationship between depression and type 2 diabetes remains unclear. Depression is often regarded as a comorbid condition that results from

the daily burden of having diabetes and/or its complications. Interestingly, there are also indications that depression in turn is an independent risk factor for the development of type 2 diabetes [4, 5]. This is an observation that dates back to 1684, when the English physician Thomas Willis noted that emotional factors such as grief or sadness could bring on diabetes [6, 7]. About 10 years ago, Eaton and colleagues were the first to report the results of an epidemiological study that confirmed Willis' hypothesis [6]. Since then, a number of studies have investigated the relation between depression and onset of type 2 diabetes longitudinally, with inconsistent findings. Some report that depression is associated with an increased risk of developing type 2 diabetes, while other studies do not find a significant association.

The aim of this study was to examine the relationship between depression and the risk of onset of type 2 diabetes by conducting a meta-analysis of longitudinal studies published on this subject in the peer-reviewed literature.

## Materials and methods

### Retrieval of studies

To identify the studies of interest, two authors (F. Pouter and M. J. Knol) independently searched Medline (1966 to January 2005) and PsycInfo (1872 to January 2005) using the search terms 'depression or depressive' and 'diabetes', limited to studies written in English and the availability of an abstract. Titles and abstracts of the retrieved studies were scanned to exclude studies that were clearly irrelevant. The full texts of the remaining studies were then read to determine whether the studies met our inclusion criteria. Furthermore, the reference lists of articles that indeed studied our topic of interest were scanned to check for additional publications. Finally, in order to minimise publication bias, all members of the Psychosocial Aspects of Diabetes (PSAD) study group of the European Association for the Study of Diabetes (EASD) and the Behavioral Research In Diabetes Group Exchange (BRIDGE) from the USA were asked by e-mail whether they had any unpublished/rejected results of studies investigating the relation between depression and onset of type 2 diabetes.

### Inclusion and exclusion criteria

In this meta-analysis we included all studies that longitudinally examined the relationship between depression and onset of type 2 diabetes, irrespective of their study design. Studies were excluded if the authors did not explicitly exclude subjects with prevalent diabetes at baseline and if there were insufficient data to estimate a relative risk, either an odds ratio, risk ratio or hazard ratio. When multiple publications from the same study popula-

tion were available, we included the most recent publication, regarding this study as an improvement of the older publication, representing both studies.

### Data extraction

The two authors who conducted the literature search (F.P. and M.J.K.) also independently extracted data from the studies, in particular regarding: (1) name of first author; (2) publication year; (3) study design; (4) follow-up time in years; (5) number of subjects in the analysis; (6) sex of subjects; (7) age of subjects; (8) method of depression assessment; (9) method of type 2 diabetes assessment; (10) relative risk and 95% CI (the one adjusted for the largest number of confounders); (11) adjustment for confounders; (12) method of exclusion of diabetes patients at baseline; and (13) overall incidence per year.

The method of depression assessment was a diagnosis of depression assessed by a diagnostic psychiatric interview, the assessment of depressive symptoms by a self-reported questionnaire, or a diagnosis by a general practitioner (with an unknown method of diagnosis). The method of assessment of type 2 diabetes was either self-report or screening, i.e. measuring blood glucose of all subjects. The method of exclusion of diabetes patients at baseline was also either self-report or screening; the latter correcting for undetected diabetes as well.

If depressive symptoms were categorised in more than two groups, the relative risk of the highest vs the lowest depressive symptoms group was used. Overall incidence per year was extracted as the crude incidence of type 2 diabetes of the whole study population, divided by follow-up duration.

### Statistical analysis

For each study, the relative risk of the most adjusted model was used to estimate a pooled relative risk. Both the fixed effects model and the random effects model were used. The fixed effects model assumes that variability between studies is exclusively due to random variation and individual studies are simply weighted by their precision. The random effects model assumes a different underlying effect for each study and takes this into consideration as an additional source of variation. A random effects meta-analysis is more conservative than a fixed effects meta-analysis, as it gives wider CIs around the point estimate, and is recommended for use when heterogeneity between studies exists [8]. In the fixed effects model the weight of each study is equal to the inverse variance of the natural logarithm of the relative risk. In the random effects model an extra term is added to the variance according to the DerSimonian and Laird method [9]. A forest plot was made to show the relative risk and 95% CI of each study and the pooled relative risk and 95% CI. To provide visual

**Table 1** Characteristics of studies included in the meta-analysis

Study	Study design	Follow-up (years)	n (% of male)	Mean age±SD	Assessment depression	Assessment diabetes	Relative risk (95% CI)	Adjustment for confounders <sup>g</sup>
Eaton et al. 1996 [13] <sup>a</sup>	Cohort	13	1,715 (37.8)	18± <sup>c</sup>	Interview: DIS	Self report	2.23 (0.90–5.55) <sup>d</sup>	1, 2, 3, 4, 5, 8, 26
Kawakami et al. 1999 [16]	Cohort	8	2,380 (100.0)	18–53 <sup>c</sup>	Self-rating: Zung SDS	Screening WHO 1981	2.31 (1.03–5.20) <sup>e</sup>	1, 5, 6, 7, 8, 12, 13, 14, 24, 29
Carnethon et al. 2003 [12]	Cohort	16	6,190 (45.7)	48±14	Self rating: GWB-DS	Self or doctor report	1.86 (1.27–2.71) <sup>e</sup>	1, 2, 3, 8, 12, 13, 14
Arroyo et al. 2004 [11]	Cohort	4	72,178 (0.0)	58±7	Self-rating: MHI-5	Self-report	1.22 (1.00–1.50) <sup>d</sup>	1, 8, 12, 13, 14, 16, 23, 29
Golden et al. 2004 [15]	Cohort	6	11,615 (44.6)	56±6	Self-rating: VES	Screening ADA, 1998	1.31 (1.04–1.64) <sup>e</sup>	1, 2, 3, 5, 8, 10, 12, 13, 15, 17, 18, 19, 20, 21
Kumari et al. 2004 [18]	Cohort	11	8,320 (69.4)	35–55 <sup>e</sup>	Self-rating: GHQ-D	Screening ADA, 1998	1.17 (0.8–1.7) <sup>d, f</sup>	1, 3, 4, 8, 11, 12, 13, 15, 22, 25, 28, 29
Palinkas et al. 2004 [19]	Cohort	8	971 (43.0)	66±9	Self rating: BDI	Screening ADA, 1998	2.50 (1.29–4.87) <sup>d</sup>	1, 2, 8, 12
van den Akker et al. 2004 [10]	Cohort	16 <sup>b</sup>	68,004 (48.8)	38±14	Diagnosis: ICHPPC-2, 1983	Diagnosis DCGP, 1999	0.98 (0.79–1.21) <sup>e</sup>	1, 2, 4, 8
Everson-Rose et al. 2004 [14]	Cohort	3	2,662 (0.0)	46±3	Self-rating: CES-D	Screening ADA, 1998	1.46 (0.90–2.36) <sup>d</sup>	1, 3, 5, 9, 12, 26, 27

ADA American Diabetes Association, *BDI* Beck depression inventory, *CES-D* Center for Epidemiological Studies Depression Scale, *DCGP* Dutch College of General Practitioners, *DIS* diagnostic interview schedule, *DM* diabetes mellitus, *GHQ-D* general health questionnaire depression, *GWB-DS* general well-being depressive symptoms, *ICHPPC* international classification of health problems in primary

care, *MHI* mental health index, *SDS* self-rating depression scale, *VES* vital exhaustion scale, *WHO* World Health Organization

<sup>a</sup>Mean duration of follow-up

<sup>b</sup>Mean age not described

<sup>c</sup>Odds ratio

<sup>d</sup>Hazard ratio

<sup>e</sup>Subgroup analysis of male subjects

<sup>f</sup>Subgroup analysis of female subjects

<sup>g</sup>1, age; 2, sex; 3, race; 4, socio-economic status; 5, education; 6, occupation; 7, shift work; 8, body mass index; 9, waist circumference;

10, waist-to-hip ratio; 11, height; 12, physical activity; 13, smoking; 14, alcohol consumption; 15, systolic blood pressure; 16, history of hypertension; 17, HDL cholesterol; 18, triglycerides; 19, fasting insulin; 20, fasting glucose; 21, caloric intake; 22, ECG abnormalities;

23, menopausal status; 24, chronic medical conditions; 25, life events; 26, use of medication for depression; 27, study site; 28, length of follow-up; 29 family history of diabetes

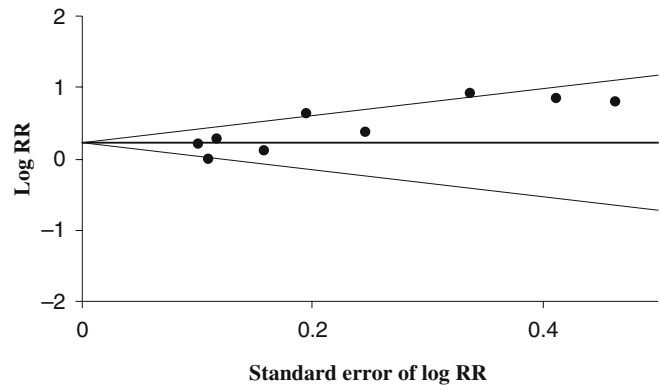
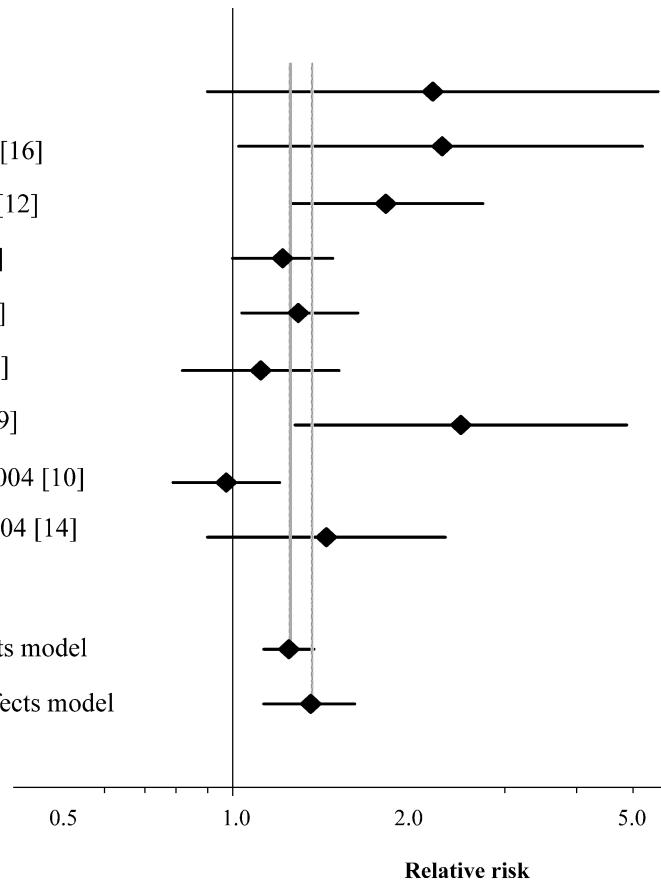
assessment of publication bias, a funnel plot was drawn. In this funnel plot, the relative risk for each study was plotted on the vertical axis (logarithmic scale) against the corresponding standard error on the horizontal axis. Asymmetry of the funnel plot is an indicator of publication bias. Publication bias was also assessed by means of the Begg-adjusted rank correlation test. To check the influence of publication bias, a pooled relative risk was calculated when excluding the three smallest studies.

The homogeneity between the studies was assessed visually with the forest plot and tested by means of Cochran's  $Q$  test, of which the null hypothesis assumes homogeneity. In trying to explain heterogeneity between studies we identified certain study characteristics and assessed whether there was an association between these characteristics and the relative risks of the included studies. Four study characteristics were identified: (1) whether studies controlled for undetected diabetes at baseline; (2) the method of diabetes assessment at follow-up; (3) the overall risk of diabetes of the particular study population; and (4) follow-up duration. The first two characteristics are categorical and therefore a stratified meta-analysis was performed. The last two characteristics are continuous and meta regression analysis was performed. In these subgroup analyses only the random effects model was used.

Finally, the influence of adjusting for certain confounders was investigated qualitatively.

**Fig. 1** Forest plot showing the relative risk and 95% CI of each study and the pooled relative risk (RR) and 95% CI using both the fixed effects model and random effects model

Eaton et al., 1996 [13]  
 Kawakami et al., 1999 [16]  
 Carnethon et al., 2003 [12]  
 Arroyo et al., 2004 [11]  
 Golden et al., 2004 [15]  
 Kumari et al., 2004 [18]  
 Palinkas et al., 2004 [19]  
 van den Akker et al., 2004 [10]  
 Everson-Rose et al., 2004 [14]  
 Pooled RR: fixed effects model  
 Pooled RR: random effects model



**Fig. 2** Funnel plot showing that studies with a large standard error (small sample size) and low relative risk (RR) are missing, which indicates publication bias

All statistical analyses were performed using STATA, version 7.0 (Stata, College Station, TX, USA).

## Results

### Search results

The literature search in MEDLINE using 'depression or depressive' and 'diabetes', limited to items with an abstract

**Table 2** Pooled relative risks (using random effects meta-analysis) stratified by exclusion of undetected diabetes at baseline and method of diabetes assessment at follow-up

	<i>n</i>	Pooled relative risk (95% CI)
Overall	9	1.37 (1.14–1.63)
Exclusion of undetected diabetes at baseline		
No	6	1.32 (1.04–1.66)
Yes	3	1.51 (1.11–2.06)
Method of diabetes assessment at follow-up		
Self-report	4	1.32 (0.98–1.78)
Screening	5	1.43 (1.12–1.81)

and written in English, resulted in 1722 articles. After careful selection, 11 studies appeared to have studied the relation between depression and onset of type 2 diabetes longitudinally [10–20]. Searching the online PsycInfo database yielded no additional studies. One of the 11 studies was excluded [17] because there was insufficient information in the article to calculate a relative risk. Two studies used data from the same cohort [12, 20], the National Health and Nutrition Examination Survey (NHANES), and the most recent publication was included [12]. All studies excluded prevalent diabetes at baseline.

The search for unpublished work among members of the PSAD and BRIDGE resulted in 20 responses to our e-mail but this yielded no additional studies that met our inclusion criteria.

The extracted data of the nine studies included in the meta-analysis are presented in Table 1. One study reported relative risks separately for men and women [18]. These two relative risks were pooled using the random effects model and this pooled relative risk (1.12) and its 95% CI (0.82–1.53) were used in further analyses.

### Meta-analysis

The forest plot shows the relative risk and 95% CI of each study and the pooled relative risk of both the fixed effects model and the random effects model (Fig. 1). The pooled relative risk (95% CI) was 1.26 (1.13–1.39) using the fixed effects model and 1.37 (1.14–1.63) using the random effects model.

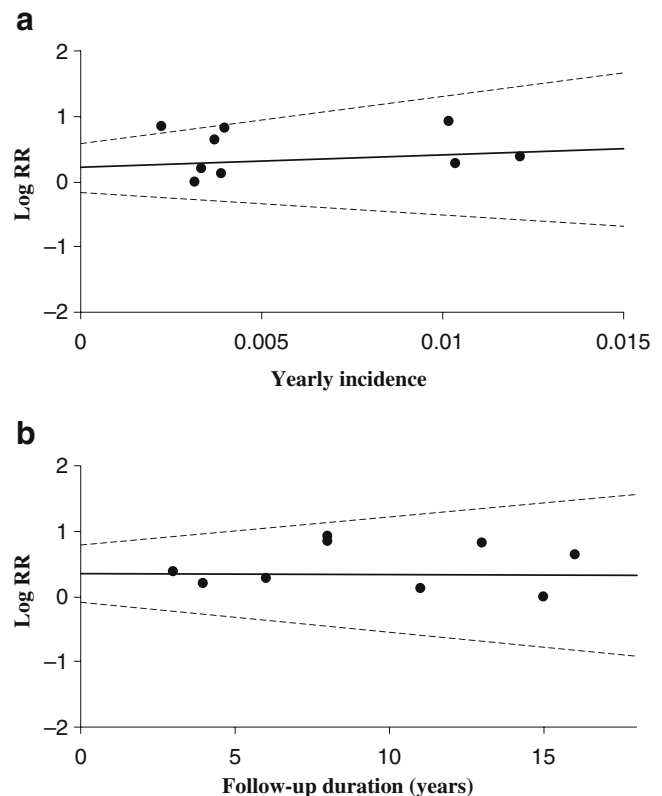
The funnel plot to detect publication bias showed some asymmetry, as six studies lay above and three studies below the line representing the pooled relative risk (Fig. 2). Studies with a large standard error (small sample size) and small relative risk are missing in the graph. This could indicate publication bias as studies showing small (or no) associations and large CIs are probably less often submitted by authors and less often published by editors. The Begg-adjusted rank correlation test for publication bias resulted in a *p* value of 0.10.

The forest plot showed heterogeneity between the studies, as the CIs of the different studies appeared to have no or only partial overlap (Fig. 1). Cochran's *Q* test was statistically significant ( $Q=18.264$ ;  $p=0.02$ ), indicating heterogeneity. Because of this heterogeneity, the pooled relative risk resulting from the fixed effects model should

be disregarded. In further analyses only random effects modelling was performed.

### Subgroup and sensitivity analyses

The pooled relative risk (95% CI) of studies that relied on self-reported diabetes to exclude prevalent diabetes at baseline, and thus did not control for undetected diabetes at baseline [10–13, 16, 18], was 1.32 (1.04–1.66) (Table 2). The pooled relative risk (95% CI) of studies that did control for undetected diabetes by screening all subjects for high blood glucose [14, 15, 19] was slightly higher, namely 1.54 (1.07–2.22).



**Fig. 3** Relation between natural logarithm of relative risk (*log RR*) and overall incidence per year (a) and follow-up duration (b) with regression line (solid line) and upper and lower limits of 95% CI (dashed lines)

The four studies [10–13] that determined type 2 diabetes at follow-up by means of self-report had a pooled relative risk (95% CI) of 1.32 (0.98–1.78) (Table 2). The studies that assessed diabetes onset by measuring glucose levels [14–16, 18, 19] instead of self-report, had a pooled relative risk (95% CI) of 1.43 (1.12–1.81).

The overall risk of diabetes in each study, i.e. the overall incidence per year, was plotted against the natural logarithm of the relative risk of each study (Fig. 3a). The regression coefficient (95% CI) was 18.6 (–35.9 to 73.1) but not significantly different from zero, which means there is no relation between overall risk of diabetes and relative risk. Also, no relation was found between follow-up duration and relative risk, as can be seen in the plot (Fig. 3b). The regression coefficient (95% CI) was –0.0018 (–0.045 to 0.042).

A sensitivity analysis was performed to determine whether excluding the Dutch study [10] influenced the pooled relative risk, as this particular study used routine care data and doctor's diagnosis to measure depression instead of screening by means of a diagnostic interview or

questionnaire. When this study [10] was excluded the pooled relative risk (95% CI) was 1.44 (1.21–1.71), which is slightly larger than the pooled relative risk if that study was included in the analysis. When the three studies with the smallest sample size [13, 16, 19] were excluded the pooled relative risk (95% CI) was 1.24 (1.06–1.46). To check the influence of our decision to include the most recent publication when multiple publications from the same study population were available, we excluded the study of Carnethon et al. [12] and included the study of Saydah et al. [20]. This resulted in a pooled relative risk (95% CI) of 1.26 (1.08–1.47).

#### Influence of adjusting for confounders

Table 3 presents an overview of the unadjusted and adjusted relative risks (95% CI) which were reported by each study, with a detailed description of the different sets of confounders that were used. Unfortunately, as the studies adjusted for many different sets of confounders, it is

**Table 3** Overview of unadjusted and adjusted relative risks reported in each study, with a description of all confounders that were used

Study	Relative risk (95% CI)	Adjustment for confounders <sup>c</sup>
Eaton et al. 1996 [13]	1.58 (0.71–3.51)	–
	2.05 (0.85–4.94)	1, 2, 3
	2.23 (0.90–5.55)	1, 2, 3, 8
Kawakami et al. 1999 [16]	2.04 (0.93–4.45)	–
	2.32 (1.06–5.08)	1
	2.31 (1.03–5.20)	1, 5, 6, 7, 8, 12, 13, 14, 24, 29
Carnethon et al. 2003 [12]	2.52 (1.73–3.67)	1, 2, 3
	1.86 (1.27–2.71)	1, 2, 3, 8, 12, 13, 14
Arroyo et al. 2004 [11]	1.47 (1.20–1.79)	–
	1.55 (1.27–1.90)	1
	1.36 (1.11–1.67)	1, 8
	1.22 (1.00–1.50)	1, 8, 12, 13, 14, 16, 23, 29
Golden et al. 2004 [15]	1.63 (1.31–2.02)	1, 2, 3, 5
	1.38 (1.10–1.73)	1, 2, 3, 5, 8, 10, 15, 17, 18, 19, 20
	1.51 (1.21–1.89)	1, 2, 3, 5, 12, 13, 21
	1.28 (1.02–1.60)	1, 2, 3, 5, 8, 10, 12, 13, 21
	1.31 (1.04–1.64)	1, 2, 3, 5, 8, 10, 12, 13, 15, 17, 18, 19, 20, 21
Kumari et al. 2004 [18]	1.17 (0.8–1.7) <sup>a</sup>	1.08 (0.6–1.9) <sup>b</sup>
	1.17 (0.8–1.7) <sup>a</sup>	1.03 (0.6–1.8) <sup>b</sup>
Palinkas et al. 2004 [19]	2.50 (1.29–4.87)	1, 3, 4, 22, 28
van den Akker et al. 2004 [10]	1.41 (1.15–1.73)	1, 3, 4, 8, 11, 12, 13, 15, 22, 25, 28, 29
	1.04 (0.84–1.28)	1, 2, 8, 12
	0.98 (0.79–1.21)	–
Everson-Rose et al. 2004 [14]	1.66 (1.05–2.61)	1, 2, 4
	1.46 (0.90–2.36)	1, 2, 4, 8
		1, 3, 5, 26, 27
		1, 3, 5, 9, 12, 26, 27

<sup>a</sup>Subgroup analysis of male subjects

<sup>b</sup>Subgroup analysis of female subjects

<sup>c</sup>1, age; 2, sex; 3, race; 4, socio-economic status; 5, education; 6, occupation; 7, shift work; 8, body mass index; 9, waist circumference; 10, waist-to-hip ratio; 11, height; 12, physical activity; 13, smoking; 14, alcohol consumption; 15, systolic blood pressure; 16, history of hypertension; 17, HDL cholesterol; 18, triglycerides; 19, fasting insulin; 20, fasting glucose; 21, caloric intake; 22, ECG abnormalities; 23, menopausal status; 24, chronic medical conditions; 25, life events; 26, use of medication for depression; 27, study site; 28, length of follow-up; 29, family history of diabetes

impossible to quantify the exact influence of adjusting for certain confounders. Qualitatively, no association was seen between adjustment for certain confounders and the magnitudes of the relative risks, as some relative risks decreased after adjusting for certain confounders and others increased.

## Discussion

To our knowledge, this study represents the first application of meta-analysis of literature regarding depression as a risk factor for the onset of type 2 diabetes mellitus.

Results of this meta-analysis of nine longitudinal studies suggest that adults with depression or high-depressive symptoms have a 37% increased risk of developing type 2 diabetes compared with those who are not depressed or have low-depressive symptoms. Heterogeneity between studies regarding relative risks could not be explained by: (1) whether studies controlled for undetected diabetes at baseline; (2) the method of diabetes assessment at follow-up; (3) the baseline overall risk of diabetes in the study population; or (4) follow-up duration. Also, adjustment for several confounders did not explain differences in effect sizes between studies.

Before drawing a conclusion on the findings of this meta-analysis, we will discuss several biases which may have confounded our results. First, reversed causality could be an issue. In reversed causality, presymptomatic persons with diabetes develop depression. These subjects are more likely to develop symptomatic diabetes and this will overestimate the effect size. However, we believe that this hypothesis is less probable, as we have found that studies that exclude cases with undetected diabetes at baseline showed a pooled relative risk similar to the overall pooled relative risk. Second, ascertainment or diagnostic bias could play a role in explaining the results of the present meta-analysis. Subjects with depression tend to visit their doctor more often and may thus be more likely to be recognised as having diabetes [21]. This bias could have occurred particularly in studies that relied on self-reported diabetes at follow-up. However, the pooled relative risk of studies that assessed diabetes by measuring glucose levels (as opposed to self-report or doctor's diagnosis) appeared to be similar to the overall pooled relative risk. These findings do not support the notion that ascertainment bias explains the results of our study. Third, although all studies adjusted for multiple potential confounders, residual confounding may have influenced our findings. Given the fact that most of the studies adjusted for a considerable number of confounders (median 7, range 4–14), we consider this as less likely. In contrast, overcorrection may have occurred. It may be true that some studies adjusted for intermediate rather than confounding factors, resulting in underestimation of the pooled relative risk. A fourth potential bias of the present meta-analysis is publication bias, which is a threat to the validity of every systematic review. We tried to minimise publication bias by asking members of relevant study groups whether they had

any unpublished/rejected results of studies investigating the relation between depression and the onset of type 2 diabetes. Still, the funnel plot did show some asymmetry, as studies with a small sample size and low relative risk were missing, which indicates publication bias. However, even after excluding the three smallest studies [13, 16, 19] a significant, pooled relative risk was found. In sum, reversed causality, ascertainment bias, confounding factors and publication bias do not seem to explain the relationship found in this meta-analysis.

Another potential problem in this meta-analysis is that each study used a different method to assess depression. These different methods can be categorised into four hierarchical groups. First, only one study used a diagnostic interview schedule [13], which is the gold standard for the diagnosis of major depression. Second, four studies used validated depression severity scales, the Zung Depression Scale, the General Health Questionnaire, the Beck Depression Inventory and the Center for Epidemiological Studies Depression Scale [14, 16, 18, 19]. In these studies, validated cutoff scores were used to define levels of depressive affect. The sensitivity and specificity of these measures proved to be acceptable [22]. As a third measure of depression, three studies used semi-depression severity scales: the General Well-Being Depression Scale, the Mental Health Index of the SF-36 and the Vital Exhaustion Scale [11, 12, 15]. These measures were not designed to measure depression severity but are commonly used as a proximal measure of negative affect. The relative risks found in the studies that used these semi-depression scales were similar to the relative risks of the studies that used the more sophisticated scales, and showed the same direction of effect. Finally, one study used the general practitioner's diagnosis of depression [10]. It has been reported that depressive symptoms are not recognised in about half of attending patients with depressive disorders in UK general practice [23] and this under-recognition of depression would result in underestimation of the effect size between depression and onset of diabetes. Therefore, we performed a sensitivity analysis excluding this study, which resulted in a slightly higher pooled relative risk: 1.44 (1.21–1.71).

A second issue in the method of assessment of depression is that two studies made three categories of depression level [12, 16] and one study divided the depression scores into quartiles [15]. This might have influenced our results, as we used the relative risk of the highest vs the lowest group of depressive symptoms. It is seen, in these three studies, that the relative risk of the highest vs the lowest group is larger than the relative risks for the other categories. An additional stratified analysis also showed that the pooled relative risk for these three studies is somewhat higher (1.59 [1.16–2.17]) than the pooled relative risk of the other studies (1.26 [1.02–1.56]). However, we still believe that the relative risk of the lowest vs the highest category of depression represents best the difference between 'no/yes' depression.

In the literature, several hypotheses have been described regarding the pathophysiological mechanisms that could explain the increased risk of type 2 diabetes in depressed

subjects. First, the hypothesis of increased activity of the hypothalamic-pituitary-adrenocortical (HPA) axis and sympathetic nervous system will be discussed. Depression is associated with increased activity of the HPA axis and the sympathetic nervous system [24], resulting in increased cortisol release and increased release of the catecholamines epinephrine and norepinephrine. Cortisol is a stress hormone, which stimulates glucose production, increases lipolysis and circulating free fatty acids, decreases insulin secretion from beta cells and decreases sensitivity to insulin [24–27]. It is postulated that a chronically high cortisol level, which is a feature of about 50% of depressed patients, results in obesity, insulin resistance and type 2 diabetes [24, 28, 29]. Some studies found evidence for this hypothesis [27, 28]. Epinephrine generates responses in glucose and fat metabolism similar to those of cortisol [26], also possibly resulting in insulin resistance and type 2 diabetes.

The credibility of this hypothesis is further strengthened by findings on other medical problems that are accompanied by hypercortisolaemia. For example, Cushing's syndrome, sleeping disorders, work stress and schizophrenia [30–33] appeared to be associated with an increased level of cortisol and also with an increased risk of type 2 diabetes and insulin resistance, although studies on sleep disorders showed inconsistent results regarding risk of diabetes [33–37].

A second hypothesis is that dysregulation of the immune system plays a role in the relationship between depression and increased risk of type 2 diabetes. Both depression and type 2 diabetes are found to be associated with increased C-reactive protein, TNF- $\alpha$  and proinflammatory cytokines, including IL-6 [38–42]. A contradiction between this hypothesis and the first hypothesis is that cortisol inhibits inflammation and the immune response, whereas depression is associated with both elevated cortisol and increased inflammatory markers. A recent finding possibly explains this contradiction by showing that melancholic depressed patients had increased HPA axis activity and no signs of inflammation, whereas non-melancholic depressed patients did show signs of inflammation and normal HPA axis activity [43].

Finally, a low intake or impaired metabolism of  $\omega$ -3 polyunsaturated fatty acids (PUFA) could contribute to both depression and type 2 diabetes.  $\omega$ -3 PUFA have direct and indirect actions on cerebral function and depletion of these fatty acids is clearly associated with psychiatric illness, including depression [44, 45]. In addition, there is evidence that a low intake of  $\omega$ -3 PUFA is associated with an increased risk of type 2 diabetes, but these results were concluded to be less convincing [44].

It is known that the most important risk factor for type 2 diabetes is obesity [46, 47], and that physical inactivity further increases the risk, independently of obesity [48]. In view of the findings in our meta-analysis, depressive affect could be regarded as an additional risk factor for type 2 diabetes, comparable in size to smoking and physical activity [47, 49]. Clinicians should be made aware of the fact that depressive affect might be an additional risk factor

for type 2 diabetes as this makes adequate detection and treatment of depression even more important than it already is. Assessing fasting glucose and advising exercise in depressed patients might also prevent type 2 diabetes.

In conclusion, this meta-analysis suggests that depression is a risk factor for the onset of type 2 diabetes mellitus, comparable in size to smoking and physical activity. However, further well-designed research with adequate control for confounding factors is needed to establish the exact size of the relationship. The influence of the duration of depression or the change in depression over time on the risk of type 2 diabetes should be studied especially. Furthermore, research is warranted to elucidate the pathophysiological mechanisms underlying the association. With the expectation of more than 100 million new cases of type 2 diabetes in the coming two decades, prevention becomes more important every day. Whether the prevention of depression or the treatment of depressed people can truly prevent or delay the onset of type 2 diabetes mellitus remains to be tested in long-term intervention studies.

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