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Review Article

Prevalence of comorbid major depressive disorder in Type 2 diabetes: a meta-analysis of comparative and epidemiological studies

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Abstract

Aims To examine the average point prevalence of major depressive disorder in people with Type 2 diabetes and its associated factors in a comprehensive meta-analysis.

Methods Two researchers independently conducted a systematic literature search of PubMed, EMBASE, PsycINFO and Cochrane databases. Studies reporting the prevalence of major depressive disorder in people with Type 2 diabetes were identified and analysed using a

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random-effects model.

Results A total of 26 studies meeting the inclusion criteria were included in the study. The point prevalence of major depressive disorder was 14.5% (95% CI 7.9–25.3; $I^2=99.65$). People with Type 2 diabetes were more likely to have major depressive disorder compared with the general population (odds ratio 1.73, 95% CI 1.38–2.16). Subgroup and meta-regression analyses showed that study site, diagnostic criteria and age significantly moderated the prevalence of major depressive disorder.

Conclusions In this meta-analysis, the average point prevalence of major depressive disorder in people with Type 2 diabetes was high. Routine screening and more effective interventions should be implemented for this population.

(Study registration no.: CRD42018096113)

What's new?

- This is the first meta-analysis to examine the prevalence of major depressive disorder in people with Type 2 diabetes in studies using standardized diagnostic instruments.
- People with Type 2 diabetes were more likely to have major depressive disorder compared with the general population.
- Routine screening and more effective treatments and interventions should be implemented for people with Type 2 diabetes and major depressive disorder.

Introduction

Type 2 diabetes mellitus is a common chronic disease that is prevalent worldwide [1]. Type 2 diabetes is associated with significant health complications, functional impairment and treatment burden [2]. The prevalence of Type 2 diabetes is rapidly growing [2,3], with the International Diabetes Federation estimating that the worldwide prevalence of diabetes mellitus will rise from 285 million in 2010 to 439 million by 2030 [4].

Major depressive disorder affects ~7% of the general population in the USA [5]. Comorbid major depressive disorder is common in people with diabetes [6], reflecting the bi-directional relationship between the two conditions [7,8]. Depression in people with diabetes is associated with

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poor adherence to low-carbohydrate diet, exercise and medication treatment, and with negative health outcomes, lower quality of life, increased risk of suicide [9] and high economic cost [10]. In order to improve treatment access and delivery of health resources to address this comorbidity, it is crucial to examine the prevalence of major depressive disorder in people with Type 2 diabetes and its associated factors.

A study by Anderson *et al.* [7] found that Type 2 diabetes doubles the risk of depression (odds ratio 2.0, 95% CI 1.8–2.2); however, that meta-analysis included both Type 1 and Type 2 diabetes, and major depressive disorder, minor and subsyndromal depression and depressive symptoms, which were identified with various screening instruments (such as the Geriatric Depression Scale, the Beck Depression Inventory and the Centre for Epidemiological Studies Depression Scale) and standardized diagnostic interviews [such as the Diagnostic Interview Schedule or the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM), third edition, revised]. The use of different diagnostic instruments and measurements increased the heterogeneity of their sample. Furthermore, sophisticated analyses, such as subgroup, meta-regression and sensitivity analyses, were not performed. A subsequent systematic review [11] had similar limitations. Furthermore, these two review papers did not include two recently published studies [12,13].

More recently, several studies have examined major depressive disorder in Type 2 diabetes using international diagnostic criteria, such as the DSM and the International Classification of Diseases (ICD), but their findings differed somewhat. For example, while the prevalence of major depressive disorder was 1.14% in people with Type 2 diabetes in the USA [14], the corresponding figure was 3.39% in Taiwan [15]. In an extensive search of the literature no meta-analysis of the prevalence of major depressive disorder in people with Type 2 diabetes was found.

The aim of the present comprehensive meta-analysis was to determine the average point prevalence of major depressive disorder in people with Type 2 diabetes and its associated factors. The odds ratios were also explored by comparing the prevalence of major depressive disorder between people with and without diabetes.

Methods

Search strategy and selection criteria

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A flow chart of the literature search is shown in Fig. 1. Two researchers (Q.-Q.Z. and S.W.) independently conducted a systematic literature search of the PubMed, EMBASE, PsycINFO and Cochrane databases from their inception to 1 February 2018 using the following search terms: ('major depressi*') AND ('diabetes mellitus' OR 'diabetes' OR 'mellitus') AND ('epidemiology' OR 'prevalence'). The asterisk '*' is a commonly used wildcard symbol that broadens the search by finding words that start with the same letters. To avoid missing any additional studies, reference lists of reviews or meta-analyses were also searched manually. If more than one paper was published using the same dataset, only the one with the largest sample size was included in the meta-analysis.

According to the Preferred Reporting Item for Systemic Review and Meta-analyses (PRISMA) statement [16], the 'PICOS' acronym was used to define the inclusion criteria as follows: participants (P), people with a diagnosis of Type 2 diabetes according to international or local diagnostic criteria, such as the WHO [17] or American Diabetes Association [18]; intervention (I), not applicable; comparison (C), people without diabetes in case-control studies; outcomes (O), not applicable; and study design (S): case-control or cohort studies (only baseline data were extracted from the latter) reporting the prevalence of major depressive disorder in people with Type 2 diabetes or any information that could generate such data. The diagnosis of major depressive disorder had to be established according to international or local (e.g. the Chinese Classification of Mental Disorders) diagnostic criteria using standardized diagnostic instruments, such as the Mini-International Neuropsychiatric Interview (MINI), the Structured Clinical Interview for DSM, third edition, revised, the Schedules for Clinical Assessment in Neuropsychiatry or the Composite International Diagnostic Interview. Studies involving Type 1 diabetes mellitus, pregnant women or other special populations were excluded. Studies that only reported the prevalence of depressive symptoms using screening questionnaires, reviews and case reports were also excluded.

Selection of studies and data extraction

Two researchers (Q.-Q.Z. and F.W.) independently screened the titles and abstracts of articles in the initial search results and read the full texts to select articles that fulfilled the inclusion criteria after removing duplicates. Any uncertainties were resolved by consensus or by discussion with a third reviewer (S.W.). The same two researchers independently performed data extraction using a standard data collection form. Information extracted included the following study characteristics:

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first author; publication year; study site; survey period; sampling method; sample size; demographic and clinical characteristics of the participants; diagnostic criteria applied; and prevalence of major depressive disorder.

Quality assessment

Two researchers (F.W. and Q.-Q.Z.) independently assessed the quality of included studies using a methodological quality assessment tool that comprises eight items [19]. Each study was scored from 0 to 8. Scores of 7–8 were regarded as ‘high quality’, 4–6 as ‘moderate quality’ and 0–3 as ‘low quality’. Any disagreement in the assessment was discussed and resolved by involving a third investigator (S.W.; Table S1).

Statistical analysis

Comprehensive Meta-Analysis software, version 2, was used to analyse the data. Pooled results were estimated using a random-effects model [20]. The I^2 statistic was used to assess the degree of heterogeneity across studies; $I^2 > 50\%$ indicated high heterogeneity. The sources of high heterogeneity were examined in subgroup and meta-regression analyses. Sensitivity analysis was carried out by excluding each study one by one to detect outlying studies that could significantly affect the primary results. Publication bias was evaluated using funnel plots and Egger’s test [21]. The significance level was set at 0.05 (two-sided).

Results

Search results and characteristics of studies

Of the 3393 studies initially identified in the literature search, 26 fulfilled the study entry criteria and were analysed (Fig. 1). Eight studies were cohort studies, 10 were case–control studies and the remaining eight were cross-sectional epidemiological studies. The sample size ranged from 61 to 778 123; three studies used the ICD, and the remainder used versions of the DSM to establish the diagnosis of major depressive disorder.

The study characteristics are shown in Table 1. The included studies were conducted between 1981 and 2015 in 15 countries in six continents: Asia (eight studies); Europe (three studies); North America (eight studies); South America (one study); Africa (three studies); and Oceania (three

studies). The mean participant age was 57.2 years in the Type 2 diabetes groups and 46.8 years in the control groups.

Average point prevalence of major depressive disorder in Type 2 diabetes

Based on the data from 26 studies comprising 96 842 people with Type 2 diabetes, the average point prevalence of major depressive disorder was 14.5% [95% CI 7.9–25.3; $I^2=99.65$ (Fig. 2)].

Comparison between people with Type 2 diabetes and general population controls

In 10 case–control studies, the point prevalence of major depressive disorder in both Type 2 diabetes and the general population groups was reported, contrasting 86 262 people with Type 2 diabetes with 1 237 414 people in the general population. The prevalence of major depressive disorder was 9.2% (95% CI 3.2–23.7; $I^2=99.2\%$) and 4.3% (95% CI 1.2–14.1; $I^2=99.9\%$) in the Type 2 diabetes group and the general population, respectively. Compared with the general population, people with Type 2 diabetes were significantly more likely to have comorbid major depressive disorder [OR 1.73, 95% CI 1.38–2.16; $P<0.001$, $I^2=81.63\%$ (Fig. 3)].

Subgroup, meta-regression and sensitivity analyses

Table 2 shows the subgroup analyses of the point prevalence of major depressive disorder in Type 2 diabetes. Significant differences were found in diagnostic criteria ($P=0.001$), study sites ($P=0.004$) and study types ($P=0.02$). The prevalence of major depressive disorder diagnosed with the DSM instrument (17.5%) was higher than that diagnosed according to the ICD (3.1%). Studies conducted in Africa (31.9%) reported a higher prevalence of major depressive disorder than those from North and South America (12.7%), Asia (16.9%), Europe (17.3%) and Oceania (4.7%). The prevalence of major depressive disorder was lower in case–control studies (7.5%) than in the other study types (21.4%).

The prevalence of major depressive disorder in women and men with Type 2 diabetes was 24.0% and 15.8%, respectively. Using a median splitting method for years (range: 1981–2016; <2008 vs ≥ 2008), studies conducted in or after 2008 (17.6%) reported a higher prevalence of major depressive disorder than those conducted before 2008 (11.5%). The prevalence of major depressive disorder in studies conducted in hospitals/diabetes clinics/primary care facilities and those conducted in the community was 21.2% and 7.7%, respectively. According to the WHO criteria

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from the year 2000, $\text{BMI} \geq 30 \text{ kg/m}^2$ defines obesity. Obese people with Type 2 diabetes also had a higher prevalence of major depressive disorder than those without obesity (14.7% vs 7.9%). The prevalence of major depressive disorder in high- and moderate-quality studies was 16.8% and 12.8%, respectively (Table 2); however, the differences in neither of these subgroup analyses reached significant levels (all P values > 0.05).

Meta-regression analysis showed a significant negative association between age and prevalence of major depressive disorder in Type 2 diabetes mellitus based on data from 17 studies (slope: -0.12 , 95% CI $-0.13, -0.11$; $P < 0.001$).

Quality assessment, publication bias and sensitivity analyses

The mean (range) quality assessment score was 6.4 (5–8). Twelve (46.2%) and 14 (53.8%) studies were rated as being of high and moderate quality, respectively (Supporting Information). Figure S1 shows the funnel plot of the 26 studies that reported the point prevalence of major depressive disorder in Type 2 diabetes. Egger's test ($t=1.88$, 95% CI -0.98 to 21.07 ; $P=0.07$) did not show publication bias. Figure S2 shows the funnel plot for the 10 case–control studies; Egger's test ($t=0.18$, 95% CI -2.33 to 2.72 ; $P=0.86$) did not show publication bias in studies comparing major depressive disorder between people with Type 2 diabetes and the general population. After removing each study sequentially, the results of the remaining studies remained consistent with the primary results (Fig. S3).

Discussion

To the best of our knowledge, the present study is the first meta-analysis to estimate the average point prevalence of major depressive disorder in people with Type 2 diabetes. The average point prevalence of major depressive disorder in people with Type 2 diabetes was 14.5%, which is slightly higher than reported in a previous study (10.9%) [7], but lower than in other meta-analyses (17.6%, [11], 14.5%, [22]). However, evaluation of depression was not uniform in these studies; depressive symptoms detected with different screening instruments and various types of depressive disorders, assessed by different diagnostic instruments, were included in the previous meta-analyses. By contrast, in the present meta-analysis, only people with major depressive disorder diagnosed according to operationalized diagnostic criteria were included, therefore, direct comparisons among

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studies should be made with caution. In the present study the higher prevalence of major depressive disorder found in people with Type 2 diabetes compared to the general population (odds ratio 1.73) is consistent with previous findings [22–24]. The impact of long-term treatment, medication-induced side effects and the high costs associated with diabetes are likely risk factors for depression [25].

Subgroup analyses showed significant differences in the prevalence of major depressive disorder across geographical areas; studies in Africa found people with Type 2 diabetes had the highest prevalence of major depressive disorder (31.9%), followed by studies from Europe (17.3%), Asia (16.9%), America (12.7%) and Oceania (4.7%). Relatively poor economic status, low diabetes treatment rates, different cultural attitudes toward mental health, and limited access to health services in low-income countries increase the likelihood of major depressive disorder in people with Type 2 diabetes [26,27]. The prevalence of major depressive disorder also varies significantly according to different diagnostic criteria; the prevalence of major depressive disorder established using the DSM (17.5%) was significantly higher compared to that established using ICD codes (3.1%). Only three studies in the present meta-analysis applied ICD criteria, which could have led to bias in the pooled prevalence of major depressive disorder. The impact of diagnostic criteria on the prevalence of major depressive disorder warrants further research attention. The discrepancy in prevalence of major depressive disorder in Type 2 diabetes between case–control and other types of study is probably attributable to different sampling methods; random sampling was used in 70% of case–control studies, while the corresponding figure was only 25% in other study types.

A study conducted in 23 European countries found that women had almost twice the prevalence of major depressive disorder compared with men [28], which could be related, in part, to the effects of hormones in women [29]. A nonsignificant gender difference trend was observed previously in people with Type 2 diabetes [24] as well as in the present study (24.0% in women and 15.8% in men).

Obesity is a significant contributing factor to the pathogenesis of depression [30]. Obesity increases insulin resistance [31], dysregulates the hypothalamic-pituitary-adrenal axis [32], and activates inflammatory pathways [33], all of which contribute to the development of depression [34]. Further, mental distress associated with weight-related stigma and discrimination could often precipitate depression in obese people [35]. Since obesity is common in diabetes, the prevalence of major depressive disorder in people with a BMI ≥ 30 kg/m² was higher than in those with a BMI < 30 kg/m². This article is protected by copyright. All rights reserved

<30 kg/m² in the present meta-analysis.

The prevalence of major depressive disorder in Type 2 diabetes significantly increases with age [11]. With advancing age, people with Type 2 diabetes experience more chronic physical and mental comorbidities, disability and cognitive impairment, all of which increase the risk of depression. Unexpectedly, in the present study, older age was associated with decreased risk of depression. We hypothesize that certain variables, such as the psychological impact of Type 2 diabetes in younger patients, may moderate the association between age and the occurrence of major depressive disorder in Type 2 diabetes. This finding needs further exploration.

The results of the meta-analysis should be interpreted with caution because of its several methodological limitations. First, a number of factors relevant for the prevalence of major depressive disorder in Type 2 diabetes mellitus, such as the severity and treatment of Type 2 diabetes and social support, were not examined because of insufficient data. Second, the causal relationship between Type 2 diabetes and major depressive disorder could not be examined because most studies had a cross-sectional design. Third, only 10 case-control studies were available to calculate the odds ratios when comparing the prevalence of major depressive disorder between people with Type 2 diabetes and people without diabetes. Fourth, similar to other meta-analyses [36–39], a high level of heterogeneity was still present in the subgroup analyses, a shortcoming which is difficult to avoid in meta-analyses of observational surveys. The heterogeneity was probably attributable to differences among the included studies, such as different study aims and inclusion/exclusion criteria. Fifth, different periods of data collection across studies could impact on the point prevalence of major depressive disorder; however, meta-regression analysis did not reveal any significant moderating effect of the period of data collection on the primary results. The weight of included studies depends on several factors, such as sample size, the precision of the effect size estimate and the confidence intervals [40]. The weight of included studies in the meta-analysis was automatically calculated by the CMA programme, therefore, the contribution of each factor to the weight could not be examined.

In conclusion, the present meta-analysis of studies in the international literature found that the prevalence of major depressive disorder in people with Type 2 diabetes was common and significantly higher than that in the general population. Screening for depression should be incorporated in the management plan for Type 2 diabetes. Pharmacological treatment and psychosocial interventions should be considered for people with Type 2 diabetes and comorbid

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major depressive disorder.

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Competing interests

None declared.

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FIGURE 1 Flow chart of literature search.

FIGURE 2 Prevalence of major depressive disorder in people with Type 2 diabetes.

FIGURE 3 Comparison between the Type 2 diabetes group and the general population.

Table 1 Characteristics of studies included in the meta-analysis

Publication year	Authors	Reference	Country	Men, %	Mean age, years	Duration of diabetes	Study setting*	Sampling method	Participants		Major depressive disorder		Diagnostic criteria	Quality assessment score
									Type 2 diabetes	Control group	Type 2 diabetes	Control group		
1996	Eaton <i>et al.</i>	[41]	USA	NR	NR	NR	Community	Random	148	1600	6.1	5.3	DIS/DSM-III	8
2003	Egede <i>et al.</i>	[10]	USA	NR	NR	NR	Community	Multiphase	1810	-	9.7	-	DSM-IV	6
2003	Saeed <i>et al.</i>	[42]	Iraqi	45.45	NR	NR	DC	Random	110	110	51.8	18.2	DSM-IV	6
2003	Thomas <i>et al.</i>	[43]	USA	19.75	NR	NR	PC	Consecutive	104	58	10.6	6.9	DSM-IV	6
2004	Larijani <i>et al.</i>	[44]	Iran	40.8	53.6(13.6)	NR	H/DC	Consecutive	375	-	23.7	-	DSM-IV	6
2007	Moreira <i>et al.</i>	[45]	Brazil	18.5	NR	NR	DC	Consecutive	65	-	7.7	-	DSM-IV	5
2007	Fisher <i>et al.</i>	[46]	USA	51.2	NR	NR	H/DC	Consecutive	506	-	9.9	-	DSM-IV	5
2009	Aarts <i>et al.</i>	[47]	Netherlands	41.54	NR	NR	NR	Random	6140	18 416	2	1.6	ICD-9	7

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2010	Agbir <i>et al.</i> [48]	Nigeria	40.99	NR	NR	H	Consecutive	160	-	19.4	-	DSM-IV	6
2010	Dirmaier <i>et al.</i> [49]	Germany	69.8	51.3(6.2)	10.7(3.5)	PC	Consecutive	866	-	11.8	-	ICD-9	7
2012	Bajaj <i>et al.</i> [50]	India	50	NR	NR	H	NR	60	60	43.3	13.3	DSM-IV	6
2013	Alvarez <i>et al.</i> [12]	Italy	NR	NR	NR	H/DC	NR	61	-	34.4	-	DSM-IV	5
2013	Badawi <i>et al.</i> [13]	Canada	43	57.8(9.86)	NR	C	Random	1265	-	50.3	-	DSM-IV	8
2013	Baradaran <i>et al.</i> [51]	Iran	46.72	63.8(NR)	NR	H/DC	Consecutive	185	-	43.2	-	DSM-IV	6
2013	Coleman <i>et al.</i> [52]	USA	58.8	53.2(11.3)	NR	H	Random	4128	-	12	-	DSM-IV	8
2013	Das <i>et al.</i> [53]	India	63.3	NR	NR	DC	Consecutive	195	-	46.2	-	DSM-IV	5
2013	Mezuk <i>et al.</i> [23]	China	49.18	62(7)	NR	Community	Consecutive, random	15981	478 039	0.9	0.6	DSM-IV	8
2014	Abuhegazy <i>et al.</i> [54]	Saudi Arabia	47	59.8(10.8)	NR	DC	Consecutive, random	172	-	16.3	-	DSM-IV	5
2014	Musselman <i>et al.</i> [55]	USA	48.1	56.1(9.5)	9.7(7.3)	DC	Random	172	-	19	-	DSM-IV	6
2015	Akena <i>et al.</i> [56]	Uganda	51.9	63.4(13.4)	9.6(9.4)	DC	Random	437	-	34.8	-	DSM-IV	7
2016	Bruce <i>et al.</i> [57]	Australia	38	50(10)	2.9	Community	Consecutive	184	184	6	0.5	DSM-IV	7
2016	Van Dooren <i>et al.</i> [58]	Netherlands	35.2	51(14.1)	NR	DC	Random	253	609	8.8	5.5	DSM-IV	8

2016	Mushtaque <i>et al.</i> [59]	India	50	NR	NR	DC	NR	80	-	38.8	-	DSM-V	5
2017	Golden <i>et al.</i> [14]	USA	54.76	NR	NR	DC	NR	103	-	8.7	-	DSM-IV	7
2017	Clarke <i>et al.</i> [60]	UK	40.93	NR	NR	H	Random	915	22 582	14.2	11.4	DSM-IV	7
2017	Huang <i>et al.</i> [24]	China (Taiwan)	48.45	NR	NR	NR	Random	62 367	715 756	1.3	0.7	ICD-9	7

DC, diabetes clinic; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSM-III, DSM third edition; DSM-IV, DSM fourth edition; H, hospital; ICD-9, International Classification of Diseases, ninth revision; NR, not reported; PC, primary care.

Table 2 Subgroup of point prevalence of major depressive disorder in people with Type 2 diabetes mellitus using a random-effects model

Subgroup	Category (number of studies)	Events	Sample size	Prevalence, % (95% CI)	I^2 , %	P value within subgroup	Q (P value) across subgroups
Gender	Men (12)	995	46 228	15.8 (5.8–36.2)	99.54	0.003	0.44 (0.51)
	Women (12)	1561	50 363	24.0 (9.9–47.6)	99.65	0.032	
Diagnostic criteria	DSM (23)	2331	27 469	17.5 (10.7–27.4)	99.22	<0.001	6.87 (0.001)
	ICD (3)	1002	69 373	3.1 (0.9–10.5)	99.56	<0.001	
Study site	Hospital/diabetes clinic (19)	1462	8947	21.2 (15.9–27.7)	96.73	<0.001	1.18 (0.28)
	Community (5)	971	19 388	7.7 (1.0–40.0)	99.82	0.02	
Study area	Africa (3)	263	782	31.9 (21.5–44.6)	90.73	0.006	15.60 (0.004)
	North and South America (9)	1424	8301	12.7 (6.2–24.0)	99.16	<0.001	
	Asia (8)	1238	79 340	16.9 (4.5–46.4)	99.71	0.031	
	Europe (3)	253	1842	17.3 (11.2–25.8)	91.09	<0.001	
	Oceania (3)	155	6577	4.7 (1.6–13.0)	95.95	<0.001	
BMI, kg/m ²	<30.0 (3)	241	16 419	7.9 (0.4–64.5)	99.72	0.12	0.18 (0.67)
	≥30.0 (6)	1322	7121	14.7 (6.1–31.3)	99.42	<0.001	

Time of survey, year	<2008 (12)	1197	24 425	11.5 (6.1–20.6)	99.04	<0.001	0.50 (0.48)
	≥2008 (14)	2136	72 417	17.6 (6.1–F41.4)	99.78	0.01	
Study quality	High quality (12)	940	70 175	16.8 (6.1–38.6)	99.80	<0.001	0.19 (0.66)
	Moderate quality (14)	2393	26 667	12.8 (6.1–25.0)	99.22	0.006	
Study type	Case–control (10)	1350	86 262	7.5 (3.2–16.8)	99.40	<0.001	5.23 (0.02)
	Other (16)	2028	10 580	21.4 (14.2–30.8)	98.72	<0.001	

DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; Q, parameter estimates of subgroup comparisons.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Quality assessment of studies included in the meta-analysis.

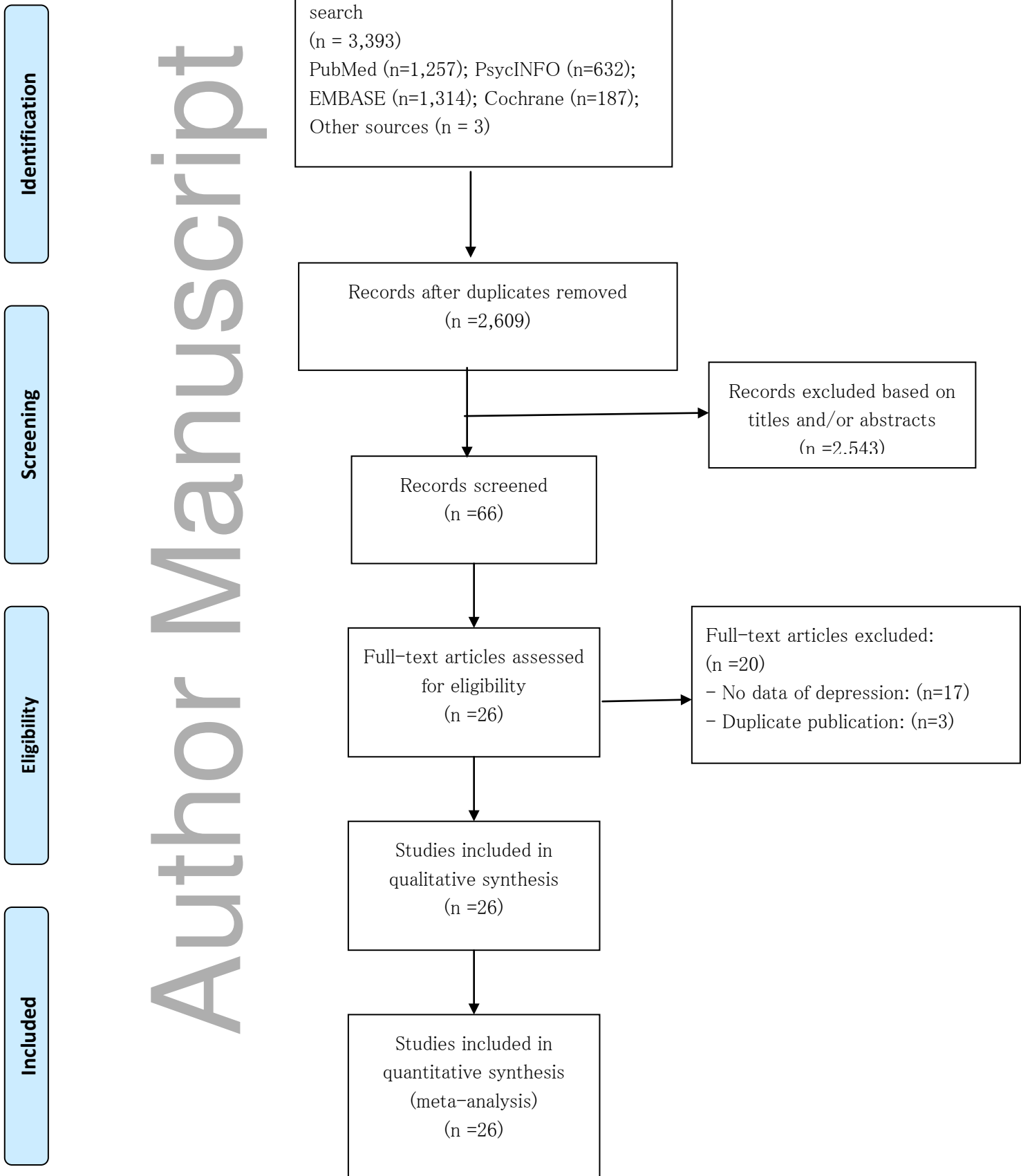
Figure S1. Publication bias regarding the point prevalence of major depressive disorder in people with Type 2 diabetes.

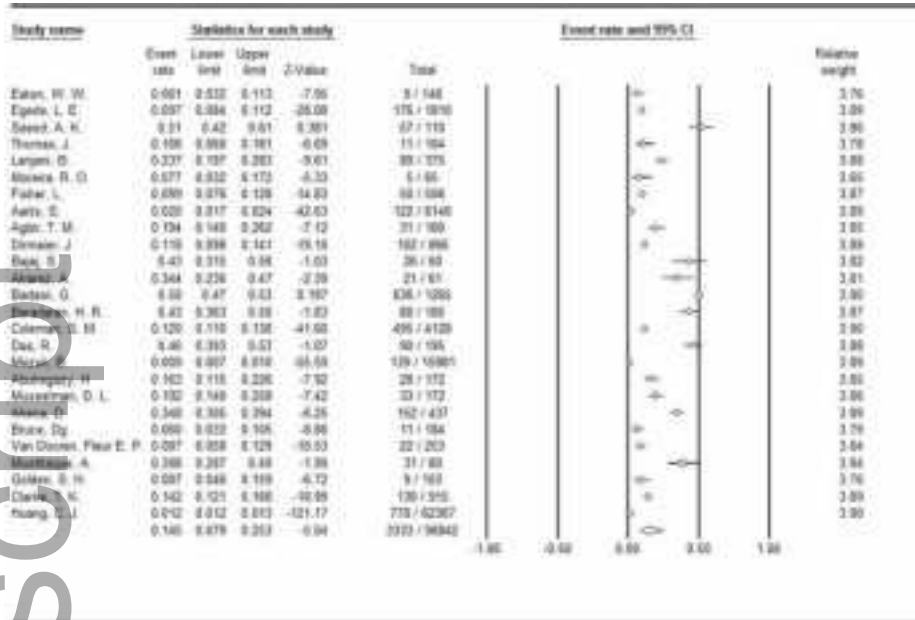
Figure S2. Publication bias concerning the prevalence of major depressive disorder between people with Type 2 diabetes and the general population.

Figure S3. Results of the sensitivity analysis.

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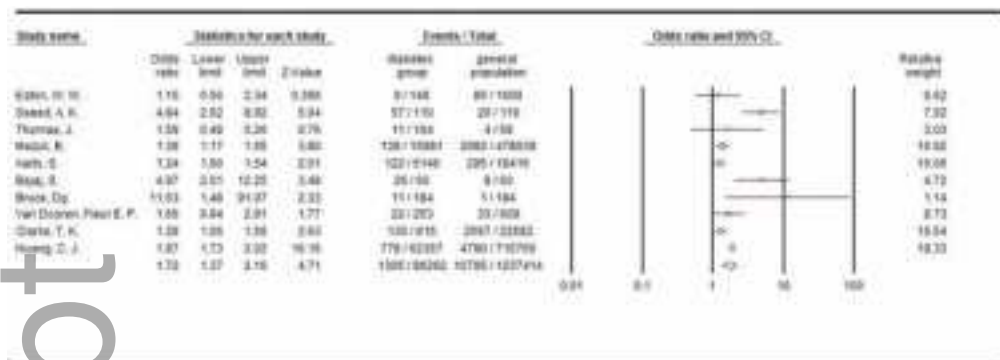
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Meta Analysis

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