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The association between insulin therapy and depression in patients with type 2 diabetes mellitus: a meta-analysis

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3 **The association between insulin therapy and depression in patients with type 2**
4 **diabetes mellitus: a meta-analysis**
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Abstract

Objectives: A large number of type 2 diabetes mellitus (T2DM) patients had depressive disorders. Whether insulin treatment was associated with increased risk of depression remained controversial. We performed a meta-analysis to evaluate the impact of insulin therapy on the development of depression.

Design: A meta-analysis.

Methods: We conducted a systematic search of PubMed, PsycINFO, Embase and the Cochrane Library from their inception to April 2016. Epidemiological studies comparing the prevalence of depression between insulin users and non-insulin users were included. Random-effects models were used for meta-analysis. The adjusted and crude data were analyzed.

Results: Twenty-eight studies were included. Twelve studies presented adjusted ORs. Insulin therapy significantly increased the risk of depression (OR = 1.41, 95% CI 1.13-1.76, P = 0.003). Twenty-four studies were available for the crude data. Insulin therapy also substantially increased the odds for developing depression (OR = 1.59, 95% CI 1.41-1.80, P < 0.001). When comparing insulin therapy with oral-antidiabetic drugs, significant correlations remained for adjusted (OR = 1.42, 95% CI 1.08-1.86, P = 0.008) and crude (OR = 1.61, 95% CI 1.35-1.93, P < 0.001) data.

Conclusions: Our meta-analysis confirmed that patients on insulin therapy had significantly increased prevalence of depressive symptoms.

Keywords: Depression; insulin; type 2 diabetes mellitus; meta-analysis; risk factor

Strengths and limitations of this study

- The primary strength of this study was the systematic and expansive search of multiple databases, which minimized the risk of missing data.
- Both of the adjusted and crude effect estimates were analyzed and demonstrated consistent results.
- Our findings mainly relied on cross-sectional data; as such, the causal and temporal relationship between insulin use and depression could not be established.

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- Some studies had a small sample size which may influence the statistical power.
- The findings of insulin therapy versus specific oral drugs and the prevalence of depression were not illustrated due to inclusion of less number of studies in each subset.

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INTRODUCTION

Diabetes and depression are major global public health problems, both of which are likely to be among the five leading causes of disease burden by 2030.[1] Approximately 90% of adults currently diagnosed with diabetes have type 2 diabetes (T2DM).[2] Recently, a bidirectional link between T2DM and depression has been recognized.[3] Meta-analysis showed that depression was associated with a 60% increased risk of T2DM.[4] Meanwhile, T2DM was associated with a 24% increased risk of depressive symptoms.[5] Further, depression adversely affected the prognosis and quality of life.[6, 7] Growing evidence showed that T2DM and depression may share similar lifestyle factors and biological origins.[3]

T2DM is a chronic and progressive disease characterized by insulin resistance and dysfunction of the pancreatic islet beta cells.[8, 9] For T2DM patients, insulin is the cornerstone of treatment for lowering glucose and HbA1c concentrations.[10] Although the optimal timing and indications for insulin therapy remained controversial,[11-13] most patients will inevitably require insulin therapy to attain adequate glycemic control in the natural history of T2DM.[11, 14]

However, insulin treatment seems less popular than oral hypoglycemic medications. Approximately 25% of the T2DM patients are reluctant to take insulin as the “last-resort” option.[15] Some patients may experience considerable psychological disorders with the transition from oral anti-diabetic drugs to insulin. Additionally, depressive symptoms was more commonly seen in patients with more frequent insulin injections per day.[16] However, the correlations between insulin use and the depression were inconsistent among the previous evidence. Several studies demonstrated positive correlation,[17-19] whereas other studies opposed.[20-22] Besides, these studies varied in enrolled population, adjustment of confounding factors, and depression assessment tools. Thus, we conducted a systematic review and meta-analysis to clarify the association between insulin therapy and the development of depression in T2DM patients.

METHODS

Search strategy

This study was guided by the Meta-analysis of Observational Studies in Epidemiology guidelines.[23] We conducted a systematic computerized search of Pubmed, Ovid PsycINFO, Embase, and the Cochrane Library for eligible studies from their inception to April 2016. The following keywords and medical subject headings were combined: (depression OR depressive) AND (diabetes OR diabetic) AND insulin AND (cross-sectional OR population-based OR cohort OR prospective OR retrospective OR prevalence OR survey OR database OR trial). The language was restricted to English. We also manually screened the reference lists of selected studies for potentially relevant records.

Inclusion and exclusion criteria

We included studies that: (1) investigated the development of depression in insulin users and non-insulin users (oral anti-diabetic drug, diet, or no treatment) among T2DM patients; (2) reported adjusted/unadjusted odds ratios (ORs) or risk ratios (RRs), or presented raw data which could produce crude effect estimates; (3) assessed depression by self-report measures or diagnostic interviews. The self-report scales including the Patient Health Questionnaire (PHQ), Beck Depression Inventory (BDI), and the Center for Epidemiologic Studies–Depression (CES-D) Scale.[24] The diagnostic interviews were based on the criteria by DSM or ICD.[25, 26] A threshold score was not defined as no consensus was available and the threshold varied in different clinical settings. Studies were excluded if: (1) T2DM was mixed with type 1 diabetes; (2) the comparison was conducted between T2DM and non-T2DM patients; (3) depression could not be distinguished from anxiety or distress; (4) ORs or RRs could not be obtained or calculated. For example, we excluded studies only reporting mean and standard deviations of outcome measures.

Data collection and quality assessment

Two reviewers independently screened titles and abstracts for eligible studies and extracted the data. Any disagreement was resolved by consensus. The following study characteristics were extracted: author, publication year, study design, country, sample size, mean or median age, proportion of males, depression diagnostic criteria,

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3 compared groups, and adjustment of effect estimates. Both of the unadjusted and
4 adjusted effect estimates and 95% CIs were directly extracted or indirectly calculated.
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6 The degree of adjustment for confounders were categorized as: “+” for age and/or sex
7 only; “++” for these further adjusted for more than 2 standard sociobehavioral risk
8 factors (i.e., education, race, marital status, insurance, exercise, occupation, smoking
9 status, alcohol consumption, family history of diabetes, and BMI); “+++” for these
10 plus two or more clinical factors, including dyslipidemia, hypertension,
11 cardiovascular disease, duration of T2DM, HbA1c level, treatment intensity, and
12 diabetic complications. The quality was assessed by the modified Newcastle-Ottawa
13 Scale (NOS).[27] This scale awarded a maximum of eight points to each study, with
14 six or less points indicating a high risk of bias.

23 **Statistical analysis**

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25 As most included studies were cross-sectional, effect sizes had to be expressed as
26 odds ratios (ORs). Given the low prevalence of depression in T2DM patients, the risk
27 ratio (RR) reported by prospective study approximated the OR. Where available, the
28 fully adjusted OR was pooled into meta-analysis to avoid the bias caused by
29 confounding factors. However, the degree of adjustment and the variables entering
30 into regression models varied between included studies. Thus, we additionally pooled
31 the unadjusted ORs for data homogeneity. When only raw data were available, the
32 crude ORs were calculated by using a random Mantel-Haenszel method. The
33 random-effects model was used for meta-analysis. Heterogeneity was assessed by the
34 Cochran Q statistics and I^2 values. $P < 0.05$ was regarded as significant heterogeneity
35 for the Q test. I^2 ranged between 0% (no heterogeneity) and 100% (high
36 heterogeneity), with values around 25, 50, and 75% suggesting low, moderate, and
37 high heterogeneity.[28] To weigh up the relative influence of each individual study,
38 sensitivity analysis was performed by excluding one study at a time and assessing
39 alteration in pooled results. Subgroup analyses and meta-regression analyses were
40 performed using the following variables: compared groups (insulin vs. non-drug
41 therapy or insulin vs. oral anti-diabetic drugs), degree of adjustment of confounders
42 (+, ++ or +++), region (USA, Asia, Europe, or Africa), identification of depression
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(self-report questionnaire or medical records), sample size (≥ 1000 or < 1000), mean age (≥ 60 or < 60), percentage male (≥ 50 or < 50), and NOS scale (7/8, or < 7). Publication bias was statistically assessed by Egger and Begg tests, with $P < 0.05$ indicating significant asymmetry.[29, 30] Also, we visually inspected the funnel plot for publication bias. All analyses were conducted by the Stata software (version 12.0; StataCorp, College Station, TX). A P value of less than 0.05 was considered significant.

RESULTS

Study selection

We identified 595 articles from Pubmed, 836 articles from PsycINFO, 359 articles from Embase, and 312 articles from Cochrane Library, with a total of 2102 records. We removed 461 duplicates. Further, 399 full-text articles were assessed for eligibility. After excluding 353 records with insufficient or irrelevant data, 46 studies were included into qualitative synthesis. We excluded 5 studies enrolling mixed type 1 and type 2 diabetic patients, 3 studies comparing depression between DM and non-DM patients, 4 studies only comparing the mean or median scores of depression questionnaire, 4 studies only reporting the regression or correlation coefficient, 1 study presenting a mixed outcome of depression and anxiety, and 2 studies reporting a mixed treatment regimen of insulin or oral drugs. Finally, 28 studies were included into meta-analysis. The flow diagram was shown in Figure 1.

Study characteristics and quality assessment

Among the 28 studies pooled into meta-analysis, except for 1 prospective cohort,[31] most were cross-sectional studies. A worldwide distribution was displayed, including 5 studies of USA, 8 European studies, 10 Asian studies, 2 African studies, 1 South-American study, and 1 study mixed of South-American and European population. The sample size ranged from 90 to 229 047. The prevalence of depression ranged from 3.4 to 51.1%. Seven studies reported both of the adjusted and unadjusted ORs,[17, 20, 21, 32-35] 5 studies only reported the adjusted ORs,[31, 36-39] and unadjusted ORs could only be retrieved from 16 studies.[18, 40-54] Descriptive data

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3 of the included studies were summarized in Table 1. In quality assessment, all studies
4 had low to moderate risk of bias, with the scores ranging from 6 to 8. The items
5 satisfied least were the control of confounding factors (12/28) and the report of
6 response rates or follow-up data (10/28) (Table 2).
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Table 1. Characteristics of included studies

Author (year)	Design	Study setting	No. of patients	Mean age, years	Country	Male, %	Depression prevalence, %	Depression assessment	Compared groups	Source of estimates	Adjusted factors
Katon et al. (2004)	Cross-sectional	Community	4193	65	USA	51	20.5	PHQ-9	Insulin vs. non-drug	Adjusted	Age, sex, education, marital status, employment, race, BMI and smoking, Rx Risk score, HbA1c, duration of diabetes, treatment intensity, number of complications
Bell et al. (2005)	Cross-sectional	Community	696	74	USA	50.7	15.8	CES-D	Insulin vs. oral medication; insulin vs. non-drug	Adjusted	Age, sex, ethnicity, education, marital status, income, diabetes duration, number of medications, BMI, HbA1c, chronic conditions, PCS score
Noh et al. (2005)	Hospital-based	Hospital	204	53	Korean	53	32.4	BDI	Insulin vs. oral medication	Adjusted	Age, sex, BMI, duration of diabetes, HbA1c, occupation, education, marital status, family

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												history of diabetes, hypertension, diabetic complications, cerebrovascular disease, IHD
Hermanns et al. (2006)	Cross-sectional	Hospital	236	52.2	Germany	60.6	33	BDI; CES-D	Insulin vs. non-insulin	Unadjusted	NA	
Paraskar et al. (2007)	Prospective cohort	Medicare Health Maintenance Organization	792	72	USA	44	17.3	CES	Insulin vs. sulfonylurea	Adjusted	Age, sex, number of prescriptions, antidiabetic medication, perceived health status, health related quality of life, number of hospitalizations, ER visits	
Li et al. (2008)	Cross-sectional	Surveillance Program	16651	≥18	USA	42	14.4	PHQ	Insulin vs. non-insulin	Unadjusted	NA	
Ali et al. (2009)	Cross-sectional	Hospital	3845	NA	Mixed (South Asia and UK)	52.8	9.3	Medical records	Insulin vs. non-insulin	Adjusted	Age, gender, comorbidities, complications, insulin and oral anti-diabetic medication use, BMI, HbA1c, duration of diabetes, and	

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Raval et al. (2010)	Cross-sectional	Hospital	300	54	India	49	41	PHQ-9	Insulin vs. non-insulin	Adjusted		Age, gender, obesity, diabetic complications, blood pressure, duration of disease, income, education, BMI, HbA1c, diabetic complications, dyslipidemia, number of medicine
Zuberi et al. (2011)	Cross-sectional	Hospital	286	52	Pakistan	39.2	50	HADS	Insulin vs. oral medication	Unadjusted		NA
Stanković et al. (2011)	Cross-sectional	Hospital	90	55.5	Serbia	34.4	51.1	PHQ, BDI, or interview	Insulin vs. oral medication	Unadjusted		NA
Lynch et al. (2012)	Cross-sectional	Hospital	201	NA	USA	27.4	19.9	CES-D	Insulin vs. non-insulin	Unadjusted		NA
Osme et al.	Cross-sectional	Outpatient	138	≥30	Brazil	27.5	44.6	HAD	Insulin	Unadjusted		NA

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Trento et al. (2012)	Cross-s	Outpatient	498	67.6	Italy	52.6	14.2	ZSDS	Insulin	Unadjusted	NA	
	ectional	clinic								vs.non-insul		
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Roy et al. (2012)	Cross-s	Outpatient	417	53.2	Banglade	50.6	34	PHQ-9	Insulin	vs. Adjusted	Age, gender, education, income,	
	ectional	clinic			sh				oral		region, CVD, hypertension,	
									medication		diabetic complications, BMI,	
									+diet;		HbA1c	
									insulin+oral			
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Joseph et al. (2013)	Cross-s	Hospital	230	53.6	India	51.7	45.2	PHQ-9	Insulin	vs. Unadjusted	NA	
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Hayashino et al. (2014)	Cross-sectional	Hospital	3573	66	Japan	61.1	3.4	PHQ-9	Insulin vs. oral medication or diet	Unadjusted	NA
Gorska-Ciebidla et al. (2014)	Cross-sectional	Outpatient clinic	276	74	Poland	46	29.7	GDS	Insulin vs. oral medication	Adjusted	Age, sex, education, marital status, smoking, physical activity, duration of diabetes, BMI, HbA1c, lipids levels, diabetic complications, previous HA or use of HA drugs, hyperlipidemia, number of comorbid conditions, hypoglycemia
Sweileh et al. (2014)	Cross-sectional	Hospital	294	60	Palestine	44.2	40.2	BDI	Insulin vs. non-insulin	Unadjusted	NA
Yi Zhang et al. (2015)	Cross-sectional	Hospital	2538	56.4	China	53	6.1	PHQ-9	Insulin vs. oral drugs	Unadjusted	NA

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Rodriguez Calvin et al. (2015)	Cross-sectional	Hospital	275	64.5	Spain	56.4	32.7	BDI	Insulin oral medication	vs. Unadjusted	NA
Camara et al. (2015)	Cross-sectional	Outpatient clinic	491	58	Guinea	37	34.4	HADS	Insulin oral medication	vs. Adjusted	Age, HbA1c, hypertension, BMI, residence zone, socioeconomic status
Sun et al. (2015)	Cross-sectional	Community	229 047	57.4	China	34.4	5.9	PHQ-9	Insulin oral medication or diet	vs. Adjusted	Age, sex, BMI, HbA1c, smoking, alcohol, physical activity, education, occupation, marital status, selfreport cardio-metabolic disorders, diabetes treatment, diabetes duration
Wu Zhang et al. (2015)	Cross-sectional	Hospital	412	59.8	China	50.2	5.7	BDI	Insulin oral medication	vs. Adjusted	Age, gender, education, marital status, occupation, insurance, HbA1c, BMI, DM history, diabetic complications, duration of DM, smoking, alcohol, exercise,

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Luca et al. (2015)	Cross-sectional	Hospital	128	64.7	Italy	58.6	50.8	HAM-D	Insulin oral medication or diet	vs. Unadjusted	NA
Kikuchi et al. (2015)	Cross-sectional	Community	4218	65.5	Japan	57.1	10.6	CES-D	Insulin non-insulin	vs. Unadjusted	NA
Jacob et al. (2016)	Cross-sectional	Community	90412	65.5	Germany	50.2	30.3	Medical records	Insulin non-insulin	vs. Adjusted	Age, gender, insurance, diabetic complications, CVD, HbA1c
Cois-Sagar et al. (2016)	Cross-sectional	Community	411	70.8	Spain	46.2	29.2	PHQ-9	Insulin oral medications or diet	vs. Unadjusted	NA
Habtewold et al. (2016)	Cross-sectional	Hospital	276	44	Ethiopia	47	44.7	PHQ-9	Insulin oral medication	vs. Unadjusted	NA

BDI, Beck Depression Inventory; BMI, body mass index; BG, blood glucose; CES-D, Center for Epidemiologic Studies Depression; DBP,

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7 diastolic blood pressure; ER, emergence room; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HAM-D,
8 Hamilton rating scale for depression; IHD, ischemic heart disease; PCS, Physical Component Summary score; PHQ, Patient Health
9 Questionnaire; SBP, systolic blood pressure; ZSDS, Zung Self-Rating Depression Scale.
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Table 2. Quality assessment of included studies by the modified Newcastle-Ottawa scale (NOS)

Author (year)	Adequate definition of cases using insulin	Representativeness of cases using insulin	Selection of the non-insulin users	Ascertainment of insulin use	Depression was not present before initiation	Control of confounding factors	Assessment of depression response rates or follow-up data	Total score
Katon et al. (2004)	1	1	1	1	1	1	1	8
Bell et al. (2005)	1	1	1	1	1	1	0	7
Noh et al. (2005)	1	0	1	1	1	1	0	6
Hermanns et al. (2006)	1	1	1	1	1	0	0	6
Pawaskar et al. (2007)	1	1	1	1	1	1	1	7
Li et al. (2008)	1	1	1	1	1	0	0	6
Ali et al. (2009)	1	1	1	1	1	1	0	7
Raval et al. (2010)	1	1	1	1	1	1	0	7
Zuberi et al. (2011)	1	1	1	1	1	0	1	7
Stanković et al. (2011)	1	1	1	1	1	0	0	6
Lynch et al. (2012)	1	1	1	1	1	0	1	7
Osme et al. (2012)	1	1	1	1	1	0	0	6

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7	Trento et al. (2012)	1	1	1	1	1	0	1	0	6
8	9	Roy et al. (2012)	1	1	1	1	1	1	1	8
10	11	Joseph et al. (2013)	1	1	1	1	1	0	1	6
12	13	Hayashino et al. (2014)	1	1	1	1	1	0	1	6
14	15	Gorska-Ciebiada et al. (2014)	0	1	1	1	1	1	1	6
16	17	Sweileh et al. (2014)	1	1	1	1	1	0	1	7
18	19	YY Zhang et al. (2015)	1	1	1	1	1	0	1	7
20	21	Rodriguez Calvin et al. (2015)	1	1	1	1	1	0	1	7
22	23	Camara et al. (2015)	1	1	1	1	1	0	1	6
24	25	Sun et al. (2015)	1	1	1	1	1	1	1	7
26	27	WJ Zhang et al. (2015)	1	1	1	1	1	1	1	8
28	29	Luca et al. (2015)	1	1	1	1	1	0	1	6
30	31	Kikuchi et al. (2015)	1	1	1	1	1	0	1	6
32	33	Jacob et al. (2016)	1	1	1	1	1	0	1	6
34	35	Cols-Sagarra et al. (2016)	1	1	1	1	1	0	1	6
		Habtewold et al. (2016)	1	1	1	1	1	0	1	7

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Meta-analysis of adjusted data

The adjusted ORs for the comparison of depression between insulin and non-insulin treated patients were reported by 12 studies. Compared with non-insulin treatment, insulin therapy was associated with a statistically significant higher risk of depression (OR = 1.41, 95% CI 1.13-1.76, P = 0.003). Significantly high heterogeneity was revealed ($I^2 = 69.7\%$, $P < 0.001$) (Figure 2).

The results of sensitivity analysis, which excluded the selected studies one by one, might vary by excluding several included studies (Supplementary Figure S1). To identify the sources of heterogeneity, we performed subgroup analyses based on several important confounding factors. Six studies particularly compared insulin with oral anti-diabetic drugs, and showed that insulin therapy was significantly associated with increased risk of depression (OR = 1.42, 95% CI 1.08-1.86, P = 0.008). For 2 studies comparing insulin with non-drug therapy, no significant association was revealed for insulin and depression (OR = 0.87, 95% CI 0.37-2.03, P = 0.745). Additionally, we investigated the impacts of degree of adjustment of confounders, region, identification of depression, sample size, mean age, percentage male, and NOS scale. The association remained significant for the subgroups of fully adjustment (+++), Asian studies, self-report questionnaires, sample size ≥ 1000 , mean age < 60.0 years, percentage of male $< 50.0\%$, prevalence of depression over 20%, and NOS scale < 6 (Table 3). Meta-regression analyses indicated a lack of effect measure modification by sample size (P = 0.93), mean age (P = 0.17), percentage male (P = 0.28) or prevalence of depression (P = 0.75).

Table 3. Subgroup analyses for the studies reporting adjusted effect estimates

Subgroups	No. of studies	OR (95% CI)	I^2 (P value)
Compared groups			
Insulin vs. oral drugs	6	1.42 (1.08-1.86)	71.3% (< 0.05)
Insulin vs. non-drugs	2	0.87 (0.37-2.03)	66.5% (0.08)
Degree of adjustment			

+++	10	1.43 (1.08-1.89)	68.9% (< 0.05)
++	2	1.24 (0.98-1.55)	25.3% (0.25)
Region			
USA	4	0.86 (0.57-1.31)	36.4% (0.19)
Asia	5	1.81 (1.18-2.79)	59% (0.05)
Europe	2	1.58 (0.85-2.94)	92.9% (< 0.05)
Africa	1	1.53 (0.99-2.37)	-
Identification of depression			
Self-report questionnaire	10	1.42 (1.06-1.91)	68.9% (< 0.05)
Medical records	2	1.31 (1.00-1.71)	65.6% (0.09)
Sample size			
≥ 1000	4	1.46 (1.10-1.94)	73.1% (< 0.05)
< 1000	8	1.34 (0.93-1.93)	70% (< 0.05)
Mean age			
≥ 60.0	5	1.12 (0.77-1.62)	78.8% (<0.05)
< 60.0	6	1.74 (1.24-2.43)	50.8% (0.07)
Percentage male (%)			
≥ 50.0	7	1.26 (0.97-1.63)	62.4% (<0.05)
< 50.0	5	1.71 (1.25-2.35)	53.9% (0.07)
Prevalence of depression			
≥ 20%	7	1.48 (1.12-1.96)	71.3% (< 0.05)
< 20%	5	1.25 (0.80-1.95)	72.7% (< 0.05)
NOS scale			
7 or 8	8	1.25 (0.94-1.66)	60.0% (<0.05)
<7	4	1.79 (1.14-2.80)	84.6% (<0.05)

Meta-analysis of unadjusted results

Twenty-four studies were available for the crude data. All studies were cross-sectional, and assessed depression by self-report scales. The studies presented three comparison types (insulin vs. non-drug therapy; insulin vs. oral anti-diabetic drugs; and insulin vs. non-insulin treatment). Data on the comparison between insulin and non-insulin therapy were preferred. The pooled results showed that T2DM patients on insulin therapy had significant higher risk of depression compared with those on non-insulin treatment (OR = 1.59, 95% CI 1.41-1.80, $P < 0.001$) (Figure 3). The heterogeneity was at a significantly high level ($I^2 = 59.8\%$, $P < 0.001$). Sensitivity analysis revealed no significant variation in the pooled OR by exclusion of any included study (Supplementary Figure S2).

Seventeen studies compared insulin with oral anti-diabetic drugs, showing a significantly increased risk of depression for insulin therapy (OR = 1.61, 95% CI 1.35-1.93, $P < 0.001$). For 6 studies comparing insulin use with non-drug treatment, a substantially higher risk of depression was revealed for insulin use (OR = 1.89, 95% CI 1.25-2.88, $P = 0.002$). In the stratified analyses based on degree of adjustment of confounders, region, identification of depression, sample size, mean age, percentage male, and NOS scale, the significant association between insulin use and depression remained significant among all subgroups except the study conducted in South America (Table 4). In meta-regression analyses, sample size ($P = 0.79$), mean age ($P = 0.56$), percentage male ($P = 0.80$), and the prevalence of depression ($P = 0.68$) demonstrated no independent effect on the depression outcomes.

Table 4. Subgroup analyses for the studies reporting the crude effect estimates

Subgroups	No. of studies	OR (95% CI)	I^2 (P value)
Compared groups			
Insulin vs. oral drugs	17	1.61 (1.35-1.93)	62.6% (< 0.05)
Insulin vs. non-drugs	6	1.89 (1.25-2.88)	68.2% (< 0.05)
Region			
USA	4	1.53 (1.21-1.93)	75.4% (< 0.05)

Asia	9	1.60 (1.22-2.10)	75.4% (0.05)
Europe	7	1.59 (1.13-2.22)	45.3% (< 0.05)
Africa	2	1.77 (1.23-2.54)	0 (0.85)
South America	1	1.28 (0.50-3.27)	-
Sample size			
≥1000	7	1.64 (1.39-1.93)	77.5% (< 0.05)
< 1000	17	1.56 (1.27-1.91)	46.7% (< 0.05)
Mean age			
≥ 60.0	10	1.60 (1.30-1.97)	61.8% (<0.05)
< 60.0	10	1.57 (1.18-2.09)	68.0% (<0.05)
Percentage male (%)			
≥ 50.0	13	1.59 (1.29-1.96)	75.1% (<0.05)
< 50.0	11	1.55 (1.43-1.68)	0.0 (0.71)
Prevalence of depression			
≥ 20%	14	1.84 (1.59-2.12)	11.7% (0.33)
< 20%	10	1.43 (1.19 -1.70)	74.0% (< 0.05)
NOS scale			
7 or 8	11	1.45 (1.16-1.82)	72.3% (<0.05)
<7	13	1.72 (1.47-2.00)	42.8% (0.05)

Publication bias

For studies reporting the adjusted ORs, the funnel plot was symmetrical (Figure 4). No publication bias was shown by the Egger test ($P = 0.94$) or Begg's test ($P = 0.67$). For studies presenting the crude ORs, the funnel plot was symmetrical (Figure 5). We did not detect publication bias by Egger ($P = 0.39$) or Begg's test ($P = 0.94$).

DISCUSSION

This is the first meta-analysis that estimated the magnitude of the association between insulin therapy and depression. The pooled data of adjusted ORs proved that T2DM

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3 patients on insulin treatment had a 41% increased prevalence of depressive syndromes
4 compared to those without insulin therapy. When pooling crude ORs, the increased
5 prevalence attained to 59%. We specifically compared insulin use with
6 oral-antidiabetic drugs. Both of the adjusted data (OR = 1.42) and the unadjusted data
7 (OR = 1.61) showed that insulin users had increased occurrence of depression.
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12 The source of heterogeneity was explored carefully. In sensitivity analysis, no
13 substantial change in heterogeneity was revealed when excluding any individual study,
14 suggesting the homogeneity of the pooled effect estimates. The prevalence of
15 depression could be different according to ethnicities.[55] In subgroup analyses of
16 adjusted data, we found that the significance displayed for Asian studies.
17 Non-significant result was shown for studies with sample size below 1000, suggesting
18 that the result was unstable for small sample size. Substantial change of heterogeneity
19 was also detected for the subgroups of insufficient degree of adjustment and
20 depression identified by medical records. However, the number of eligible studies was
21 rather small to draw firm conclusions. For studies of depression prevalence below
22 20%, substantial change in the effect estimates was shown for adjusted data, and
23 obvious change in heterogeneity for crude data. Thus, it may partly account for the
24 heterogeneity. Finally, the treatment effect was detected if the mean age was < 60.0
25 years, percentage male < 50.0%, and NOS < 7 for adjusted data. This might be due to
26 that younger patients were associated with higher prevalence of depression, and
27 women receiving insulin therapy might be under greater risk of depression compared
28 to men.
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43 The mechanisms link diabetes and depression were complex and still unclear.
44 Depression and T2DM could develop in parallel through shared biological processes.
45 The involved pathways include the innate inflammatory response, the
46 hypothalamic-pituitary-adrenal axis, circadian rhythms, and insulin resistance.[3]
47 Although the overall prevalence of depression is high in diabetic patients, the
48 DESMOND trial reported that it was not so in newly diagnosed T2DM.[56]
49 Screen-detected patients with T2DM showed low distress and anxiety at the time of
50 diagnosis, with a significant increase during the following 12 months.[57] In
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3 accordance with these findings, we confirmed that insulin therapy was associated with
4 increased prevalence of depression. For patients on insulin therapy, they had less
5 endogenous insulin and were therefore more susceptible to metabolic dysregulation
6 than patients who might have some residual insulin secretory activity. Especially,
7 patients who are more metabolically labile are more vulnerable to depression.[16]
8 Besides, insulin therapy is always a symbol of more advanced type 2 diabetes. The
9 patients' negative attitudes toward insulin therapy may contribute to delays for insulin
10 initiation, prolonged duration of hyperglycemia, and increased risk of diabetic
11 complications.[58] Psychological insulin resistance (PIR) has been defined as
12 psychological opposition towards insulin treatment in both diabetic patients and their
13 prescribers. They may display fear of insulin injection and self-testing, complex
14 regimen, hypoglycemia, and weight gain; a perceived loss of control over one's life;
15 poor self-efficacy concerning insulin treatment; and perceived lack of positive
16 outcomes related to insulin.[58-60] These psychological aspects may explain for the
17 increased risk of depression when insulin was prescribed.
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31 The primary strength of this study was the systematic and expansive search of
32 multiple databases, which minimized the risk of missing data. The meta-analysis
33 identified 28 studies enrolling worldwide-distributed participants. Both of the adjusted
34 and crude effect estimates were analyzed and demonstrated consistent results. The
35 confidential intervals were narrow, suggesting the precision of pooled results.[61] For
36 adjusted data, most studies had full adjustment for confounders. The subtypes of
37 non-insulin therapy, including oral drug and non-drug treatment, were analyzed
38 separately. The between-study heterogeneity was intensively explored by sensitivity,
39 subgroup, and meta-regression analyses. Besides, no publication bias was detected
40 among the selected studies.
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49 We were aware of the limitations of this meta-analysis. Our findings mainly
50 relied on cross-sectional data; as such, the causal and temporal relationship between
51 insulin use and depression could not be established. Some studies had a small sample
52 size which may influence the statistical power. The response rate was only reported by
53 several studies. The unmeasured differences between respondents and nonrespondents
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3 may potentially influence the pooled results. Most of the studies used self-reported
4 scales rather than clinical interview-based assessments to identify depression.
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6 Prevalence of depression was generally much higher using the self-reported scales
7 than standardized diagnostic interviews.[20, 62] Furthermore, the findings of insulin
8 therapy versus specific oral drugs and the prevalence of depression were not
9 illustrated due to inclusion of less number of studies in each subset. Finally, the
10 impact of the total number of daily insulin injections with depression development
11 was included only in few studies, and these contributed as potential confounders in
12 patients who received insulin therapy and the progression of depression.
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21 **CONCLUSIONS**

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23 In conclusion, we provided solid evidence that type 2 diabetic patients who were
24 prescribed insulin presented more depressive syndromes compared to those not using
25 insulin. For insulin-users, careful monitoring of depressive symptoms should be
26 incorporated into the disease management. Intensified psychological and education
27 programs should be carried out to prevent depressive illness after insulin initiation in
28 the primary care settings.
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Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

XSB contributed to study concepts, manuscript preparation, literature research and drafting the manuscript. ZML, ZSL and DWY carried out literature research, data analysis and revising the manuscript for important content. All authors read and approved the final manuscript.

Data sharing statement

No additional data available.

References

- 1 Tabak AG, Akbaraly TN, Batty GD, et al. Depression and type 2 diabetes: a causal association? *Lancet Diabetes Endocrinol* 2014;2:236-45.
- 2 Type 2 Diabetes in Adults: Management. National Institute for Health and Care Excellence: Clinical Guidelines. London 2015.
- 3 Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. *Lancet Diabetes Endocrinol* 2015;3:461-71.
- 4 Mezuk B, Eaton WW, Albrecht S, et al. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care* 2008;31:2383-90.
- 5 Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia* 2010;53:2480-6.
- 6 van Dooren FE, Nefs G, Schram MT, et al. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One* 2013;8:e57058.
- 7 Kan C, Silva N, Golden SH, et al. A systematic review and meta-analysis of the association between depression and insulin resistance. *Diabetes Care* 2013;36:480-9.
- 8 Ismail-Beigi F. Clinical practice. Glycemic management of type 2 diabetes mellitus. *N Engl J Med* 2012;366:1319-27.
- 9 Ohn JH, Kwak SH, Cho YM, et al. 10-year trajectory of beta-cell function and insulin sensitivity in the development of type 2 diabetes: a community-based prospective cohort study. *Lancet Diabetes Endocrinol* 2016;4:27-34.
- 10 Cahn A, Miccoli R, Dardano A, et al. New forms of insulin and insulin therapies for the treatment of type 2 diabetes. *Lancet Diabetes Endocrinol* 2015;3:638-52.
- 11 Home P, Riddle M, Cefalu WT, et al. Insulin therapy in people with type 2 diabetes: opportunities and challenges? *Diabetes Care* 2014;37:1499-508.
- 12 Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet* 2008;371:1753-60.
- 13 Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in

1
2
3 type 2 diabetes mellitus: a systematic review and meta-analysis. *Lancet Diabetes*
4 *Endocrinol* 2013;1:28-34.

6 14 Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose
7 control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.

10 15 Holmes-Truscott E, Skinner TC, Pouwer F, et al. Explaining psychological
11 insulin resistance in adults with non-insulin-treated type 2 diabetes: The roles of
12 diabetes distress and current medication concerns. Results from Diabetes
13 MILES-Australia. *Prim Care Diabetes* 2016;10:75-82.

16 16 Surwit RS, van Tilburg MA, Parekh PI, et al. Treatment regimen determines the
17 relationship between depression and glycemic control. *Diabetes Res Clin Pract*
18 2005;69:78-80.

21 17 Noh JH, Park JK, Lee HJ, et al. Depressive symptoms of type 2 diabetics treated
22 with insulin compared to diabetics taking oral anti-diabetic drugs: a Korean study.
23 *Diabetes Res Clin Pract* 2005;69:243-8.

26 18 Li C, Ford ES, Strine TW, et al. Prevalence of depression among U.S. adults with
27 diabetes: findings from the 2006 behavioral risk factor surveillance system. *Diabetes*
28 *Care* 2008;31:105-7.

31 19 Al-Amer RM, Sobeh MM, Zayed AA, et al. Depression among adults with
32 diabetes in Jordan: risk factors and relationship to blood sugar control. *J Diabetes*
33 *Complications* 2011;25:247-52.

36 20 Bell RA, Smith SL, Arcury TA, et al. Prevalence and correlates of depressive
37 symptoms among rural older African Americans, Native Americans, and whites with
38 diabetes. *Diabetes Care* 2005;28:823-9.

41 21 Katon W, von Korff M, Ciechanowski P, et al. Behavioral and clinical factors
42 associated with depression among individuals with diabetes. *Diabetes Care*
43 2004;27:914-20.

46 22 Mikailiukstiene A, Juozulynas A, Narkauskaite L, et al. Quality of life in relation
47 to social and disease factors in patients with type 2 diabetes in Lithuania. *Med Sci*
48 *Monit* 2013;19:165-74.

51 23 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in

1
2
3 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in
4 Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.

5
6
7 24 Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck
8 Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale
9 (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale
10 (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res (Hoboken)*
11 2011;63 Suppl 11:S454-66.

12
13
14
15
16 25 Organization WH. The ICD-10 classification of mental and behavioural disorders:
17 clinical descriptions and diagnostic guidelines. Geneva: World Health Organization
18 1992.

19
20
21 26 Association D-AP. Diagnostic and statistical manual of mental disorders.
22 Arlington: American Psychiatric Publishing 2013.

23
24
25 27 Wells GA, Shea B, D OC. The Newcastle-Ottawa Scale (NOS) for assessing the
26 quality of nonrandomised studies in meta-analyses.
27 http://www.ohrica/programs/clinical_epidemiology/oxfordasp (accessed April 27,
28 29 2016) 2008.

30
31
32 28 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in
33 meta-analyses. *BMJ* 2003;327:557-60.

34
35
36 29 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for
37 publication bias. *Biometrics* 1994;50:1088-101.

38
39
40 30 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a
41 simple, graphical test. *BMJ* 1997;315:629-34.

42
43
44 31 Pawaskar MD, Anderson RT, Balkrishnan R. Self-reported predictors of
45 depressive symptomatology in an elderly population with type 2 diabetes mellitus: a
46 prospective cohort study. *Health Qual Life Outcomes* 2007;5:50.

47
48
49 32 Zhang W, Xu H, Zhao S, et al. Prevalence and influencing factors of co-morbid
50 depression in patients with type 2 diabetes mellitus: a General Hospital based study.
51 *Diabetol Metab Syndr* 2015;7:60.

52
53
54 33 Ali S, Davies MJ, Taub NA, et al. Prevalence of diagnosed depression in South
55 Asian and white European people with type 1 and type 2 diabetes mellitus in a UK

1
2
3 secondary care population. *Postgrad Med J* 2009;85:238-43.
4

5 34 Gorska-Ciebiada M, Saryusz-Wolska M, Ciebiada M, et al. Mild cognitive
6 impairment and depressive symptoms in elderly patients with diabetes: prevalence,
7 risk factors, and comorbidity. *J Diabetes Res* 2014;2014:179648.
8
9

10 35 Camara A, Balde NM, Enoru S, et al. Prevalence of anxiety and depression
11 among diabetic African patients in Guinea: association with HbA1c levels. *Diabetes*
12 *Metab* 2015;41:62-8.
13
14

15 36 Raval A, Dhanaraj E, Bhansali A, et al. Prevalence & determinants of depression
16 in type 2 diabetes patients in a tertiary care centre. *Indian J Med Res*
17 2010;132:195-200.
18
19

20 37 Roy T, Lloyd CE, Parvin M, et al. Prevalence of co-morbid depression in
21 out-patients with type 2 diabetes mellitus in Bangladesh. *BMC Psychiatry*
22 2012;12:123.
23
24

25 38 Jacob L, Kostev K. Prevalence of depression in type 2 diabetes patients in
26 German primary care practices. *J Diabetes Complications* 2016;30:432-7.
27
28

29 39 Sun JC, Xu M, Lu JL, et al. Associations of depression with impaired glucose
30 regulation, newly diagnosed diabetes and previously diagnosed diabetes in Chinese
31 adults. *Diabet Med* 2015;32:935-43.
32
33

34 40 Hermanns N, Kulzer B, Krichbaum M, et al. How to screen for depression and
35 emotional problems in patients with diabetes: comparison of screening characteristics
36 of depression questionnaires, measurement of diabetes-specific emotional problems
37 and standard clinical assessment. *Diabetologia* 2006;49:469-77.
38
39

40 41 Stankovic Z, Jasovic-Gasic M, Zamaklar M. Psycho-social and clinical variables
41 associated with depression in patients with type 2 diabetes. *Psychiatr Danub*
42 2011;23:34-44.
43
44

45 42 Zuberi SI, Syed EU, Bhatti JA. Association of depression with treatment
46 outcomes in Type 2 Diabetes Mellitus: a cross-sectional study from Karachi, Pakistan.
47 *BMC Psychiatry* 2011;11:27.
48
49

50 43 Lynch CP, Hernandez-Tejada MA, Strom JL, et al. Association between
51 spirituality and depression in adults with type 2 diabetes. *Diabetes Educ*
52
53

1
2
3 2012;38:427-35.

4
5 44 Osme SF, Ferreira L, Jorge MT, et al. Difference between the prevalence of
6 symptoms of depression and anxiety in non-diabetic smokers and in patients with type
7 2 diabetes with and without nicotine dependence. *Diabetol Metab Syndr* 2012;4:39.

8
9
10 45 Trento M, Raballo M, Trevisan M, et al. A cross-sectional survey of depression,
11 anxiety, and cognitive function in patients with type 2 diabetes. *Acta Diabetol*
12 2012;49:199-203.

13
14
15 46 Joseph N, Unnikrishnan B, Raghavendra Babu YP, et al. Proportion of depression
16 and its determinants among type 2 diabetes mellitus patients in various tertiary care
17 hospitals in Mangalore city of South India. *Indian J Endocrinol Metab*
18 2013;17:681-8.

19
20
21 47 Hayashino Y, Mashitani T, Tsujii S, et al. Elevated Levels of hs-CRP Are
22 Associated With High Prevalence of Depression in Japanese Patients With Type 2
23 Diabetes: The Diabetes Distress and Care Registry at Tenri (DDCRT 6). *Diabetes*
24 *Care* 2014;37:2459-65.

25
26
27 48 Sweileh WM, Abu-Hadeed HM, Al-Jabi SW, et al. Prevalence of depression
28 among people with type 2 diabetes mellitus: a cross sectional study in Palestine. *BMC*
29 *Public Health* 2014;14:163.

30
31
32 49 Kikuchi Y, Iwase M, Fujii H, et al. Association of severe hypoglycemia with
33 depressive symptoms in patients with type 2 diabetes: the Fukuoka Diabetes Registry.
34 *BMJ Open Diabetes Res Care* 2015;3:e000063.

35
36
37 50 Luca A, Luca M, Di Mauro M, et al. Alexithymia, more than depression,
38 influences glycaemic control of type 2 diabetic patients. *J Endocrinol Invest*
39 2015;38:653-60.

40
41
42 51 Rodríguez Calvín JL, Zapatero Gaviria A, Martín Ríos MD. Prevalence of
43 depression in type 2 diabetes mellitus. *Revista Clínica Española (English Edition)*
44 2015;215:156-64.

45
46
47 52 Zhang Y, Ting RZ, Yang W, et al. Depression in Chinese patients with type 2
48 diabetes: associations with hyperglycemia, hypoglycemia, and poor treatment
49 adherence. *J Diabetes* 2015;7:800-8.

- 1
2
3 53 Cols-Sagarra C, Lopez-Simarro F, Alonso-Fernandez M, et al. Prevalence of
4 depression in patients with type 2 diabetes attended in primary care in Spain. *Prim*
5 *Care Diabetes* 2016.
6
7
8 54 Habtewold TD, Alemu SM, Haile YG. Sociodemographic, clinical, and
9 psychosocial factors associated with depression among type 2 diabetic outpatients in
10 Black Lion General Specialized Hospital, Addis Ababa, Ethiopia: a cross-sectional
11 study. *BMC Psychiatry* 2016;16:103.
12
13
14 55 Harris PA. The impact of age, gender, race, and ethnicity on the diagnosis and
15 treatment of depression. *J Manag Care Pharm* 2004;10:S2-7.
16
17
18 56 Skinner TC, Carey ME, Cradock S, et al. Depressive symptoms in the first year
19 from diagnosis of Type 2 diabetes: results from the DESMOND trial. *Diabet Med*
20 2010;27:965-7.
21
22
23 57 Thoolen BJ, de Ridder DT, Bensing JM, et al. Psychological outcomes of patients
24 with screen-detected type 2 diabetes: the influence of time since diagnosis and
25 treatment intensity. *Diabetes Care* 2006;29:2257-62.
26
27
28 58 Petrak F, Stridde E, Leverkus F, et al. Development and validation of a new
29 measure to evaluate psychological resistance to insulin treatment. *Diabetes Care*
30 2007;30:2199-204.
31
32
33 59 Brod M, Kongso JH, Lessard S, et al. Psychological insulin resistance: patient
34 beliefs and implications for diabetes management. *Qual Life Res* 2009;18:23-32.
35
36
37 60 Polonsky WH, Hajos TR, Dain MP, et al. Are patients with type 2 diabetes
38 reluctant to start insulin therapy? An examination of the scope and underpinnings of
39 psychological insulin resistance in a large, international population. *Curr Med Res*
40 *Opin* 2011;27:1169-74.
41
42
43 61 Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality
44 of evidence--imprecision. *J Clin Epidemiol* 2011;64:1283-93.
45
46
47 62 Anderson RJ, Freedland KE, Clouse RE, et al. The prevalence of comorbid
48 depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24:1069-78.
49
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52
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Figure legends

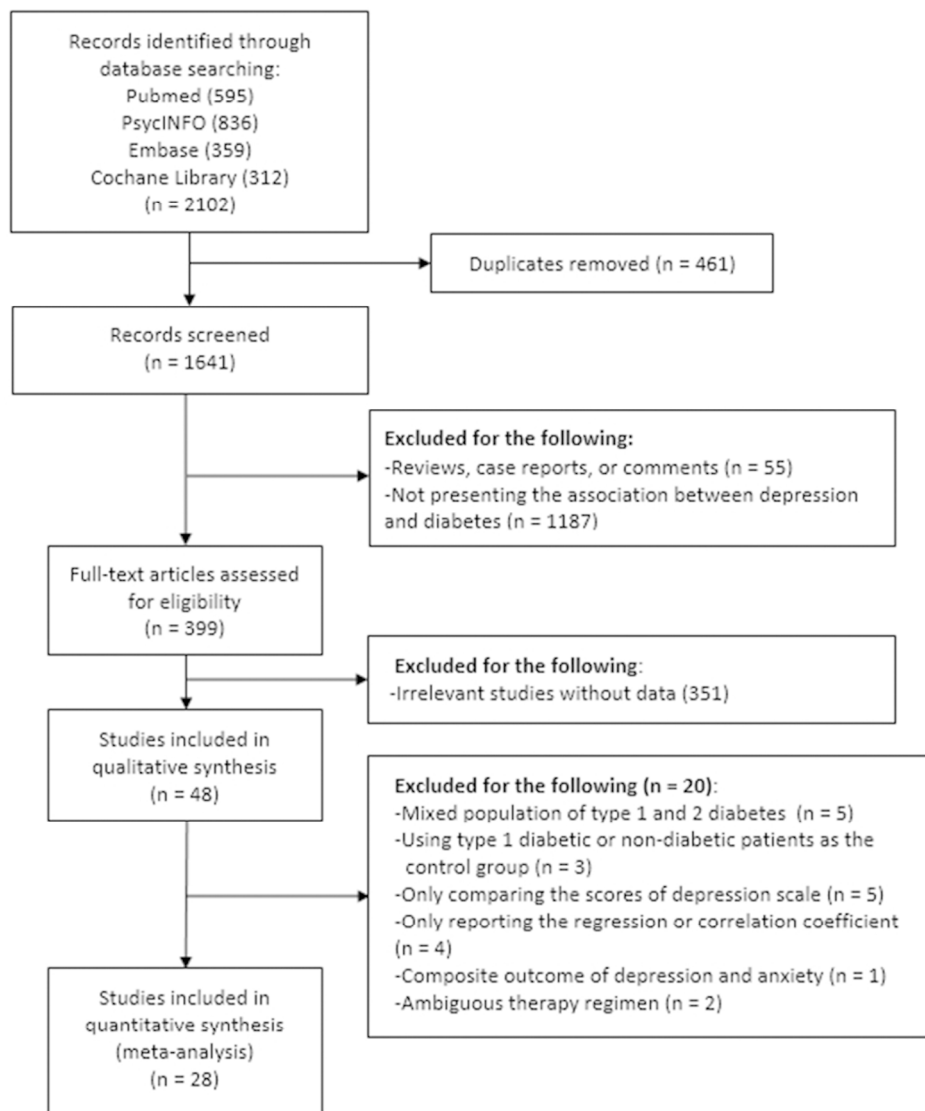
Figure 1. The selection process for eligible studies.

Figure 2. The pooled adjusted odds ratio for the risk of depression in insulin-prescribed patients compared with those without insulin therapy.

Figure 3. The pooled crude odds ratio for the risk of depression in insulin-prescribed patients compared with those without insulin therapy.

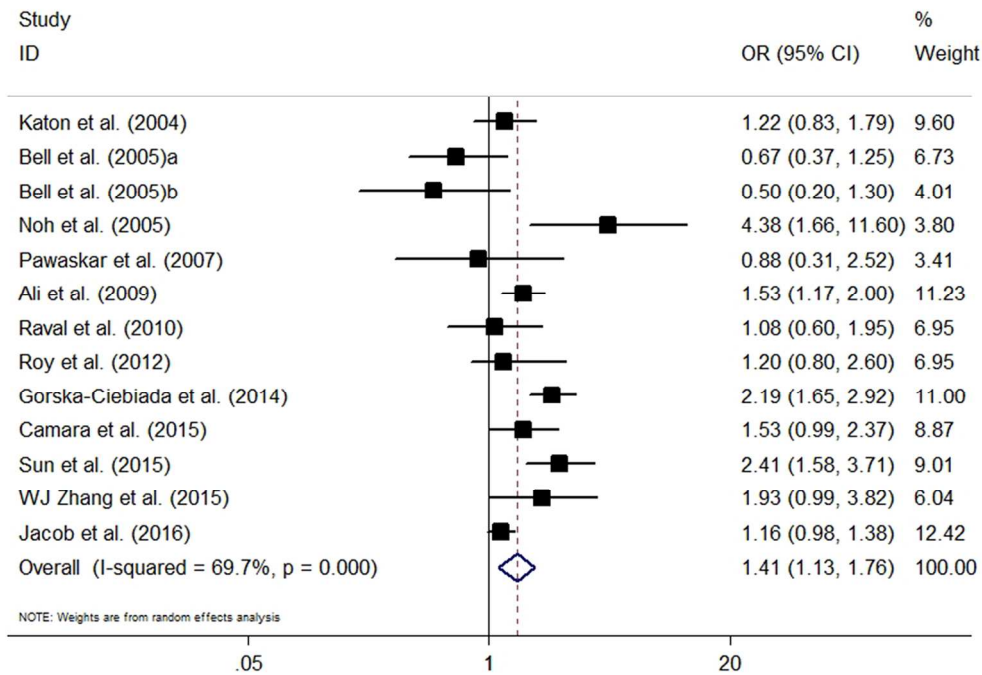
Figure 4. The funnel plot for the studies reporting adjusted odds ratios.

Figure 5. The funnel plot for the studies presenting crude odds ratios.



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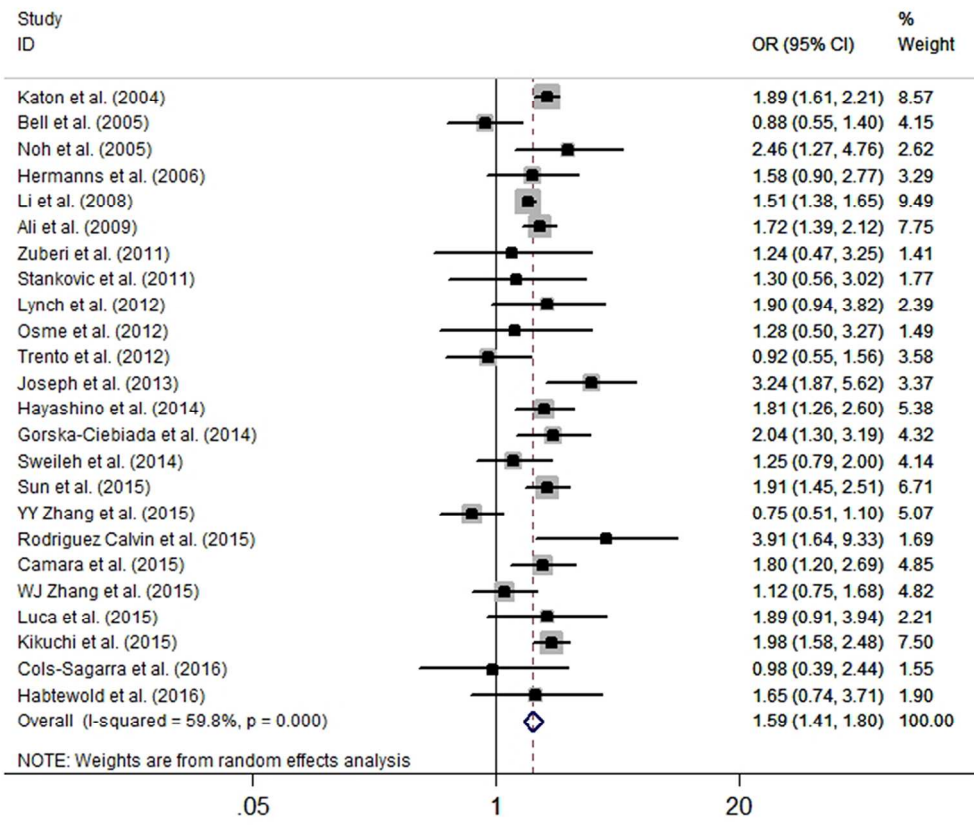
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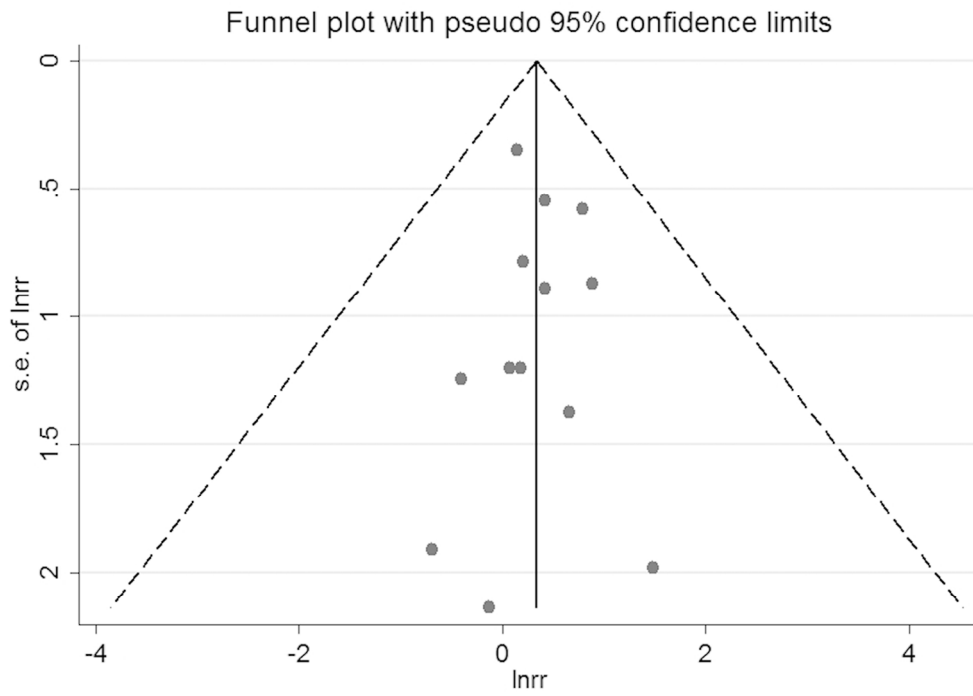
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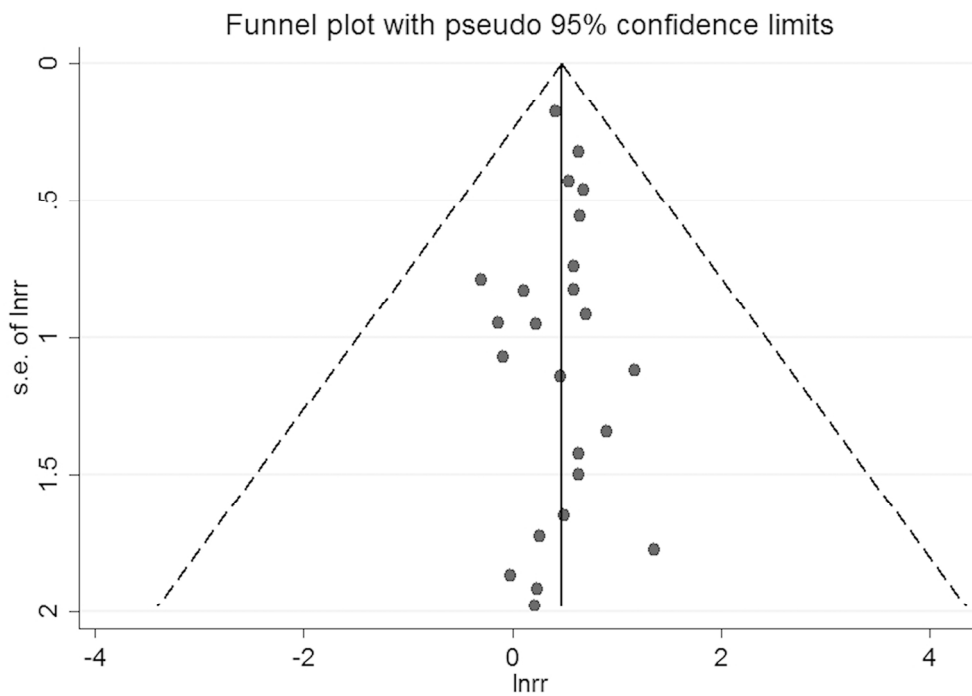
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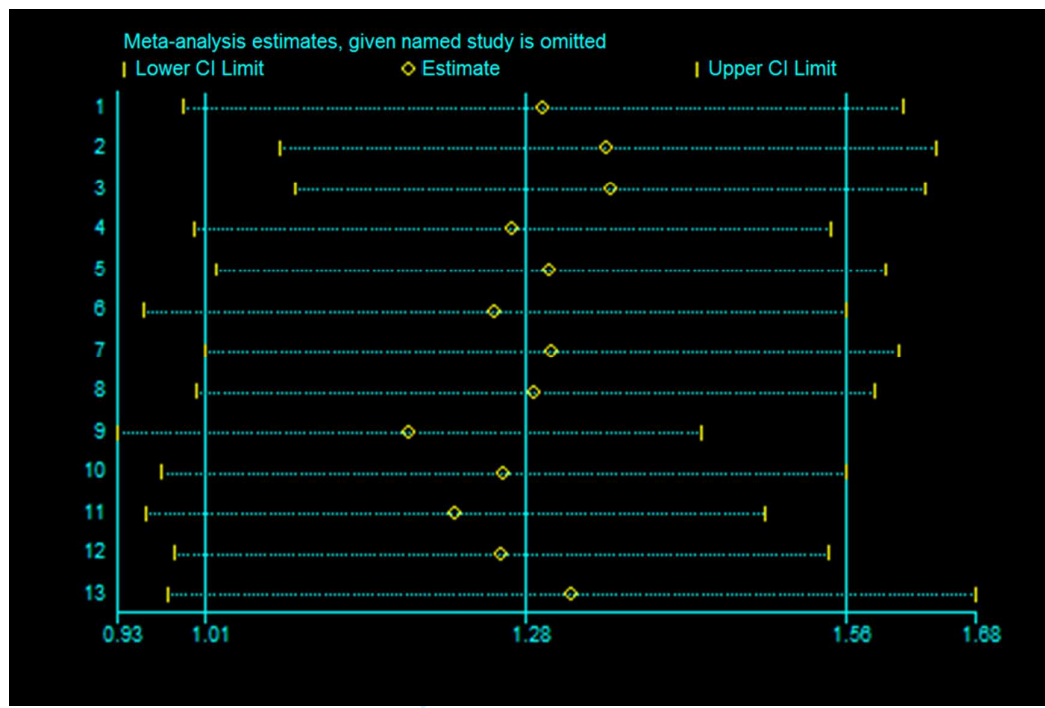


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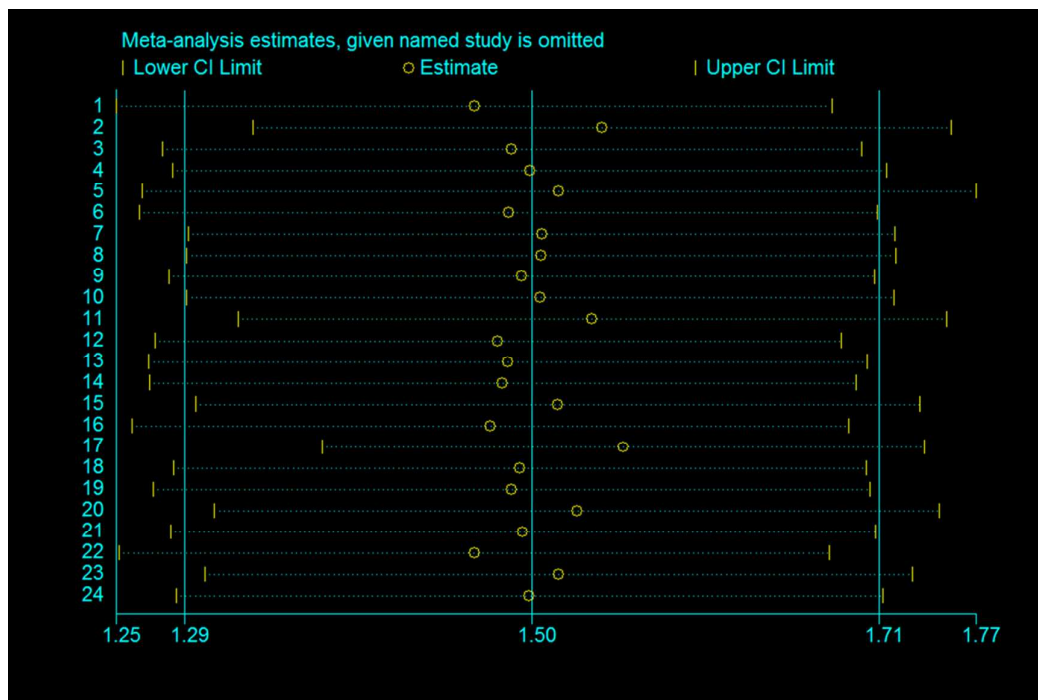
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Supplementary Figure S1. Sensitivity analysis for adjusted data



review only

Supplementary Figure S2. Sensitivity analysis for crude data



review only



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	22
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19-22
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	22
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	22-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	24-25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	26

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Page 2 of 2

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BMJ Open

The association between insulin therapy and depression in patients with type 2 diabetes mellitus: a meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020062.R1
Article Type:	Research
Date Submitted by the Author:	27-Jul-2018
Complete List of Authors:	Bai, Xiaosu; People's Hospital of Longhua New District, Department of Endocrinology Liu, Zhiming; People's Hospital of Longhua New District, Department of Endocrinology Li, Zhisen; People's Hospital of Longhua New District, Department of Endocrinology Yan, Dewen; the Second People's Hospital of Shenzhen, Department of Endocrinology
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Mental health, Diabetes and endocrinology
Keywords:	Depression, insulin, type 2 diabetes mellitus, meta-analysis, risk factor

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3 **The association between insulin therapy and depression in patients with type 2**
4 **diabetes mellitus: a meta-analysis**
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Abstract

Objectives: A large number of type 2 diabetes mellitus (T2DM) patients had depressive disorders. Whether insulin treatment was associated with increased risk of depression remained controversial. We performed a meta-analysis to evaluate the association of insulin therapy and depression.

Design: A meta-analysis.

Methods: We conducted a systematic search of PubMed, PsycINFO, Embase and the Cochrane Library from their inception to April 2016. Epidemiological studies comparing the prevalence of depression between insulin users and non-insulin users were included. Random-effects models were used for meta-analysis. The adjusted and crude data were analyzed.

Results: Twenty-eight studies were included. Twelve studies presented adjusted ORs. Insulin therapy was significantly associated with an increased risk of depression (OR = 1.41, 95% CI 1.13-1.76, P = 0.003). Twenty-four studies were available for the crude data. Insulin therapy also associated with the odds for developing depression (OR = 1.59, 95% CI 1.41-1.80, P < 0.001). When comparing insulin therapy with oral-antidiabetic drugs, significant associations remained for adjusted (OR = 1.42, 95% CI 1.08-1.86, P = 0.008) and crude (OR = 1.61, 95% CI 1.35-1.93, P < 0.001) data.

Conclusions: Our meta-analysis confirmed that patients on insulin therapy was significantly associated with the risk of depressive symptoms.

Keywords: Depression; insulin; type 2 diabetes mellitus; meta-analysis; risk factor

Strengths and limitations of this study

- The primary strength of this study was the systematic and expansive search of

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3 multiple databases, which minimized the risk of missing data.
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6 • Both of the adjusted and crude effect estimates were analyzed and demonstrated
7 consistent results.
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10 • Our findings mainly relied on cross-sectional data; as such, the causal and temporal
11 relationship between insulin use and depression could not be established.
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14 • Some studies had a small sample size which may influence the statistical power.
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17 • The findings of insulin therapy versus specific oral drugs and the prevalence of
18 depression were not illustrated due to inclusion of less number of studies in each
19 subset.
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INTRODUCTION

Diabetes and depression are major global public health problems, both of which are likely to be among the five leading causes of disease burden by 2030.[1] Approximately 90% of adults currently diagnosed with diabetes have type 2 diabetes (T2DM).[2] Recently, a bidirectional link between T2DM and depression has been recognized.[3] Meta-analysis showed that depression was associated with a 60% increased risk of T2DM.[4] Meanwhile, T2DM was associated with a 24% increased risk of depressive symptoms.[5] Further, depression adversely affected the prognosis and quality of life.[6, 7] Growing evidence showed that T2DM and depression may share similar lifestyle factors and biological origins.[3]

T2DM is a chronic and progressive disease characterized by insulin resistance and dysfunction of the pancreatic islet beta cells.[8, 9] For T2DM patients, insulin is the cornerstone of treatment for lowering glucose and HbA1c concentrations.[10] Although the optimal timing and indications for insulin therapy remained controversial,[11-13] most patients will inevitably require insulin therapy to attain adequate glycemic control in the natural history of T2DM.[11, 14]

However, insulin treatment seems less popular than oral hypoglycemic medications. Approximately 25% of the T2DM patients are reluctant to take insulin as the “last-resort” option.[15] Some patients may experience considerable psychological disorders with the transition from oral anti-diabetic drugs to insulin. Additionally, depressive symptoms was more commonly seen in patients with more frequent insulin injections per day.[16] However, the correlations between insulin use and the depression were inconsistent among the previous evidence. Several studies demonstrated positive correlation,[17-19] whereas other studies opposed.[20-22] Besides, these studies varied in enrolled population, adjustment of confounding factors, and depression assessment tools. Thus, we conducted a systematic review and meta-analysis to clarify the association between insulin therapy and the development of depression in T2DM patients.

METHODS

Patient and Public Involvement

Not applicable.

Search strategy

This study was guided by the Meta-analysis of Observational Studies in Epidemiology guidelines.[23] We conducted a systematic computerized search of Pubmed, Ovid PsycINFO, Embase, and the Cochrane Library for eligible studies from their inception to April 2016. The following keywords and medical subject headings were combined: (depression OR depressive) AND (diabetes OR diabetic) AND insulin AND (cross-sectional OR population-based OR cohort OR prospective OR retrospective OR prevalence OR survey OR database OR trial). The language was restricted to English. We also manually screened the reference lists of selected studies for potentially relevant records.

Inclusion and exclusion criteria

We included studies that: (1) investigated the development of depression in insulin users and non-insulin users (oral anti-diabetic drug, diet, or no treatment) among T2DM patients; (2) reported adjusted/unadjusted odds ratios (ORs) or risk ratios (RRs), or presented raw data which could produce crude effect estimates; (3) assessed depression by self-report measures or diagnostic interviews. The self-report scales including the Patient Health Questionnaire (PHQ), Beck Depression Inventory (BDI), and the Center for Epidemiologic Studies–Depression (CES-D) Scale.[24] The diagnostic interviews were based on the criteria by DSM or ICD.[25, 26] A threshold score was not defined as no consensus was available and the threshold varied in different clinical settings. Studies were excluded if: (1) T2DM was mixed with type 1 diabetes; (2) the comparison was conducted between T2DM and non-T2DM patients;

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3 (3) depression could not be distinguished from anxiety or distress; (4) ORs or RRs
4 could not be obtained or calculated. For example, we excluded studies only reporting
5 mean and standard deviations of outcome measures.
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8 9 **Data collection and quality assessment**

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11 Two reviewers independently screened titles and abstracts for eligible studies and
12 extracted the data. Any disagreement was resolved by consensus. The following study
13 characteristics were extracted: author, publication year, study design, country, sample
14 size, mean or median age, proportion of males, depression diagnostic criteria,
15 compared groups, and adjustment of effect estimates. Both of the unadjusted and
16 adjusted effect estimates and 95% CIs were directly extracted or indirectly calculated.
17 The degree of adjustment for confounders were categorized as: “+” for age and/or sex
18 only; “++” for these further adjusted for more than 2 standard sociobehavioral risk
19 factors (i.e., education, race, marital status, insurance, exercise, occupation, smoking
20 status, alcohol consumption, family history of diabetes, and BMI); “+++” for these
21 plus two or more clinical factors, including dyslipidemia, hypertension,
22 cardiovascular disease, duration of T2DM, HbA1c level, treatment intensity, and
23 diabetic complications. The quality was assessed by the modified Newcastle-Ottawa
24 Scale (NOS).[27] This scale awarded a maximum of eight points to each study, with
25 six or less points indicating a high risk of bias.
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40 **Statistical analysis**

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42 As most included studies were cross-sectional, effect sizes had to be expressed as
43 odds ratios (ORs). Given the low prevalence of depression in T2DM patients, the risk
44 ratio (RR) reported by prospective study approximated the OR. Where available, the
45 fully adjusted OR was pooled into meta-analysis to avoid the bias caused by
46 confounding factors. However, the degree of adjustment and the variables entering
47 into regression models varied between included studies. Thus, we additionally pooled
48 the unadjusted ORs for data homogeneity. The random-effects model was used for
49 meta-analysis. Heterogeneity was assessed by the Cochrane Q statistics and I^2 values.
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3 P < 0.05 was regarded as significant heterogeneity for the Q test. I² ranged between 0%
4 (no heterogeneity) and 100% (high heterogeneity), with values around 25, 50, and 75%
5 suggesting low, moderate, and high heterogeneity.[28] To weigh up the relative
6 influence of each individual study, sensitivity analysis was performed by excluding
7 one study at a time and assessing alteration in pooled results. Subgroup analyses and
8 meta-regression analyses were performed using the following variables: compared
9 groups (insulin vs. non-drug therapy or insulin vs. oral anti-diabetic drugs), degree of
10 adjustment of confounders (+, ++ or +++), region (USA, Asia, Europe, or Africa),
11 identification of depression (self-report questionnaire or medical records), sample size
12 (≥ 1000 or < 1000), mean age (≥ 60 or < 60), percentage male (≥ 50 or < 50), and
13 NOS scale (7/8, or <7). Publication bias was statistically assessed by Egger and Begg
14 tests, with P < 0.05 indicating significant asymmetry.[29, 30] Also, we visually
15 inspected the funnel plot for publication bias. All analyses were conducted by the
16 Stata software (version 12.0; StataCorp, College Station, TX). A P value of less than
17 0.05 was considered significant.

34 RESULTS

36 Study selection

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39 We identified 595 articles from Pubmed, 836 articles from PsycINFO, 359 articles
40 from Embase, and 312 articles from Cochrane Library, with a total of 2,102 records.
41 We removed 461 duplicates. Further, 399 full-text articles were assessed for eligibility.
42 After excluding 353 records with insufficient or irrelevant data, 46 studies were
43 included into qualitative synthesis. We excluded 5 studies enrolling mixed type 1 and
44 type 2 diabetic patients, 3 studies comparing depression between DM and non-DM
45 patients, 4 studies only comparing the mean or median scores of depression
46 questionnaire, 4 studies only reporting the regression or correlation coefficient, 1
47 study presenting a mixed outcome of depression and anxiety, and 2 studies reporting a

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3 mixed treatment regimen of insulin or oral drugs. Finally, 28 studies were included
4 into meta-analysis. The flow diagram was shown in Figure 1.
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7 **Study characteristics and quality assessment**

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10 Among the 28 studies pooled into meta-analysis, except for 1 prospective cohort,[31]
11 most were cross-sectional studies. A worldwide distribution was displayed, including
12 5 studies of USA, 8 European studies, 10 Asian studies, 2 African studies, 1
13 South-American study, and 1 study mixed of South-American and European
14 population. The sample size ranged from 90 to 229 047. The prevalence of depression
15 ranged from 3.4 to 51.1%. Seven studies reported both of the adjusted and unadjusted
16 ORs,[17, 20, 21, 32-35] 5 studies only reported the adjusted ORs,[31, 36-39] and
17 unadjusted ORs could only be retrieved from 16 studies.[18, 40-54] Descriptive data
18 of the included studies were summarized in Table 1. In quality assessment, all studies
19 had low to moderate risk of bias, with the scores ranging from 6 to 8. The items
20 satisfied least were the control of confounding factors (12/28) and the report of
21 response rates or follow-up data (10/28) (Table 2).
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Table 1. Characteristics of included studies

Author (year)	Design	Study setting	No. of patients	Mean age, years	Country	Male, %	Depression prevalence, %	Depression assessment	Compared groups	Source estimates	Adjusted factors
Katon et al. (2004)	Cross-sectional	Community	4193	65	USA	51	20.5	PHQ-9	Insulin vs. non-drug	Adjusted	Age, sex, education, marital status, employment, race, BMI and smoking, Rx Risk score, HbA1c, duration of diabetes, treatment intensity, number of complications
Bell et al. (2005)	Cross-sectional	Community	696	74	USA	50.7	15.8	CES-D	Insulin vs. oral medication; insulin vs. non-drug	Adjusted	Age, sex, ethnicity, education, marital status, income, diabetes duration, number of medications, BMI, HbA1c, chronic conditions, PCS score
Noh et al.	Hospital	Hospital	204	53	Korean	53	32.4	BDI	Insulin vs.	Adjusted	Age, sex, BMI, duration of

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(2005) l-based oral diabetes, HbA1c, occupation, medication education, marital status, family history of diabetes, hypertension, diabetic complications, cerebrovascular disease, IHD

Hermanns et al. Cross-sectional Hospital 236 52.2 Germany 60.6 33 BDI; Insulin vs. Unadjusted NA
CES-D non-insulin

(2006) Pawaskar et al. Prospective cohort Medicare Health Maintenance Organization 792 72 USA 44 17.3 CES Insulin vs. Adjusted Age, sex, number of prescriptions, antidiabetic medication, perceived health status, health related quality of life, number of hospitalizations, ER visits
sulfonyleurea

(2008) Li et al. Cross-sectional Surveillance Program 16651 ≥18 USA 42 14.4 PHQ Insulin vs. Unadjusted NA
non-insulin

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Ali et al. (2009)	Cross-sectional	Hospital	3845	NA	Mixed (South Asia and UK)	52.8	9.3	Medical records	Insulin vs. non-insulin	Adjusted	Age, gender, comorbidities, complications, insulin and oral anti-diabetic medication use, BMI, HbA1c, duration of diabetes, and deprivation
Raval et al. (2010)	Cross-sectional	Hospital	300	54	India	49	41	PHQ-9	Insulin vs. non-insulin	Adjusted	Age, gender, obesity, diabetic complications, blood pressure, duration of disease, income, education, BMI, HbA1c, diabetic complications, dyslipidemia, number of medicine
Zuberi et al. (2011)	Cross-sectional	Hospital	286	52	Pakistan	39.2	50	HADS	Insulin vs. oral medication	Unadjusted	NA
Stanković	Cross-sectional	Hospital	90	55.5	Serbia	34.4	51.1	PHQ, BDI,	Insulin vs.	Unadjusted	NA

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(2011)										medication		
Lynch et al.	Cross-sectional	Hospital	201	NA	USA	27.4	19.9	CES-D	Insulin vs. non-insulin	Unadjusted	NA	
(2012)												
Osme et al.	Cross-sectional	Outpatient clinic	138	≥30	Brazil	27.5	44.6	HAD	Insulin vs. non-insulin	Unadjusted	NA	
(2012)												
Taranto et al.	Cross-sectional	Outpatient clinic	498	67.6	Italy	52.6	14.2	ZSDS	Insulin vs. non-insulin	Unadjusted	NA	
(2012)												
Roy et al.	Cross-sectional	Outpatient clinic	417	53.2	Bangladesh	50.6	34	PHQ-9	Insulin vs. oral medication + diet;	Adjusted	Age, gender, education, income, region, CVD, hypertension, diabetic complications, BMI, HbA1c	
(2012)												

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insulin+oral
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Joseph et al (2013) Cross-sectional Hospital 230 53.6 India 51.7 45.2 PHQ-9 Insulin vs. Unadjusted NA

oral
medication

Hayashino et al. (2014) Cross-sectional Hospital 3573 66 Japan 61.1 3.4 PHQ-9 Insulin vs. Unadjusted NA

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medication
or diet

Gorska-Ciechanowska et al. (2014) Cross-sectional Outpatient clinic 276 74 Poland 46 29.7 GDS Insulin vs. Adjusted Age, sex, education,

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of diabetes, BMI, HbA1c, lipids
levels, diabetic complications,
previous HA or use of HA drugs,
hyperlipidemia, number of
comorbid conditions, hypoglycemia

Sweileh et al. (2014)	Cross-sectional	Hospital	294	60	Palestine	44.2	40.2	BDI	Insulin vs. non-insulin	Unadjusted	NA
Yan Zhang et al. (2015)	Cross-sectional	Hospital	2538	56.4	China	53	6.1	PHQ-9	Insulin vs. oral drugs	Unadjusted	NA
Rodríguez-Carvalín et al. (2015)	Cross-sectional	Hospital	275	64.5	Spain	56.4	32.7	BDI	Insulin vs. oral medication	Unadjusted	NA
Camara et al.	Cross-sectional	Outpatient	491	58	Guinea	37	34.4	HADS	Insulin vs. oral	Adjusted	Age, HbA1c, hypertension, BMI, residence zone, socioeconomic

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al (2015)	ectional	clinic								medication		status
Sun et al. (2015)	Cross-sectional	Community	229	57.4	China	34.4	5.9	PHQ-9	Insulin vs. Adjusted	oral medication or diet		Age, sex, BMI, HbA1c, smoking, alcohol, physical activity, education, occupation, marital status, selfreport cardio-metabolic disorders, diabetes treatment, diabetes duration
Wang et al. (2015)	Cross-sectional	Hospital	412	59.8	China	50.2	5.7	BDI	Insulin vs. Adjusted	oral medication		Age, gender, education, marital status, occupation, insurance, HbA1c, BMI, DM history, diabetic complications, duration of DM, smoking, alcohol, exercise, sleeping hours
Li et al. (2015)	Cross-sectional	Hospital	128	64.7	Italy	58.6	50.8	HAM-D	Insulin vs. Unadjusted	oral medication		NA

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Kikuchi et al. (2015)	Cross-sectional	Community	4218	65.5	Japan	57.1	10.6	CES-D	Insulin vs. non-insulin	Unadjusted	NA
Jacob et al. (2016)	Cross-sectional	Community	90412	65.5	Germany	50.2	30.3	Medical records	Insulin vs. non-insulin	Adjusted	Age, gender, insurance, diabetic complications, CVD, HbA1c
Cois-Sagar et al. (2016)	Cross-sectional	Community	411	70.8	Spain	46.2	29.2	PHQ-9	Insulin vs. oral medications	Unadjusted	NA
Habtewold et al. (2016)	Cross-sectional	Hospital	276	44	Ethiopia	47	44.7	PHQ-9	Insulin vs. oral medication	Unadjusted	NA

BDI, Beck Depression Inventory; BMI, body mass index; BG, blood glucose; CES-D, Center for Epidemiologic Studies Depression; DBP, diastolic blood pressure; ER, emergency room; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton rating scale for depression; IHD, ischemic heart disease; PCS, Physical Component Summary score; PHQ, Patient Health

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Questionnaire; SBP, systolic blood pressure; ZSDS, Zung Self-Rating Depression Scale.

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Table 2. Quality assessment of included studies by the modified Newcastle-Ottawa scale (NOS)

Author (year)	Adequate definition of cases using insulin	Representativeness of cases using insulin	Selection of the non-insulin users	Ascertainment of insulin use	Depression was not present before initiation	Control of confounding factors	Assessment of depression	Report response or follow-up data	Total score
Katon et al. (2004)	1	1	1	1	1	1	1	1	8
Bell et al. (2005)	1	1	1	1	1	1	1	0	7
Noh et al. (2005)	1	0	1	1	1	1	1	0	6
Hermanns et al. (2006)	1	1	1	1	1	0	1	0	6
Pawaskar et al. (2007)	1	1	1	1	1	1	1	1	7
Li et al. (2008)	1	1	1	1	1	0	1	0	6
Ali et al. (2009)	1	1	1	1	1	1	1	0	7
Raval et al. (2010)	1	1	1	1	1	1	1	0	7

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7	Zuberi et al. (2011)	1	1	1	1	1	0	1	1	7
8										
9	Stanković et al. (2011)	1	1	1	1	1	0	1	0	6
10										
11										
12	Lynch et al. (2012)	1	1	1	1	1	0	1	1	7
13										
14										
15	Osme et al. (2012)	1	1	1	1	1	0	1	0	6
16										
17	Trento et al. (2012)	1	1	1	1	1	0	1	0	6
18										
19										
20	Roy et al. (2012)	1	1	1	1	1	1	1	1	8
21										
22										
23	Joseph et al. (2013)	1	1	1	1	1	0	1	0	6
24										
25	Hayashino et al. (2014)	1	1	1	1	1	0	1	0	6
26										
27										
28	Gorska-Ciebiada et al. (2014)	0	1	1	1	1	1	1	0	6
29										
30										
31	Sweileh et al. (2014)	1	1	1	1	1	0	1	1	7
32										
33	YY Zhang et al. (2015)	1	1	1	1	1	0	1	1	7
34										
35										
36	Rodriguez Calvin et al. (2015)	1	1	1	1	1	0	1	1	7
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7	Camara et al. (2015)	1	1	1	1	1	0	1	0	6
9	Sun et al. (2015)	1	1	1	1	1	1	1	0	7
12	WJ Zhang et al. (2015)	1	1	1	1	1	1	1	1	8
15	Luca et al. (2015)	1	1	1	1	1	0	1	0	6
17	Kikuchi et al. (2015)	1	1	1	1	1	0	1	0	6
20	Jacob et al. (2016)	1	1	1	1	1	0	1	0	6
22	Cols-Sagarra et al. (2016)	1	1	1	1	1	0	1	0	6
25	Habtewold et al. (2016)	1	1	1	1	1	0	1	1	7

Meta-analysis of adjusted data

The adjusted ORs for the comparison of depression between insulin and non-insulin treated patients were reported by 12 studies. Compared with non-insulin treatment, insulin therapy was associated with a statistically significant higher risk of depression (OR = 1.41, 95% CI 1.13-1.76, P = 0.003). Significantly high heterogeneity was revealed ($I^2 = 69.7\%$, $P < 0.001$) (Figure 2).

The results of sensitivity analysis, which excluded the selected studies one by one, might vary by excluding several included studies (Supplementary Figure S1). To identify the sources of heterogeneity, we performed subgroup analyses based on several important confounding factors. Six studies particularly compared insulin with oral anti-diabetic drugs, and showed that insulin therapy was significantly associated with increased risk of depression (OR = 1.42, 95% CI 1.08-1.86, P = 0.008). For 2 studies comparing insulin with non-drug therapy, no significant association was revealed for insulin and depression (OR = 0.87, 95% CI 0.37-2.03, P = .745). Additionally, we conducted a subgroup analysis based on the degree of adjustment of confounders, region, identification of depression, sample size, mean age, percentage male, and NOS scale. The association remained significant for the subgroups of fully adjustment (+++), Asian studies, self-report questionnaires, sample size ≥ 1000 , mean age < 60.0 years, percentage of male $< 50.0\%$, prevalence of depression over 20%, and NOS scale < 6 (Table 3). Meta-regression analyses indicated a lack of effect measure modification by sample size (P = 0.93), mean age (P = 0.17), percentage male (P = 0.28) or prevalence of depression (P = 0.75).

Table 3. Subgroup analyses for the studies reporting adjusted effect estimates

Subgroups	No. of studies	OR (95% CI)	P value	I^2	P value for heterogeneity	P value between subgroups
Compared groups						

Insulin vs. oral drugs	6	1.42 (1.08-1.86)	<0.05	71.3%	<0.05	0.28
Insulin vs. non-drugs	2	0.87 (0.37-2.03)	>0.05	66.5%	0.08	
Degree of adjustment						
+++	10	1.43 (1.08-1.89)	<0.05	68.9%	<0.05	0.44
++	2	1.24 (0.98-1.55)	>0.05	25.3%	0.25	
Region						
USA	4	0.86 (0.57-1.31)	>0.05	36.4%	0.19	0.12
Asia	5	1.81 (1.18-2.79)	<0.05	59%	0.05	
Europe	2	1.58 (0.85-2.94)	>0.05	92.9%	<0.05	
Africa	1	1.53 (0.99-2.37)	>0.05	-	-	
Identification of depression						
Self-report questionnaire	10	1.42 (1.06-1.91)	<0.05	68.9%	<0.05	0.69
Medical records	2	1.31 (1.00-1.71)	>0.05	65.6%	0.09	
Sample size						
≥ 1000	4	1.46 (1.10-1.94)	<0.05	73.1%	<0.05	0.72
< 1000	8	1.34 (0.93-1.93)	>0.05	70%	<0.05	
Mean age						
≥ 60.0	5	1.12 (0.77-1.62)	>0.05	78.8%	<0.05	0.08

< 60.0	6	1.74 (1.24-2.43)	<0.05	50.8%	0.07	
Percentage male (%)						
≥ 50.0	7	1.26 (0.97-1.63)	>0.05	62.4%	<0.05	0.14
< 50.0	5	1.71 (1.25-2.35)	<0.05	53.9%	0.07	
Prevalence of depression						
≥ 20%	7	1.48 (1.12-1.96)	<0.05	71.3%	<0.05	0.53
< 20%	5	1.25 (0.80-1.95)	>0.05	72.7%	<0.05	
NOS scale						
7 or 8	8	1.25 (0.94-1.66)	>0.05	60.0%	<0.05	0.19
<7	4	1.79 (1.14-2.80)	<0.05	84.6%	<0.05	

Meta-analysis of unadjusted results

Twenty-four studies were available for the crude data. All studies were cross-sectional, and assessed depression by self-report scales. The studies presented three comparison types (insulin vs. non-drug therapy; insulin vs. oral anti-diabetic drugs; and insulin vs. non-insulin treatment). Data on the comparison between insulin and non-insulin therapy were preferred. The pooled results showed that T2DM patients on insulin therapy were associated with an increased risk of depression compared with those on non-insulin treatment (OR = 1.59, 95% CI 1.41-1.80, P < 0.001) (Figure 3). The heterogeneity was at a significantly high level ($I^2 = 59.8\%$, P < 0.001). Sensitivity analysis revealed no significant variation in the pooled OR by exclusion of any included study (Supplementary Figure S2).

Seventeen studies compared insulin with oral anti-diabetic drugs, showing a significantly association for the risk of depression (OR = 1.61, 95% CI 1.35-1.93, $P < 0.001$). For 6 studies comparing insulin use with non-drug treatment, we noted insulin use was associated with an increased risk of depression (OR = 1.89, 95% CI 1.25-2.88, $P = 0.002$). In the stratified analyses based on degree of adjustment of confounders, region, identification of depression, sample size, mean age, percentage male, and NOS scale, the significant association between insulin use and depression remained significant among all subgroups except the study conducted in South America (Table 4). In meta-regression analyses, sample size ($P = 0.79$), mean age ($P = 0.56$), percentage male ($P = 0.80$), and the prevalence of depression ($P = 0.68$) demonstrated no independent effect on the depression outcomes.

Table 4. Subgroup analyses for the studies reporting the crude effect estimates

Subgroups	No. of studies	OR (95% CI)	P value	I ² (P value)	P value for heterogeneity	P value between subgroups
Compared groups						
Insulin vs. oral drugs	17	1.61 (1.35-1.93)	<0.05	62.6%	<0.05	0.49
Insulin vs. non-drugs	6	1.89 (1.25-2.88)	<0.05	68.2%	<0.05	
Region						
USA	4	1.53 (1.21-1.93)	<0.05	75.4%	<0.05	0.31
Asia	9	1.60 (1.22-2.10)	<0.05	75.4%	0.05	
Europe	7	1.59 (1.13-2.22)	<0.05	45.3%	<0.05	
Africa	2	1.77 (1.23-2.54)	<0.05	0.0	0.85	
South America	1	1.28 (0.50-3.27)	>0.05	-	-	
Sample size						

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3	≥1000	7	1.64 (1.39-1.93)	<0.05	77.5%	<0.05	0.71
4							
5	< 1000	17	1.56 (1.27-1.91)	<0.05	46.7%	<0.05	
6							
7							
8	Mean age						
9							
10							
11	≥ 60.0	10	1.60 (1.30-1.97)	<0.05	61.8%	<0.05	0.92
12							
13	< 60.0	10	1.57 (1.18-2.09)	<0.05	68.0%	<0.05	
14							
15							
16	Percentage						
17	male						
18	(%)						
19							
20							
21	≥ 50.0	13	1.59 (1.29-1.96)	<0.05	75.1%	<0.05	0.82
22							
23	< 50.0	11	1.55 (1.43-1.68)	<0.05	0.0	0.71	
24							
25							
26	Prevalence						
27	of						
28	depression						
29							
30	≥ 20%	14	1.84 (1.59-2.12)	<0.05	11.7%	0.33	<0.05
31							
32	< 20%	10	1.43 (1.19 -1.70)	<0.05	74.0%	<0.05	
33							
34							
35							
36	NOS scale						
37							
38	7 or 8	11	1.45 (1.16-1.82)	<0.05	72.3%	<0.05	0.22
39							
40	<7	13	1.72 (1.47-2.00)	<0.05	42.8%	0.05	
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Publication bias

For studies reporting the adjusted ORs, the funnel plot was symmetrical (Figure 4). No publication bias was shown by the Egger test (P = 0.94) or Begg's test (P = 0.67). For studies presenting the crude ORs, the funnel plot was symmetrical (Figure 5). We did not detect publication bias by Egger (P = 0.39) or Begg's test (P = 0.94).

DISCUSSION

This is the first meta-analysis that estimated the magnitude of the association between insulin therapy and depression. The pooled data of adjusted ORs proved that T2DM patients on insulin treatment was associated with the prevalence of depressive syndromes compared to those without insulin therapy. When pooling crude ORs, this significant association was permanent. We specifically compared insulin use with oral-antidiabetic drugs. Both of the adjusted data (OR = 1.42) and the unadjusted data (OR = 1.61) showed that insulin users were relation to the greater risk of depression.

The source of heterogeneity was explored carefully. In sensitivity analysis, no substantial change in heterogeneity was revealed when excluding any individual study, suggesting the homogeneity of the pooled effect estimates. The prevalence of depression could be different according to ethnicities.[55] In subgroup analyses of adjusted data, we found that the significance displayed for Asian studies. Non-significant result was shown for studies with sample size below 1000, suggesting that the result was unstable for small sample size. Substantial change of heterogeneity was also detected for the subgroups of insufficient degree of adjustment and depression identified by medical records. However, the number of eligible studies was rather small to draw firm conclusions. For studies of depression prevalence below 20%, substantial change in the effect estimates was shown for adjusted data, and obvious change in heterogeneity for crude data. Thus, it may partly account for the heterogeneity. Finally, the significant association was detected if the mean age was < 60.0 years, percentage male < 50.0%, and NOS < 7 for adjusted data. This might be due to that younger patients were associated with higher prevalence of depression, and women receiving insulin therapy might be under greater risk of depression compared to men.

The mechanisms link diabetes and depression were complex and still unclear. Depression and T2DM could develop in parallel through shared biological processes.

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3 The involved pathways include the innate inflammatory response, the
4 hypothalamic-pituitary-adrenal axis, circadian rhythms, and insulin resistance.[3]
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6 Although the overall prevalence of depression is high in diabetic patients, the
7 DESMOND trial reported that it was not so in newly diagnosed T2DM.[56]
8
9 Screen-detected patients with T2DM showed low distress and anxiety at the time of
10 diagnosis, with a significant increase during the following 12 months.[57] In
11 accordance with these findings, we confirmed that insulin therapy was associated with
12 increased prevalence of depression. For patients on insulin therapy, they had less
13 endogenous insulin and were therefore more susceptible to metabolic dysregulation
14 than patients who might have some residual insulin secretory activity. Especially,
15 patients who are more metabolically labile are more vulnerable to depression.[16]
16
17 Besides, insulin therapy is always a symbol of more advanced type 2 diabetes. The
18 patients' negative attitudes toward insulin therapy may contribute to delays for insulin
19 initiation, prolonged duration of hyperglycemia, and increased risk of diabetic
20 complications.[58] Psychological insulin resistance (PIR) has been defined as
21 psychological opposition towards insulin treatment in both diabetic patients and their
22 prescribers. They may display fear of insulin injection and self-testing, complex
23 regimen, hypoglycemia, and weight gain; a perceived loss of control over one's life;
24 poor self-efficacy concerning insulin treatment; and perceived lack of positive
25 outcomes related to insulin.[58-60] These psychological aspects may explain for the
26 increased risk of depression when insulin was prescribed.
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42 The primary strength of this study was the systematic and expansive search of
43 multiple databases, which minimized the risk of missing data. The meta-analysis
44 identified 28 studies enrolling worldwide-distributed participants. Both of the adjusted
45 and crude effect estimates were analyzed and demonstrated consistent results. The
46 confidential intervals were narrow, suggesting the precision of pooled results.[61] For
47 adjusted data, most studies had full adjustment for confounders. The subtypes of
48 non-insulin therapy, including oral drug and non-drug treatment, were analyzed
49 separately. The between-study heterogeneity was intensively explored by sensitivity,
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3 subgroup, and meta-regression analyses. Besides, no publication bias was detected
4 among the selected studies.
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8 We were aware of the limitations of this meta-analysis. Our findings mainly
9 relied on cross-sectional data; as such, the causal and temporal relationship between
10 insulin use and depression could not be established. Some studies had a small sample
11 size which may influence the statistical power. The response rate was only reported by
12 several studies. The unmeasured differences between respondents and nonrespondents
13 may potentially influence the pooled results. Most of the studies used self-reported
14 scales rather than clinical interview-based assessments to identify depression.
15 Prevalence of depression was generally much higher using the self-reported scales
16 than standardized diagnostic interviews.[20, 62] Furthermore, the findings of insulin
17 therapy versus specific oral drugs and the prevalence of depression were not
18 illustrated due to inclusion of less number of studies in each subset. Moreover,
19 background oral anti-diabetic drug uses in insulin group might affect the associations
20 of insulin use with the risk of depressive syndromes, while these information was not
21 available in mostly included studies. In addition, although subgroup analyses based on
22 several factors were conducted, while substantial residual heterogeneity were
23 observed in numerous subsets. These results were restricted by uncontrolled baseline
24 characteristics of included patients and studies. Finally, the impact of the total number
25 of daily insulin injections with depression development was included only in few
26 studies, and these contributed as potential confounders in patients who received
27 insulin therapy and the progression of depression.
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48 **CONCLUSIONS**

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50 In conclusion, we noted type 2 diabetic patients who were prescribed insulin was
51 relation to depressive syndromes. For insulin-users, careful monitoring of depressive
52 symptoms should be incorporated into the disease management. Intensified
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psychological and education programs should be carried out to prevent depressive illness after insulin initiation in the primary care settings.

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Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

XSB contributed to study concepts, manuscript preparation, literature research and drafting the manuscript. ZML, ZSL and DWY carried out literature research, data analysis and revising the manuscript for important content. All authors read and approved the final manuscript.

Data sharing statement

No additional data available.

References

- 1 Tabak AG, Akbaraly TN, Batty GD, et al. Depression and type 2 diabetes: a causal association? *Lancet Diabetes Endocrinol* 2014;2:236-45.
- 2 Type 2 Diabetes in Adults: Management. National Institute for Health and Care Excellence: Clinical Guidelines. London 2015.
- 3 Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. *Lancet Diabetes Endocrinol* 2015;3:461-71.
- 4 Mezuk B, Eaton WW, Albrecht S, et al. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care* 2008;31:2383-90.
- 5 Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia* 2010;53:2480-6.
- 6 van Dooren FE, Nefs G, Schram MT, et al. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One* 2013;8:e57058.
- 7 Kan C, Silva N, Golden SH, et al. A systematic review and meta-analysis of the association between depression and insulin resistance. *Diabetes Care* 2013;36:480-9.
- 8 Ismail-Beigi F. Clinical practice. Glycemic management of type 2 diabetes mellitus. *N Engl J Med* 2012;366:1319-27.
- 9 Ohn JH, Kwak SH, Cho YM, et al. 10-year trajectory of beta-cell function and insulin sensitivity in the development of type 2 diabetes: a community-based prospective cohort study. *Lancet Diabetes Endocrinol* 2016;4:27-34.
- 10 Cahn A, Miccoli R, Dardano A, et al. New forms of insulin and insulin therapies for the treatment of type 2 diabetes. *Lancet Diabetes Endocrinol* 2015;3:638-52.
- 11 Home P, Riddle M, Cefalu WT, et al. Insulin therapy in people with type 2

1
2
3 diabetes: opportunities and challenges? *Diabetes Care* 2014;37:1499-508.

4
5
6 12 Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function
7 and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre
8 randomised parallel-group trial. *Lancet* 2008;371:1753-60.

9
10
11
12 13 Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in
14 type 2 diabetes mellitus: a systematic review and meta-analysis. *Lancet Diabetes*
15 *Endocrinol* 2013;1:28-34.

16
17
18 14 Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose
19 control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.

20
21
22
23 15 Holmes-Truscott E, Skinner TC, Pouwer F, et al. Explaining psychological
24 insulin resistance in adults with non-insulin-treated type 2 diabetes: The roles of
25 diabetes distress and current medication concerns. Results from Diabetes
26 MILES-Australia. *Prim Care Diabetes* 2016;10:75-82.

27
28
29
30
31 16 Surwit RS, van Tilburg MA, Parekh PI, et al. Treatment regimen determines the
32 relationship between depression and glycemic control. *Diabetes Res Clin Pract*
33 2005;69:78-80.

34
35
36
37 17 Noh JH, Park JK, Lee HJ, et al. Depressive symptoms of type 2 diabetics treated
38 with insulin compared to diabetics taking oral anti-diabetic drugs: a Korean study.
39 *Diabetes Res Clin Pract* 2005;69:243-8.

40
41
42
43 18 Li C, Ford ES, Strine TW, et al. Prevalence of depression among U.S. adults with
44 diabetes: findings from the 2006 behavioral risk factor surveillance system. *Diabetes*
45 *Care* 2008;31:105-7.

46
47
48
49 19 Al-Amer RM, Sobeh MM, Zayed AA, et al. Depression among adults with
50 diabetes in Jordan: risk factors and relationship to blood sugar control. *J Diabetes*
51 *Complications* 2011;25:247-52.

52
53
54
55
56 20 Bell RA, Smith SL, Arcury TA, et al. Prevalence and correlates of depressive

1
2
3 symptoms among rural older African Americans, Native Americans, and whites with
4 diabetes. *Diabetes Care* 2005;28:823-9.

5
6
7
8 21 Katon W, von Korff M, Ciechanowski P, et al. Behavioral and clinical factors
9 associated with depression among individuals with diabetes. *Diabetes Care*
10 2004;27:914-20.

11
12
13
14 22 Mikailiukstiene A, Juozulynas A, Narkauskaite L, et al. Quality of life in relation
15 to social and disease factors in patients with type 2 diabetes in Lithuania. *Med Sci*
16 *Monit* 2013;19:165-74.

17
18
19
20 23 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in
21 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in
22 Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.

23
24
25
26 24 Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck
27 Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale
28 (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale
29 (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res (Hoboken)*
30 2011;63 Suppl 11:S454-66.

31
32
33
34
35
36 25 Organization WH. The ICD-10 classification of mental and behavioural disorders:
37 clinical descriptions and diagnostic guidelines: Geneva: World Health Organization
38 1992.

39
40
41
42 26 Association D-AP. Diagnostic and statistical manual of mental disorders.
43 Arlington: American Psychiatric Publishing 2013.

44
45
46
47 27 Wells GA, Shea B, D OC. The Newcastle-Ottawa Scale (NOS) for assessing the
48 quality of nonrandomised studies in meta-analyses.
49 http://www.ohrica/programs/clinical_epidemiology/oxfordasp (accessed April 27,
50 2016) 2008.

51
52
53
54
55 28 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in

1
2
3 meta-analyses. *BMJ* 2003;327:557-60.

4
5
6 29 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for
7 publication bias. *Biometrics* 1994;50:1088-101.

8
9
10 30 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a
11 simple, graphical test. *BMJ* 1997;315:629-34.

12
13
14 31 Pawaskar MD, Anderson RT, Balkrishnan R. Self-reported predictors of
15 depressive symptomatology in an elderly population with type 2 diabetes mellitus: a
16 prospective cohort study. *Health Qual Life Outcomes* 2007;5:50.

17
18
19 32 Zhang W, Xu H, Zhao S, et al. Prevalence and influencing factors of co-morbid
20 depression in patients with type 2 diabetes mellitus: a General Hospital based study.
21 *Diabetol Metab Syndr* 2015;7:60.

22
23
24 33 Ali S, Davies MJ, Taub NA, et al. Prevalence of diagnosed depression in South
25 Asian and white European people with type 1 and type 2 diabetes mellitus in a UK
26 secondary care population. *Postgrad Med J* 2009;85:238-43.

27
28
29 34 Gorska-Ciebiada M, Saryusz-Wolska M, Ciebiada M, et al. Mild cognitive
30 impairment and depressive symptoms in elderly patients with diabetes: prevalence,
31 risk factors, and comorbidity. *J Diabetes Res* 2014;2014:179648.

32
33
34 35 Camara A, Balde NM, Enoru S, et al. Prevalence of anxiety and depression
35 among diabetic African patients in Guinea: association with HbA1c levels. *Diabetes*
36 *Metab* 2015;41:62-8.

37
38
39 36 Raval A, Dhanaraj E, Bhansali A, et al. Prevalence & determinants of depression
40 in type 2 diabetes patients in a tertiary care centre. *Indian J Med Res*
41 2010;132:195-200.

42
43
44 37 Roy T, Lloyd CE, Parvin M, et al. Prevalence of co-morbid depression in
45 out-patients with type 2 diabetes mellitus in Bangladesh. *BMC Psychiatry*
46 2012;12:123.

1
2
3 38 Jacob L, Kostev K. Prevalence of depression in type 2 diabetes patients in
4 German primary care practices. *J Diabetes Complications* 2016;30:432-7.
5

6
7 39 Sun JC, Xu M, Lu JL, et al. Associations of depression with impaired glucose
8 regulation, newly diagnosed diabetes and previously diagnosed diabetes in Chinese
9 adults. *Diabet Med* 2015;32:935-43.
10
11

12
13 40 Hermanns N, Kulzer B, Krichbaum M, et al. How to screen for depression and
14 emotional problems in patients with diabetes: comparison of screening characteristics
15 of depression questionnaires, measurement of diabetes-specific emotional problems
16 and standard clinical assessment. *Diabetologia* 2006;49:469-77.
17
18
19

20
21 41 Stankovic Z, Jasovic-Gasic M, Zamaklar M. Psycho-social and clinical variables
22 associated with depression in patients with type 2 diabetes. *Psychiatr Danub*
23 2011;23:34-44.
24
25
26

27
28 42 Zuberi SI, Syed EU, Bhatti JA. Association of depression with treatment
29 outcomes in Type 2 Diabetes Mellitus: a cross-sectional study from Karachi, Pakistan.
30 *BMC Psychiatry* 2011;11:27.
31
32
33

34
35 43 Lynch CP, Hernandez-Tejada MA, Strom JL, et al. Association between
36 spirituality and depression in adults with type 2 diabetes. *Diabetes Educ*
37 2012;38:427-35.
38
39
40

41 44 Osme SF, Ferreira L, Jorge MT, et al. Difference between the prevalence of
42 symptoms of depression and anxiety in non-diabetic smokers and in patients with type
43 2 diabetes with and without nicotine dependence. *Diabetol Metab Syndr* 2012;4:39.
44
45
46

47 45 Trento M, Raballo M, Trevisan M, et al. A cross-sectional survey of depression,
48 anxiety, and cognitive function in patients with type 2 diabetes. *Acta Diabetol*
49 2012;49:199-203.
50
51
52

53 46 Joseph N, Unnikrishnan B, Raghavendra Babu YP, et al. Proportion of depression
54 and its determinants among type 2 diabetes mellitus patients in various tertiary care
55
56

1
2
3 hospitals in Mangalore city of South India. *Indian J Endocrinol Metab*
4 2013;17:681-8.
5

6
7 47 Hayashino Y, Mashitani T, Tsujii S, et al. Elevated Levels of hs-CRP Are
8 Associated With High Prevalence of Depression in Japanese Patients With Type 2
9 Diabetes: The Diabetes Distress and Care Registry at Tenri (DDCRT 6). *Diabetes*
10 *Care* 2014;37:2459-65.
11
12

13
14 48 Sweileh WM, Abu-Hadeed HM, Al-Jabi SW, et al. Prevalence of depression
15 among people with type 2 diabetes mellitus: a cross sectional study in Palestine. *BMC*
16 *Public Health* 2014;14:163.
17
18

19
20 49 Kikuchi Y, Iwase M, Fujii H, et al. Association of severe hypoglycemia with
21 depressive symptoms in patients with type 2 diabetes: the Fukuoka Diabetes Registry.
22 *BMJ Open Diabetes Res Care* 2015;3:e000063.
23
24
25

26
27 50 Luca A, Luca M, Di Mauro M, et al. Alexithymia, more than depression,
28 influences glycaemic control of type 2 diabetic patients. *J Endocrinol Invest*
29 2015;38:653-60.
30
31
32

33
34 51 Rodríguez Calvín JL, Zapatero Gaviria A, Martín Ríos MD. Prevalence of
35 depression in type 2 diabetes mellitus. *Revista Clínica Española (English Edition)*
36 2015;215:156-64.
37
38
39

40
41 52 Zhang Y, Ting RZ, Yang W, et al. Depression in Chinese patients with type 2
42 diabetes: associations with hyperglycemia, hypoglycemia, and poor treatment
43 adherence. *J Diabetes* 2015;7:800-8.
44
45
46

47 53 Cols-Sagarra C, Lopez-Simarro F, Alonso-Fernandez M, et al. Prevalence of
48 depression in patients with type 2 diabetes attended in primary care in Spain. *Prim*
49 *Care Diabetes* 2016.
50
51

52
53 54 Habtewold TD, Alemu SM, Haile YG. Sociodemographic, clinical, and
54 psychosocial factors associated with depression among type 2 diabetic outpatients in
55
56

1
2
3 Black Lion General Specialized Hospital, Addis Ababa, Ethiopia: a cross-sectional
4 study. *BMC Psychiatry* 2016;16:103.

5
6
7 55 Harris PA. The impact of age, gender, race, and ethnicity on the diagnosis and
8 treatment of depression. *J Manag Care Pharm* 2004;10:S2-7.

9
10
11 56 Skinner TC, Carey ME, Cradock S, et al. Depressive symptoms in the first year
12 from diagnosis of Type 2 diabetes: results from the DESMOND trial. *Diabet Med*
13 2010;27:965-7.

14
15
16 57 Thoolen BJ, de Ridder DT, Bensing JM, et al. Psychological outcomes of patients
17 with screen-detected type 2 diabetes: the influence of time since diagnosis and
18 treatment intensity. *Diabetes Care* 2006;29:2257-62.

19
20
21 58 Petrak F, Stridde E, Leverkus F, et al. Development and validation of a new
22 measure to evaluate psychological resistance to insulin treatment. *Diabetes Care*
23 2007;30:2199-204.

24
25
26 59 Brod M, Kongso JH, Lessard S, et al. Psychological insulin resistance: patient
27 beliefs and implications for diabetes management. *Qual Life Res* 2009;18:23-32.

28
29
30 60 Polonsky WH, Hajos TR, Dain MP, et al. Are patients with type 2 diabetes
31 reluctant to start insulin therapy? An examination of the scope and underpinnings of
32 psychological insulin resistance in a large, international population. *Curr Med Res*
33 *Opin* 2011;27:1169-74.

34
35
36 61 Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality
37 of evidence--imprecision. *J Clin Epidemiol* 2011;64:1283-93.

38
39
40 62 Anderson RJ, Freedland KE, Clouse RE, et al. The prevalence of comorbid
41 depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24:1069-78.

Figure legends

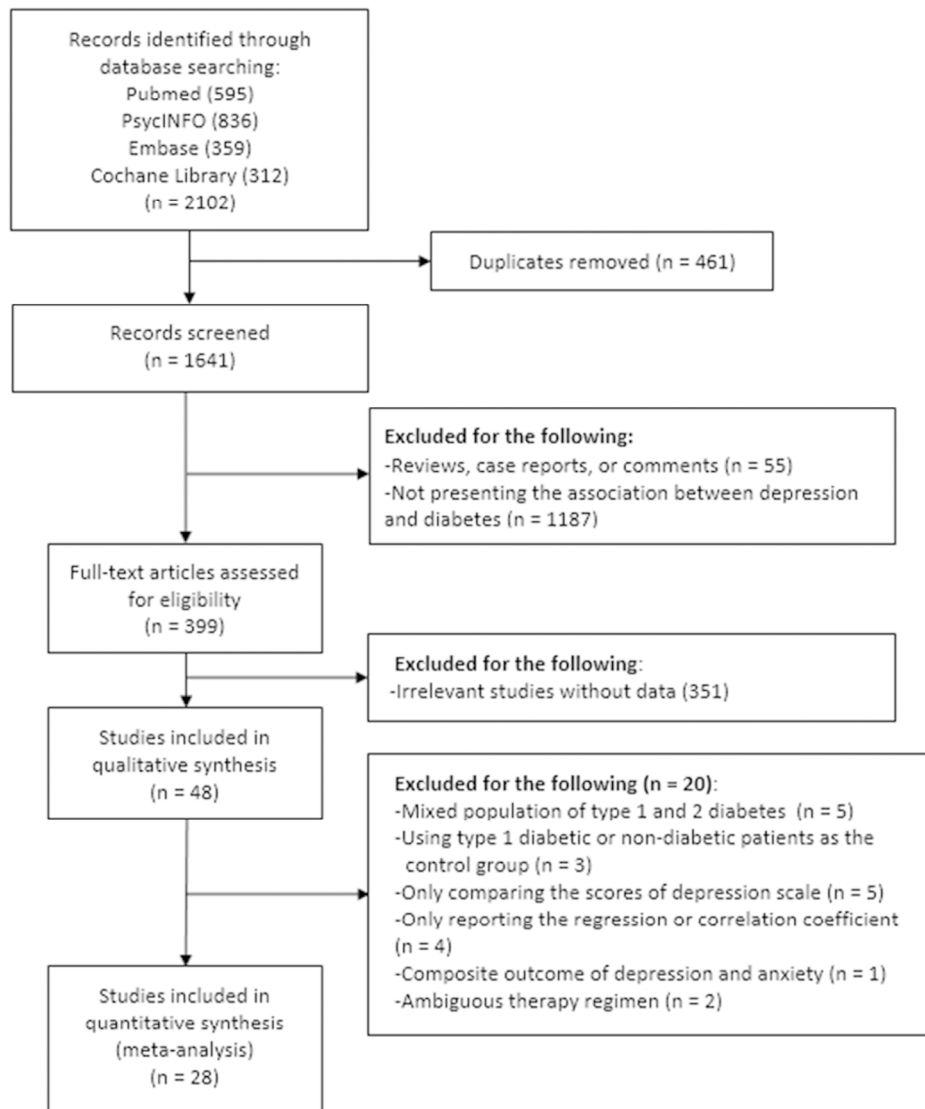
Figure 1. The selection process for eligible studies.

Figure 2. The pooled adjusted odds ratio for the risk of depression in insulin-prescribed patients compared with those without insulin therapy.

Figure 3. The pooled crude odds ratio for the risk of depression in insulin-prescribed patients compared with those without insulin therapy.

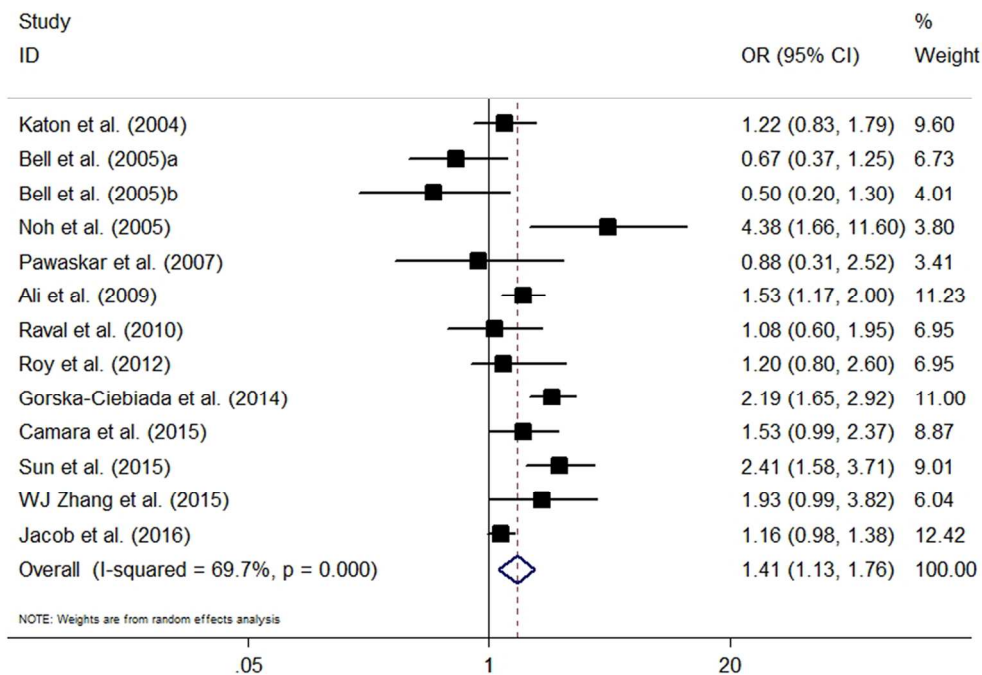
Figure 4. The funnel plot for the studies reporting adjusted odds ratios.

Figure 5. The funnel plot for the studies presenting crude odds ratios.



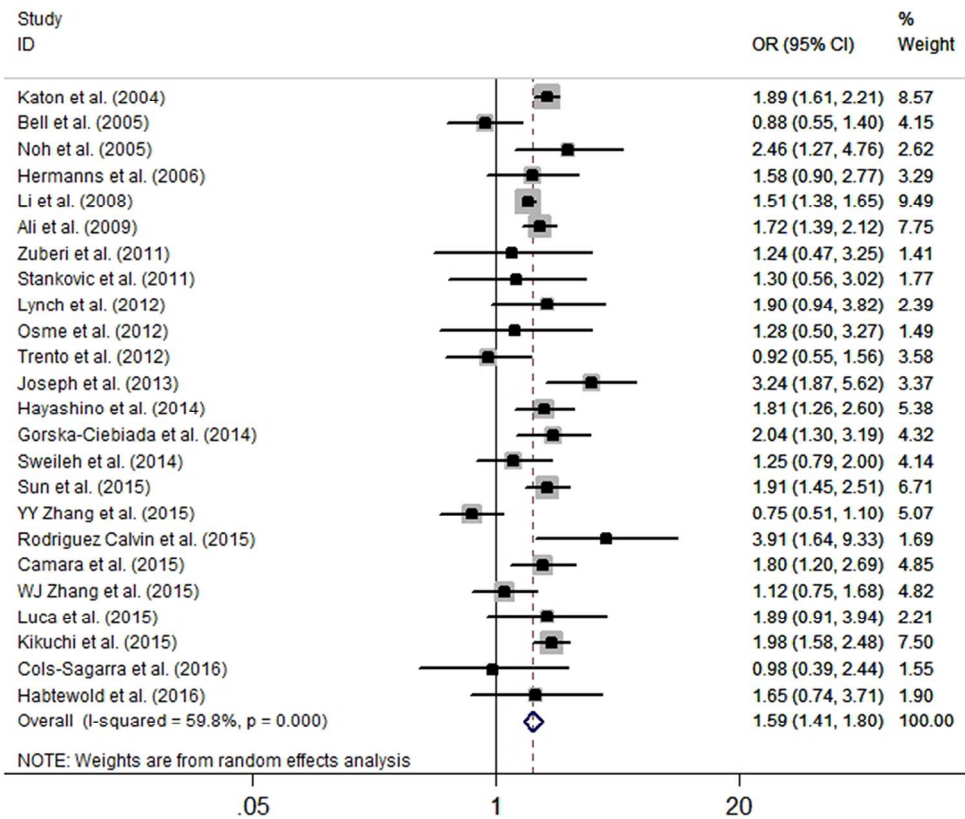
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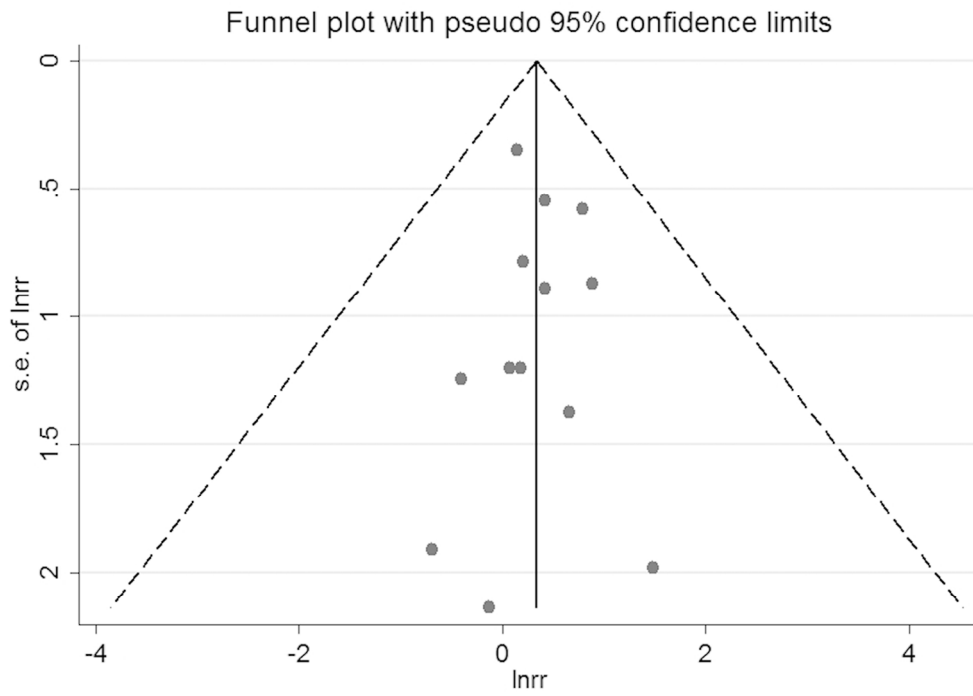
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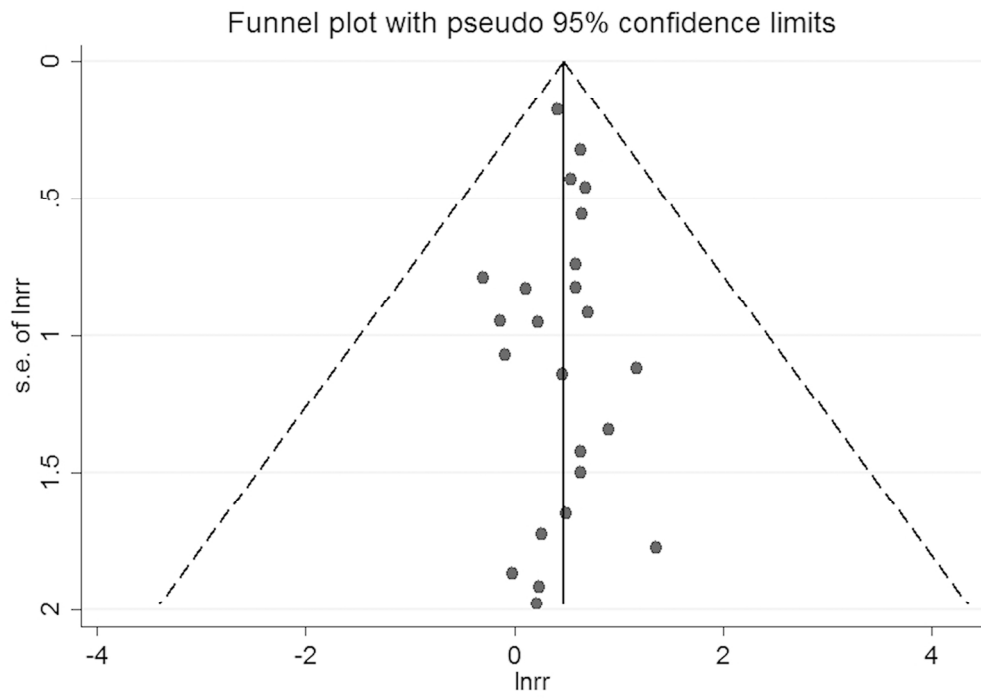
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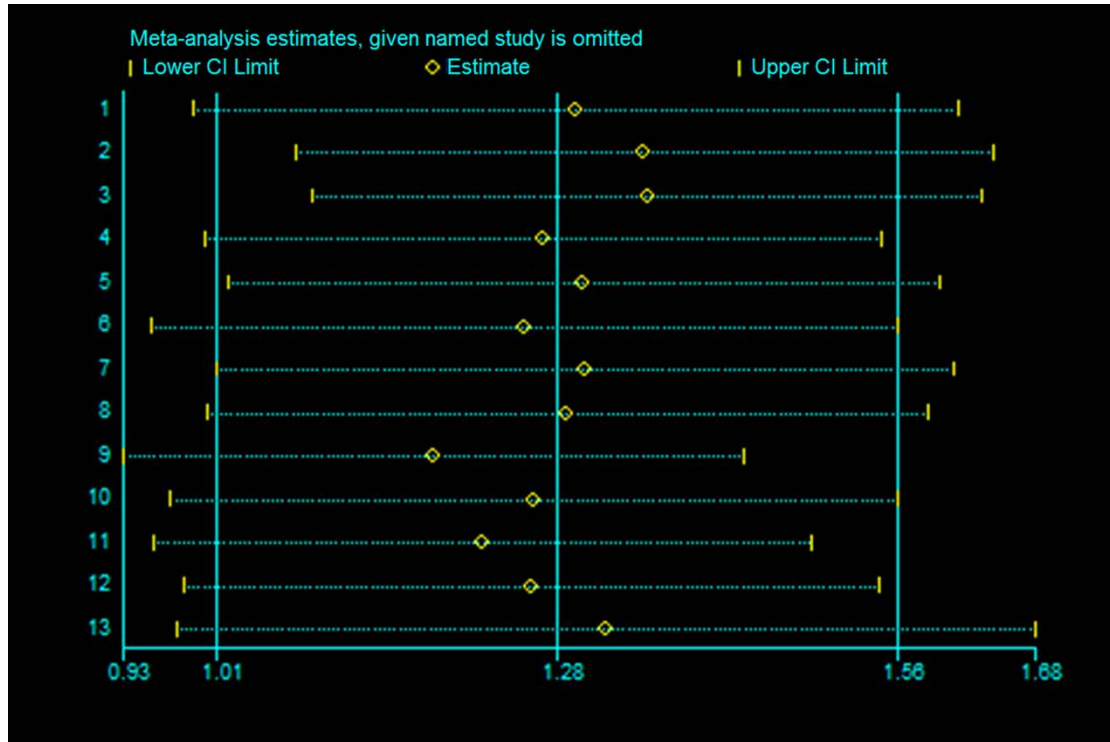
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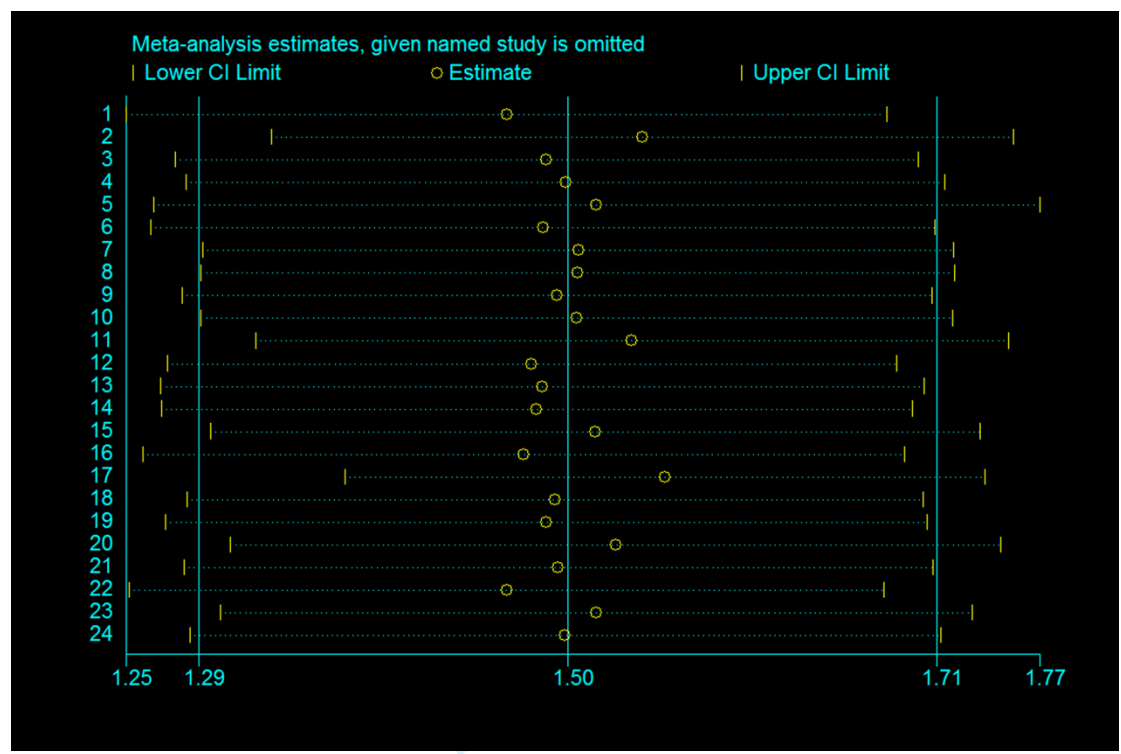
Supplementary Figure S1. Sensitivity analysis for adjusted data



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Supplementary Figure S2. Sensitivity analysis for crude data



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MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Reporting Criteria	Reported (Yes/No)	Reported on Page
Reporting of background should include		
Problem definition	Yes	4
Hypothesis statement	Yes	4
Description of study outcomes	Yes	4
Type of exposure or intervention used	Yes	4
Type of study designs used	Yes	4
Study population	Yes	4
Reporting of search strategy should include		
Qualifications of searchers (eg librarians and investigators)	Yes	5
Search strategy, including time period used in the synthesis and key words	Yes	5
Effort to include all available studies, including contact with authors	Yes	5
Databases and registries searched	Yes	5
Search software used, name and version, including special features used (eg explosion)	Yes	5
Use of hand searching (eg reference lists of obtained articles)	Yes	5
List of citations located and those excluded, including justification	Yes	7
Method of addressing articles published in languages other than English	Yes	5
Method of handling abstracts and unpublished studies	Yes	5
Description of any contact with authors	No	NA
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	No	NA
Rationale for the selection and coding of data (eg sound clinical principles or convenience)	Yes	5
Documentation of how data were classified and coded (eg multiple raters, blinding and interrater reliability)	Yes	6
Assessment of confounding (eg comparability of cases and controls in studies where appropriate)	Yes	6
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Yes	6

Assessment of heterogeneity	Yes	6
Description of statistical methods (eg complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	6
Provision of appropriate tables and graphics	Yes	6
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Yes	9-15
Table giving descriptive information for each study included	Yes	9-15
Results of sensitivity testing (eg subgroup analysis)	Yes	19-22
Indication of statistical uncertainty of findings	Yes	19-22
Reporting of discussion should include		
Quantitative assessment of bias (eg publication bias)	Yes	23
Justification for exclusion (eg exclusion of non-English language citations)	No	23
Assessment of quality of included studies	Yes	Table 2
Strengths and weaknesses	Yes	24-25
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	Yes	23-24
Generalization of the conclusions (eg appropriate for the data presented and within the domain of the literature review)	Yes	25
Guidelines for future research	Yes	25
Disclosure of funding source	Yes	26

NA: Not Applicable

BMJ Open

The association between insulin therapy and depression in patients with type 2 diabetes mellitus: a meta-analysis

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Mental health, Diabetes and endocrinology
Keywords:	Depression, insulin, type 2 diabetes mellitus, meta-analysis, risk factor

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3 **The association between insulin therapy and depression in patients with type 2**
4 **diabetes mellitus: a meta-analysis**
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Abstract

Objectives: Several type 2 diabetes mellitus (T2DM) patients have depressive disorders. Whether insulin treatment was associated with increased risk of depression remains controversial. We performed a meta-analysis to evaluate the association of insulin therapy and depression.

Design: A meta-analysis.

Methods: We conducted a systematic search of PubMed, PsycINFO, Embase and the Cochrane Library from their inception to April 2016. Epidemiological studies comparing the prevalence of depression between insulin users and non-insulin users were included. Random-effects model was used for meta-analysis. The adjusted and crude data were analyzed.

Results: Twenty-eight studies were included. Of these, twelve studies presented adjusted ORs. Insulin therapy was significantly associated with increased risk of depression (OR = 1.41, 95% CI 1.13-1.76, P = 0.003). Twenty-four studies provided crude data. Insulin therapy was also associated with the odds for developing depression (OR = 1.59, 95% CI 1.41-1.80, P < 0.001). When comparing insulin therapy with oral-antidiabetic drugs, significant association was observed for adjusted (OR = 1.42, 95% CI 1.08-1.86, P = 0.008) and crude (OR = 1.61, 95% CI 1.35-1.93, P < 0.001) data.

Conclusions: Our meta-analysis confirmed that patients on insulin therapy were significantly associated with the risk of depressive symptoms.

Keywords: Depression; insulin; type 2 diabetes mellitus; meta-analysis; risk factor

Strengths and limitations of this study

- The primary strength of this study was the systematic and expansive search of multiple databases, which minimized the risk of missing data.
- Both the adjusted and crude effect estimates were analyzed and demonstrated consistent results.
- Our findings mainly relied on cross-sectional data; and as such could not establish the causal and temporal relationship between insulin use and depression.
- Some studies had small sample size, which may influence the statistical power.
- The findings of insulin therapy versus specific oral drugs and the prevalence of depression were not illustrated due to inclusion of less number of studies in each subset.

INTRODUCTION

Diabetes and depression are major global public health problems, and both of which are likely to be among the five leading causes of disease burden by 2030 [1]. Approximately 90% of adults diagnosed with diabetes have type 2 diabetes (T2DM) currently [2]. Recently, a bidirectional link between T2DM and depression has been recognized [3]. According to a meta-analysis study, depression was associated with 60% increased risk of T2DM [4]. Meanwhile, T2DM was associated with 24% increased risk of depressive symptoms [5]. Further, depression adversely affects the prognosis and reduces the patient quality of life [6, 7]. Growing evidences have shown that T2DM and depression may share similar lifestyle factors and biological origins [3].

T2DM is a chronic and progressive disease characterized by insulin resistance and dysfunction of pancreatic islet beta cells [8, 9]. For T2DM patients, insulin is the cornerstone of treatment for lowering glucose and HbA1c concentrations [10]. Although the optimal timing and indications for insulin therapy remained controversial [11-13], most of the patients inevitably requires insulin therapy to attain adequate glycemic control in the natural history of T2DM [11, 14].

However, insulin treatment seems to be less popular than oral hypoglycemic medications. Approximately 25% of the T2DM patients are reluctant to take insulin as the “last-resort” option [15]. Some patients may experience considerable psychological disorders with the transition from oral anti-diabetic drugs to insulin. Additionally, depressive symptoms were more commonly seen in patients who undergo more frequent insulin injections per day [16]. However, there were inconsistent results regarding the correlations between insulin use and depression among the previous studies. Several studies have demonstrated positive correlation [17-19], whereas other studies opposed [20-22]. Besides, these studies varied in enrolled population, adjustment of confounding factors, and usage of depression assessment tools. Thus, we conducted a systematic review and meta-analysis to clarify the association between insulin therapy and the development of depression in

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8 **METHODS**

10 **Patient and Public Involvement**

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13 No patients were involved in study design or conduct of the study.
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16 **Search strategy**

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19 This study is reported in accordance with the Meta-analysis of Observational Studies
20 in Epidemiology guidelines [23]. We conducted a systematic computerized search of
21 Pubmed, Ovid PsycINFO, Embase, and the Cochrane Library for eligible studies from
22 their inception to April 2016. The following keywords and medical subject headings
23 were used for the search: (depression OR depressive) AND (diabetes OR diabetic)
24 AND insulin AND (cross-sectional OR population-based OR cohort OR prospective
25 OR retrospective OR prevalence OR survey OR database OR trial). The full search
26 strategy for Pubmed is shown in Supplementary file. The language was restricted to
27 English. We also manually screened the reference lists of selected studies to obtain
28 potentially relevant records.
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38 **Inclusion and exclusion criteria**

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41 We included studies that: (1) investigated the development of depression in insulin
42 users and non-insulin users (oral anti-diabetic drug, diet, or no treatment) among
43 T2DM patients; (2) reported adjusted/unadjusted odds ratios (ORs) or risk ratios
44 (RRs), or presented raw data that could produce crude effect estimates; (3) assessed
45 depression by self-report measures or diagnostic interviews. The self-report scales
46 including the Patient Health Questionnaire (PHQ), Beck Depression Inventory (BDI),
47 and the Center for Epidemiologic Studies–Depression (CES-D) Scale were used [24].
48 The diagnostic interviews were based on the criteria of DSM or ICD [25, 26]. A
49 threshold score was not defined as no consensus was available and the threshold
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3 varied in different clinical settings. Studies were excluded if: (1) T2DM was mixed
4 with type 1 diabetes; (2) comparison was conducted between T2DM and non-T2DM
5 patients; (3) depression could not be distinguished from anxiety or distress; (4) odds
6 ratios (ORs) or risk ratios (RRs) could not be obtained or calculated, for example, we
7 excluded studies that reported only mean and standard deviations of outcome
8 measures.
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14 15 **Data collection and quality assessment**

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17 Two reviewers independently screened the titles and abstracts of eligible studies and
18 extracted the data. Any disagreement was resolved by consensus. The following study
19 characteristics were extracted: author, publication year, study design, country, sample
20 size, mean or median age, proportion of males, depression diagnostic criteria,
21 compared groups, and adjustment of effect estimates. Both of the unadjusted and
22 adjusted effect estimates and 95% CIs were directly extracted or indirectly calculated.
23 The degree of adjustment for confounders were categorized as: “+” for age and/or sex
24 only; “++” for those with further adjusted for more than 2 standard sociobehavioral
25 risk factors (i.e., education, race, marital status, insurance, exercise, occupation,
26 smoking status, alcohol consumption, family history of diabetes, and BMI); “+++” for
27 those with plus two or more clinical factors, including dyslipidemia, hypertension,
28 cardiovascular disease, duration of T2DM, HbA1c level, treatment intensity, and
29 diabetic complications. The quality was assessed by the modified Newcastle-Ottawa
30 Scale (NOS) [27]. This scale awarded a maximum of eight points to each study, with
31 six or less points indicating a high risk of bias.
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46 **Statistical analysis**

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48 As most of the included studies were cross-sectional, effect sizes were expressed as
49 ORs. Given the low prevalence of depression in T2DM patients, the RR reported by
50 prospective study approximated the OR. Where available, the fully adjusted OR was
51 pooled into meta-analysis to avoid the bias caused by confounding factors. However,
52 the degree of adjustment and the variables entering into regression models varied
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3 between the included studies. Thus, we additionally pooled the unadjusted ORs for
4 data homogeneity. The random-effects model was used for meta-analysis.
5 Heterogeneity was assessed by Cochran Q statistics and I^2 values. $P < 0.05$ was
6 regarded as significant heterogeneity for Q test. I^2 ranged between 0% (no
7 heterogeneity) and 100% (high heterogeneity), with values around 25, 50, and 75%
8 suggesting as low, moderate, and high heterogeneity [28]. To weigh up the relative
9 influence of each individual study, sensitivity analysis was performed by excluding
10 one study at a time and assessed the alteration in pooled results. Subgroup analyses
11 and meta-regression analyses were performed using the following variables:
12 compared groups (insulin vs. non-drug therapy or insulin vs. oral anti-diabetic drugs),
13 degree of adjustment of confounders (+, ++ or +++), region (USA, Asia, Europe, or
14 Africa), identification of depression (self-report questionnaire or medical records),
15 sample size (≥ 1000 or < 1000), mean age (≥ 60 or < 60), percentage male (≥ 50 or $<$
16 50), and NOS scale (7/8, or < 7). Publication bias was assessed by Egger and Begg
17 tests, with $P < 0.05$ indicating significant asymmetry [29, 30]. Also, we visually
18 inspected the funnel plot for publication bias. All analyses were conducted by the
19 Stata software (version 12.0; StataCorp, College Station, TX). A P value of less than
20 0.05 was considered to be significant.
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40 RESULTS

41 Study selection

42 A total of 2,102 records were identified including 595 articles from Pubmed, 836
43 articles from PsycINFO, 359 articles from Embase, and 312 articles from Cochrane
44 Library. We removed 461 duplicates. Further, 399 full-text articles were assessed for
45 eligibility. After excluding 353 records with insufficient or irrelevant data, 46 studies
46 were included into qualitative synthesis. We excluded 5 studies enrolling mixed type 1
47 and type 2 diabetic patients, 3 studies comparing depression between DM and
48 non-DM patients, 4 studies comparing the mean or median scores of depression
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3 questionnaire, 4 studies reporting the regression or correlation coefficient, 1 study
4 presenting a mixed outcome of depression and anxiety, and 2 studies reporting a
5 mixed treatment regimen of insulin or oral drugs. Finally, 28 studies were included
6 into the meta-analysis. The flow diagram was shown in Figure 1.
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10 11 **Study characteristics and quality assessment** 12

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14 Among the 28 studies pooled in the meta-analysis, except 1 prospective cohort [31],
15 most of them were cross-sectional studies. A worldwide distribution was displayed,
16 including 5 studies of USA, 8 European studies, 10 Asian studies, 2 African studies, 1
17 South-American study, and 1 study mixed of South-American and European
18 population. The sample size ranged from 90 to 229 047. The prevalence of depression
19 ranged from 3.4 to 51.1%. Seven studies reported both the adjusted and unadjusted
20 ORs [17, 20, 21, 32-35], 5 studies reported the adjusted ORs [31, 36-39], and
21 unadjusted ORs were retrieved from 16 studies [18, 40-54]. Descriptive data of the
22 included studies were summarized in Table 1. In quality assessment, all studies had
23 low to moderate risk of bias, with scores ranging from 6 to 8. The items satisfied least
24 were the control of confounding factors (12/28) and the report of response rates or
25 follow-up data (10/28), (Table 2).
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Table 1. Characteristics of included studies

Author (year)	Design	Study setting	No. of patients	Mean age, years	Country	Male, %	Depression prevalence, %	Depression assessment	Compared groups	Source estimates	Adjusted factors
Katon et al. (2004)	Cross-sectional	Community	4193	65	USA	51	20.5	PHQ-9	Insulin vs. non-drug	Adjusted	Age, sex, education, marital status, employment, race, BMI and smoking, Rx Risk score, HbA1c, duration of diabetes, treatment intensity, number of complications
Bell et al. (2005)	Cross-sectional	Community	696	74	USA	50.7	15.8	CES-D	Insulin vs. oral medication; insulin vs. non-drug	Adjusted	Age, sex, ethnicity, education, marital status, income, diabetes duration, number of medications, BMI, HbA1c, chronic conditions, PCS score
Ng et al.	Hospital	Hospital	204	53	Korean	53	32.4	BDI	Insulin vs.	Adjusted	Age, sex, BMI, duration of

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(2005)	l-based									oral medication		diabetes, HbA1c, occupation, education, marital status, family history of diabetes, hypertension, diabetic complications, cerebrovascular disease, IHD
Hermanns et al. (2006)	Cross-sectional	Hospital	236	52.2	Germany	60.6	33	BDI; CES-D	Insulin vs. non-insulin	Unadjusted	NA	
Pawaskar et al. (2007)	Prospective cohort	Medicare Health Maintenance Organization	792	72	USA	44	17.3	CES	Insulin vs. sulfonylurea	Adjusted		Age, sex, number of prescriptions, antidiabetic medication, perceived health status, health related quality of life, number of hospitalizations, ER visits
Li et al. (2008)	Cross-sectional	Surveillance Program	16651	≥18	USA	42	14.4	PHQ	Insulin vs. non-insulin	Unadjusted	NA	

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Ali et al. (2009)	Cross-sectional	Hospital	3845	NA	Mixed (South Asia and UK)	52.8	9.3	Medical records	Insulin vs. non-insulin	Adjusted	Age, gender, comorbidities, complications, insulin and oral anti-diabetic medication use, BMI, HbA1c, duration of diabetes, and deprivation
Raval et al. (2010)	Cross-sectional	Hospital	300	54	India	49	41	PHQ-9	Insulin vs. non-insulin	Adjusted	Age, gender, obesity, diabetic complications, blood pressure, duration of disease, income, education, BMI, HbA1c, diabetic complications, dyslipidemia, number of medicine
Zuberi et al. (2011)	Cross-sectional	Hospital	286	52	Pakistan	39.2	50	HADS	Insulin vs. oral medication	Unadjusted	NA
Stanković	Cross-sectional	Hospital	90	55.5	Serbia	34.4	51.1	PHQ, BDI,	Insulin vs.	Unadjusted	NA

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11	et al. (2011)	ectional							or interview	oral		
12										medication		
13	Lynch et al. (2012)	Cross-s	Hospital	201	NA	USA	27.4	19.9	CES-D	Insulin	Unadjusted	NA
14		ectional								vs.non-insul		
15										in		
16												
17	Osme et al. (2012)	Cross-s	Outpatient	138	≥30	Brazil	27.5	44.6	HAD	Insulin	Unadjusted	NA
18		ectional	clinic							vs.non-insul		
19										in		
20												
21												
22	Trento et al. (2012)	Cross-s	Outpatient	498	67.6	Italy	52.6	14.2	ZSDS	Insulin	Unadjusted	NA
23		ectional	clinic							vs.non-insul		
24										in		
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30	Roy et al. (2012)	Cross-s	Outpatient	417	53.2	Banglade	50.6	34	PHQ-9	Insulin vs. oral	Adjusted	Age, gender, education, income, region, CVD, hypertension, diabetic complications, BMI, HbA1c
31		ectional	clinic			sh				medication		
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insulin+oral
medication
vs. oral
medication
+diet

Joseph et al. (2013) Cross-sectional Hospital 230 53.6 India 51.7 45.2 PHQ-9 Insulin vs. Unadjusted NA

oral
medication

Hayashino et al. (2014) Cross-sectional Hospital 3573 66 Japan 61.1 3.4 PHQ-9 Insulin vs. Unadjusted NA

oral
medication
or diet

Gorska-Ciechanowska et al. (2014) Cross-sectional Outpatient clinic 276 74 Poland 46 29.7 GDS Insulin vs. Adjusted Age, sex, education,

oral
medication

marital status, smoking, physical activity, duration

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of diabetes, BMI, HbA1c, lipids
levels, diabetic complications,
previous HA or use of HA drugs,
hyperlipidemia, number of
comorbid conditions, hypoglycemia

Sweileh et al. (2014)	Cross-sectional	Hospital	294	60	Palestine	44.2	40.2	BDI	Insulin vs. non-insulin	Unadjusted	NA
Yan Zhang et al. (2015)	Cross-sectional	Hospital	2538	56.4	China	53	6.1	PHQ-9	Insulin vs. oral drugs	Unadjusted	NA
Rodríguez Calvin et al. (2015)	Cross-sectional	Hospital	275	64.5	Spain	56.4	32.7	BDI	Insulin vs. oral medication	Unadjusted	NA
Camara et al.	Cross-sectional	Outpatient	491	58	Guinea	37	34.4	HADS	Insulin vs. oral	Adjusted	Age, HbA1c, hypertension, BMI, residence zone, socioeconomic

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al (2015)	ectional	clinic								medication		status
Sun et al. (2015)	Cross-sectional	Community	229	57.4	China	34.4	5.9	PHQ-9	Insulin vs. Adjusted	oral medication or diet		Age, sex, BMI, HbA1c, smoking, alcohol, physical activity, education, occupation, marital status, selfreport cardio-metabolic disorders, diabetes treatment, diabetes duration
Wang et al. (2015)	Cross-sectional	Hospital	412	59.8	China	50.2	5.7	BDI	Insulin vs. Adjusted	oral medication		Age, gender, education, marital status, occupation, insurance, HbA1c, BMI, DM history, diabetic complications, duration of DM, smoking, alcohol, exercise, sleeping hours
Li et al. (2015)	Cross-sectional	Hospital	128	64.7	Italy	58.6	50.8	HAM-D	Insulin vs. Unadjusted	oral medication		NA

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or diet

Kikuchi et al. (2015)	Cross-sectional	Community	4218	65.5	Japan	57.1	10.6	CES-D	Insulin vs. non-insulin	Unadjusted	NA
Jacob et al. (2016)	Cross-sectional	Community	90412	65.5	Germany	50.2	30.3	Medical records	Insulin vs. non-insulin	Adjusted	Age, gender, insurance, diabetic complications, CVD, HbA1c
Coils-Sagar et al. (2016)	Cross-sectional	Community	411	70.8	Spain	46.2	29.2	PHQ-9	Insulin vs. oral medications	Unadjusted	NA
Habtewold et al. (2016)	Cross-sectional	Hospital	276	44	Ethiopia	47	44.7	PHQ-9	Insulin vs. oral medication	Unadjusted	NA

BDI, Beck Depression Inventory; BMI, body mass index; BG, blood glucose; CES-D, Center for Epidemiologic Studies Depression; DBP, diastolic blood pressure; ER, emergency room; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton rating scale for depression; IHD, ischemic heart disease; PCS, Physical Component Summary score; PHQ, Patient Health

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Questionnaire; SBP, systolic blood pressure; ZSDS, Zung Self-Rating Depression Scale.

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Table 2. Quality assessment of included studies by the modified Newcastle-Ottawa scale (NOS)

Author (year)	Adequate definition of cases using insulin	Representativeness of cases using insulin	Selection of the non-insulin users	Ascertainment of insulin use	Depression was not present before initiation	Control of confounding factors	Assessment of depression	Report of response or follow-up data	Total score
Katon et al. (2004)	1	1	1	1	1	1	1	1	8
Bell et al. (2005)	1	1	1	1	1	1	1	0	7
Noh et al. (2005)	1	0	1	1	1	1	1	0	6
Hermanns et al. (2006)	1	1	1	1	1	0	1	0	6
Pawaskar et al. (2007)	1	1	1	1	1	1	1	1	7
Li et al. (2008)	1	1	1	1	1	0	1	0	6
Ali et al. (2009)	1	1	1	1	1	1	1	0	7
Raval et al. (2010)	1	1	1	1	1	1	1	0	7

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7	Zuberi et al. (2011)	1	1	1	1	1	0	1	1	7
8										
9	Stanković et al. (2011)	1	1	1	1	1	0	1	0	6
10										
11										
12	Lynch et al. (2012)	1	1	1	1	1	0	1	1	7
13										
14										
15	Osme et al. (2012)	1	1	1	1	1	0	1	0	6
16										
17	Trento et al. (2012)	1	1	1	1	1	0	1	0	6
18										
19										
20	Roy et al. (2012)	1	1	1	1	1	1	1	1	8
21										
22										
23	Joseph et al. (2013)	1	1	1	1	1	0	1	0	6
24										
25	Hayashino et al. (2014)	1	1	1	1	1	0	1	0	6
26										
27										
28	Gorska-Ciebiada et al. (2014)	0	1	1	1	1	1	1	0	6
29										
30										
31	Sweileh et al. (2014)	1	1	1	1	1	0	1	1	7
32										
33	YY Zhang et al. (2015)	1	1	1	1	1	0	1	1	7
34										
35										
36	Rodriguez Calvin et al. (2015)	1	1	1	1	1	0	1	1	7
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7	Camara et al. (2015)	1	1	1	1	1	0	1	0	6
9	Sun et al. (2015)	1	1	1	1	1	1	1	0	7
12	WJ Zhang et al. (2015)	1	1	1	1	1	1	1	1	8
15	Luca et al. (2015)	1	1	1	1	1	0	1	0	6
17	Kikuchi et al. (2015)	1	1	1	1	1	0	1	0	6
20	Jacob et al. (2016)	1	1	1	1	1	0	1	0	6
22	Cols-Sagarra et al. (2016)	1	1	1	1	1	0	1	0	6
25	Habtewold et al. (2016)	1	1	1	1	1	0	1	1	7

Meta-analysis of adjusted data

The adjusted ORs for comparison of depression between insulin and non-insulin treated patients were reported by 12 studies. Compared with non-insulin treatment, insulin therapy was associated with a significantly higher risk of depression (OR = 1.41, 95% CI 1.13-1.76, P = 0.003). Significantly high heterogeneity was revealed ($I^2 = 69.7\%$, P < 0.001) (Figure 2).

The results of sensitivity analysis, which was done by excluding one by one study, might vary when several included studies were excluded (Supplementary Figure S1). To identify the sources of heterogeneity, we performed subgroup analyses based on several important confounding factors. Six studies particularly compared insulin with oral anti-diabetic drugs, and showed that insulin therapy was significantly associated with increased risk of depression (OR = 1.42, 95% CI 1.08-1.86, P = 0.008). Two studies that compared insulin with non-drug therapy showed no significant association for insulin and depression (OR = 0.87, 95% CI 0.37-2.03, P = .745). Additionally, we conducted a subgroup analysis based on the degree of adjustment of confounders, region, identification of depression, sample size, mean age, percentage male, and NOS scale. The association was significant for the subgroups of fully adjustment (+++), Asian studies, self-report questionnaires, sample size ≥ 1000 , mean age < 60.0 years, percentage of male < 50.0%, prevalence of depression over 20%, and NOS scale < 6 (Table 3). Meta-regression analyses indicated a lack of effect measure modification by sample size (P = 0.93), mean age (P = 0.17), percentage male (P = 0.28) or prevalence of depression (P = 0.75).

Table 3. Subgroup analyses for the studies reporting adjusted effect estimates

Subgroups	No. of studies	OR (95% CI)	P value	I^2	P value for within-stratum heterogeneity	P value for between-stratum heterogeneity
Compared groups						

Insulin vs. oral drugs	6	1.42 (1.08-1.86)	<0.05	71.3%	<0.05	0.28
Insulin vs. non-drugs	2	0.87 (0.37-2.03)	>0.05	66.5%	0.08	
Degree of adjustment						
+++	10	1.43 (1.08-1.89)	<0.05	68.9%	<0.05	0.44
++	2	1.24 (0.98-1.55)	>0.05	25.3%	0.25	
Region						
USA	4	0.86 (0.57-1.31)	>0.05	36.4%	0.19	0.12
Asia	5	1.81 (1.18-2.79)	<0.05	59%	0.05	
Europe	2	1.58 (0.85-2.94)	>0.05	92.9%	<0.05	
Africa	1	1.53 (0.99-2.37)	>0.05	-	-	
Identification of depression						
Self-report questionnaire	10	1.42 (1.06-1.91)	<0.05	68.9%	<0.05	0.69
Medical records	2	1.31 (1.00-1.71)	>0.05	65.6%	0.09	
Sample size						
≥ 1000	4	1.46 (1.10-1.94)	<0.05	73.1%	<0.05	0.72
< 1000	8	1.34 (0.93-1.93)	>0.05	70%	<0.05	
Mean age						
≥ 60.0	5	1.12 (0.77-1.62)	>0.05	78.8%	<0.05	0.08

< 60.0	6	1.74 (1.24-2.43)	<0.05	50.8%	0.07	
Percentage male (%)						
≥ 50.0	7	1.26 (0.97-1.63)	>0.05	62.4%	<0.05	0.14
< 50.0	5	1.71 (1.25-2.35)	<0.05	53.9%	0.07	
Prevalence of depression						
≥ 20%	7	1.48 (1.12-1.96)	<0.05	71.3%	<0.05	0.53
< 20%	5	1.25 (0.80-1.95)	>0.05	72.7%	<0.05	
NOS scale						
7 or 8	8	1.25 (0.94-1.66)	>0.05	60.0%	<0.05	0.19
<7	4	1.79 (1.14-2.80)	<0.05	84.6%	<0.05	

Meta-analysis of unadjusted results

Twenty-four studies provided the crude data. All studies were cross-sectional, and assessed depression by self-report scales. The studies presented three comparison types (insulin vs. non-drug therapy; insulin vs. oral anti-diabetic drugs; and insulin vs. non-insulin treatment). Data that compared insulin and non-insulin therapy were preferred. The pooled results showed that T2DM patients on insulin therapy was associated with an increased risk of depression compared with those on non-insulin treatment (OR = 1.59, 95% CI 1.41-1.80, P < 0.001) (Figure 3). The heterogeneity was at a significantly higher level ($I^2 = 59.8\%$, P < 0.001). Sensitivity analysis revealed no significant variation in the pooled OR by exclusion of any included study (Supplementary Figure S2).

Seventeen studies compared insulin with oral anti-diabetic drugs, and showed a significant association for the risk of depression (OR = 1.61, 95% CI 1.35-1.93, $P < 0.001$). For 6 studies that compared insulin use with non-drug treatment, insulin use was associated with an increased risk of depression (OR = 1.89, 95% CI 1.25-2.88, $P = 0.002$). In stratified analyses based on the degree of adjustment of confounders, region, identification of depression, sample size, mean age, percentage male, and NOS scale, there was a significant association between insulin use and depression among all subgroups except the study conducted in South America (Table 4). In meta-regression analyses, sample size ($P = 0.79$), mean age ($P = 0.56$), percentage male ($P = 0.80$), and the prevalence of depression ($P = 0.68$) demonstrated no independent effect on the depression outcomes.

Table 4. Subgroup analyses for the studies reporting the crude effect estimates

Subgroups	No. of studies	OR (95% CI)	P value	I ² (P value)	P value for within-stratum heterogeneity	P value for between-stratum heterogeneity
Compared groups						
Insulin vs. oral drugs	17	1.61 (1.35-1.93)	<0.05	62.6%	<0.05	0.49
Insulin vs. non-drugs	6	1.89 (1.25-2.88)	<0.05	68.2%	<0.05	
Region						
USA	4	1.53 (1.21-1.93)	<0.05	75.4%	<0.05	0.31
Asia	9	1.60 (1.22-2.10)	<0.05	75.4%	0.05	
Europe	7	1.59 (1.13-2.22)	<0.05	45.3%	<0.05	
Africa	2	1.77 (1.23-2.54)	<0.05	0.0	0.85	

South America	1	1.28 (0.50-3.27)	>0.05	-	-	
Sample size						
≥1000	7	1.64 (1.39-1.93)	<0.05	77.5%	<0.05	0.71
< 1000	17	1.56 (1.27-1.91)	<0.05	46.7%	<0.05	
Mean age						
≥ 60.0	10	1.60 (1.30-1.97)	<0.05	61.8%	<0.05	0.92
< 60.0	10	1.57 (1.18-2.09)	<0.05	68.0%	<0.05	
Percentage male						
(%)						
≥ 50.0	13	1.59 (1.29-1.96)	<0.05	75.1%	<0.05	0.82
< 50.0	11	1.55 (1.43-1.68)	<0.05	0.0	0.71	
Prevalence of depression						
≥ 20%	14	1.84 (1.59-2.12)	<0.05	11.7%	0.33	<0.05
< 20%	10	1.43 (1.19 -1.70)	<0.05	74.0%	<0.05	
NOS scale						
7 or 8	11	1.45 (1.16-1.82)	<0.05	72.3%	<0.05	0.22
<7	13	1.72 (1.47-2.00)	<0.05	42.8%	0.05	

Publication bias

For studies reporting the adjusted ORs, the funnel plot was symmetrical (Figure 4).

No publication bias was shown by the Egger test (P = 0.94) or Begg's test (P = 0.67).

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3 For studies presenting the crude ORs, the funnel plot was symmetrical (Figure 5). We
4 did not detect publication bias by Egger ($P = 0.39$) or Begg test ($P = 0.94$).
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10 **DISCUSSION**

11
12 This is the first meta-analysis that estimated the magnitude of association between
13 insulin therapy and depression. The pooled data of adjusted ORs proved that T2DM
14 patients on insulin treatment were associated with the prevalence of depressive
15 syndromes compared to those without insulin therapy. When pooling the crude ORs,
16 the results showed a permanent and significant association. We specifically compared
17 insulin use with oral-antidiabetic drugs. Both of the adjusted data ($OR = 1.42$) and the
18 unadjusted data ($OR = 1.61$) showed that insulin users were related to the greater risk
19 of depression.
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28 The source of heterogeneity was explored carefully. In sensitivity analysis, no
29 substantial change in heterogeneity was revealed when excluding any individual study,
30 suggesting the homogeneity of the pooled effect estimates. The prevalence of
31 depression could be different according to different ethnicities [55]. In subgroup
32 analyses of adjusted data, we found significant results for Asian studies.
33 Non-significant results were shown for studies with sample size below 1000,
34 suggesting that the results were unstable for small sample size. Substantial change of
35 heterogeneity was also detected for subgroups of insufficient degree of adjustment
36 and depression identified by medical records. However, the number of eligible studies
37 was rather small to draw firm conclusions. For studies with the prevalence of
38 depression below 20%, substantial change in the effect estimates was observed for
39 adjusted data, and obvious change in heterogeneity for crude data. Thus, this may
40 partly account for the heterogeneity. Finally, significant association was detected if
41 the mean age was <60.0 years, percentage male $< 50.0\%$, and NOS < 7 for adjusted
42 data. This might be due to that the younger patients were associated with higher
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3 prevalence of depression, and women receiving insulin therapy might be under greater
4 risk of depression compared to men.
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8 The mechanisms that link diabetes and depression were complex and still unclear.
9 Depression and T2DM could develop in parallel through shared biological processes.
10 The involved pathways include the innate inflammatory response, the
11 hypothalamic-pituitary-adrenal axis, circadian rhythms, and insulin resistance [3].
12 Although the overall prevalence of depression is high in diabetic patients, the
13 DESMOND trial reported that it was not so in the newly diagnosed T2DM patients
14 [56]. Screen-detected patients with T2DM showed low distress and anxiety at the time
15 of diagnosis, with a significant increase during the 12 months follow-up period [57].
16 In accordance with these findings, we confirmed that insulin therapy was associated
17 with increased prevalence of depression. For patients on insulin therapy, they had less
18 endogenous insulin and were therefore more susceptible to metabolic dysregulation
19 than patients who might have some residual insulin secretory activity. Especially,
20 patients who are more metabolically labile are more vulnerable to depression [16].
21 Besides, insulin therapy is always a symbol of more advanced type 2 diabetes. The
22 patients' negative attitude towards insulin therapy may contribute to the delay for
23 insulin initiation, prolonged duration of hyperglycemia, and increased risk of diabetic
24 complications [58]. Psychological insulin resistance (PIR) has been defined as
25 psychological opposition towards insulin treatment in both diabetic patients and their
26 prescribers. They may display fear of insulin injection and self-testing, complex
27 regimen, hypoglycemia, and weight gain; a perceived loss of control over one's life;
28 poor self-efficacy concerning insulin treatment; and lack of positive outcomes related
29 to insulin [58-60]. These psychological aspects may explain the increased risk of
30 depression when insulin was prescribed.
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51 The primary strength of this study was the systematic and expansive search of
52 multiple databases, which minimized the risk of missing data. The meta-analysis
53 identified 28 studies that enrolled worldwide-distributed participants. Both the
54 adjusted and crude effect estimates were analyzed and demonstrated consistent results.
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3 The confidential intervals were narrow, suggesting the precision of pooled results [61].
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5 For adjusted data, most of the studies had full adjustment for confounders. The
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7 subtypes of non-insulin therapy, including oral drug and non-drug treatment, were
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9 analyzed separately. The between-study heterogeneity was intensively explored by
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11 sensitivity, subgroup, and meta-regression analyses. Besides, no publication bias was
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13 detected among the selected studies.
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15 We were aware of the limitations of this meta-analysis. Our findings mainly
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17 relied on cross-sectional data; and as such, the causal and temporal relationship
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19 between insulin use and depression could not be established. Some studies have small
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21 sample size, which may influence the statistical power. Several studies have reported
22
23 the response rates. The unmeasured differences between respondents and
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25 nonrespondents may potentially influence the pooled results. Most of the studies used
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27 self-reported scales rather than clinical interview-based assessments to identify
28
29 depression. Prevalence of depression was generally much higher using the
30
31 self-reported scales than standardized diagnostic interviews [20, 62]. Furthermore, the
32
33 findings of insulin therapy versus specific oral drugs and the prevalence of depression
34
35 were not illustrated due to inclusion of less number of studies in each subset.
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37 Moreover, background oral anti-diabetic drug uses in insulin group might affect the
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39 association of insulin use with the risk of depressive syndromes, while this
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41 information was not available in most of the included studies. In addition, although
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43 subgroup analyses based on several factors were conducted, substantial residual
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45 heterogeneity was observed in numerous subsets. These results were restricted due to
46
47 uncontrolled baseline characteristics of included patients and studies. Finally, the
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49 impact of the total number of daily insulin injections with depression development
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51 was included only in few studies, and these contributed as potential confounders in
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53 patients who received insulin therapy and with progression of depression.
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55 CONCLUSIONS

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3 In conclusion, type 2 diabetic patients who were prescribed insulin were associated
4 with depressive syndromes. For insulin-users, careful monitoring of depressive
5 symptoms should be incorporated in the disease management. Intensified
6 psychological and education programs should be carried out to prevent depressive
7 illness after insulin initiation in the primary care settings.
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For peer review only

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Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

XSB contributed to study concepts, manuscript preparation, literature research and drafting the manuscript. ZML, ZSL and DWY carried out literature research, data analysis and revising the manuscript for important content. All authors read and approved the final manuscript.

Data sharing statement

No additional data available.

References

- 1 Tabak AG, Akbaraly TN, Batty GD, et al. Depression and type 2 diabetes: a causal association? *Lancet Diabetes Endocrinol* 2014;2:236-45.
- 2 Type 2 Diabetes in Adults: Management. National Institute for Health and Care Excellence: Clinical Guidelines. London 2015.
- 3 Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. *Lancet Diabetes Endocrinol* 2015;3:461-71.
- 4 Mezuk B, Eaton WW, Albrecht S, et al. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care* 2008;31:2383-90.
- 5 Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia* 2010;53:2480-6.
- 6 van Dooren FE, Nefs G, Schram MT, et al. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One* 2013;8:e57058.
- 7 Kan C, Silva N, Golden SH, et al. A systematic review and meta-analysis of the association between depression and insulin resistance. *Diabetes Care* 2013;36:480-9.
- 8 Ismail-Beigi F. Clinical practice. Glycemic management of type 2 diabetes mellitus. *N Engl J Med* 2012;366:1319-27.
- 9 Ohn JH, Kwak SH, Cho YM, et al. 10-year trajectory of beta-cell function and insulin sensitivity in the development of type 2 diabetes: a community-based prospective cohort study. *Lancet Diabetes Endocrinol* 2016;4:27-34.
- 10 Cahn A, Miccoli R, Dardano A, et al. New forms of insulin and insulin therapies for the treatment of type 2 diabetes. *Lancet Diabetes Endocrinol* 2015;3:638-52.
- 11 Home P, Riddle M, Cefalu WT, et al. Insulin therapy in people with type 2

1
2
3 diabetes: opportunities and challenges? *Diabetes Care* 2014;37:1499-508.

4
5
6 12 Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function
7 and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre
8 randomised parallel-group trial. *Lancet* 2008;371:1753-60.

9
10
11
12 13 Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in
14 type 2 diabetes mellitus: a systematic review and meta-analysis. *Lancet Diabetes*
15 *Endocrinol* 2013;1:28-34.

16
17
18 14 Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose
19 control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.

20
21
22
23 15 Holmes-Truscott E, Skinner TC, Pouwer F, et al. Explaining psychological
24 insulin resistance in adults with non-insulin-treated type 2 diabetes: The roles of
25 diabetes distress and current medication concerns. Results from Diabetes
26 MILES-Australia. *Prim Care Diabetes* 2016;10:75-82.

27
28
29
30
31 16 Surwit RS, van Tilburg MA, Parekh PI, et al. Treatment regimen determines the
32 relationship between depression and glycemic control. *Diabetes Res Clin Pract*
33 2005;69:78-80.

34
35
36
37 17 Noh JH, Park JK, Lee HJ, et al. Depressive symptoms of type 2 diabetics treated
38 with insulin compared to diabetics taking oral anti-diabetic drugs: a Korean study.
39 *Diabetes Res Clin Pract* 2005;69:243-8.

40
41
42
43 18 Li C, Ford ES, Strine TW, et al. Prevalence of depression among U.S. adults with
44 diabetes: findings from the 2006 behavioral risk factor surveillance system. *Diabetes*
45 *Care* 2008;31:105-7.

46
47
48
49 19 Al-Amer RM, Sobeh MM, Zayed AA, et al. Depression among adults with
50 diabetes in Jordan: risk factors and relationship to blood sugar control. *J Diabetes*
51 *Complications* 2011;25:247-52.

52
53
54
55
56 20 Bell RA, Smith SL, Arcury TA, et al. Prevalence and correlates of depressive

1
2
3 symptoms among rural older African Americans, Native Americans, and whites with
4 diabetes. *Diabetes Care* 2005;28:823-9.

6
7
8 21 Katon W, von Korff M, Ciechanowski P, et al. Behavioral and clinical factors
9 associated with depression among individuals with diabetes. *Diabetes Care*
10 2004;27:914-20.

12
13
14 22 Mikailiukstiene A, Juozulynas A, Narkauskaite L, et al. Quality of life in relation
15 to social and disease factors in patients with type 2 diabetes in Lithuania. *Med Sci*
16 *Monit* 2013;19:165-74.

18
19
20 23 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in
21 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in
22 Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.

24
25
26 24 Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck
27 Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale
28 (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale
29 (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res (Hoboken)*
30 2011;63 Suppl 11:S454-66.

32
33
34 25 Organization WH. The ICD-10 classification of mental and behavioural disorders:
35 clinical descriptions and diagnostic guidelines: Geneva: World Health Organization
36 1992.

38
39
40 26 Association D-AP. Diagnostic and statistical manual of mental disorders.
41 Arlington: American Psychiatric Publishing 2013.

42
43
44 27 Wells GA, Shea B, D OC. The Newcastle-Ottawa Scale (NOS) for assessing the
45 quality of nonrandomised studies in meta-analyses.
46 http://www.ohrica/programs/clinical_epidemiology/oxfordasp (accessed April 27,
47 2016) 2008.

48
49
50 28 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in

1
2
3 meta-analyses. *BMJ* 2003;327:557-60.

4
5
6 29 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for
7 publication bias. *Biometrics* 1994;50:1088-101.

8
9
10 30 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a
11 simple, graphical test. *BMJ* 1997;315:629-34.

12
13
14 31 Pawaskar MD, Anderson RT, Balkrishnan R. Self-reported predictors of
15 depressive symptomatology in an elderly population with type 2 diabetes mellitus: a
16 prospective cohort study. *Health Qual Life Outcomes* 2007;5:50.

17
18
19 32 Zhang W, Xu H, Zhao S, et al. Prevalence and influencing factors of co-morbid
20 depression in patients with type 2 diabetes mellitus: a General Hospital based study.
21 *Diabetol Metab Syndr* 2015;7:60.

22
23
24 33 Ali S, Davies MJ, Taub NA, et al. Prevalence of diagnosed depression in South
25 Asian and white European people with type 1 and type 2 diabetes mellitus in a UK
26 secondary care population. *Postgrad Med J* 2009;85:238-43.

27
28
29 34 Gorska-Ciebiada M, Saryusz-Wolska M, Ciebiada M, et al. Mild cognitive
30 impairment and depressive symptoms in elderly patients with diabetes: prevalence,
31 risk factors, and comorbidity. *J Diabetes Res* 2014;2014:179648.

32
33
34 35 Camara A, Balde NM, Enoru S, et al. Prevalence of anxiety and depression
35 among diabetic African patients in Guinea: association with HbA1c levels. *Diabetes*
36 *Metab* 2015;41:62-8.

37
38
39 36 Raval A, Dhanaraj E, Bhansali A, et al. Prevalence & determinants of depression
40 in type 2 diabetes patients in a tertiary care centre. *Indian J Med Res*
41 2010;132:195-200.

42
43
44 37 Roy T, Lloyd CE, Parvin M, et al. Prevalence of co-morbid depression in
45 out-patients with type 2 diabetes mellitus in Bangladesh. *BMC Psychiatry*
46 2012;12:123.

1
2
3 38 Jacob L, Kostev K. Prevalence of depression in type 2 diabetes patients in
4 German primary care practices. *J Diabetes Complications* 2016;30:432-7.
5

6
7 39 Sun JC, Xu M, Lu JL, et al. Associations of depression with impaired glucose
8 regulation, newly diagnosed diabetes and previously diagnosed diabetes in Chinese
9 adults. *Diabet Med* 2015;32:935-43.
10
11

12
13 40 Hermanns N, Kulzer B, Krichbaum M, et al. How to screen for depression and
14 emotional problems in patients with diabetes: comparison of screening characteristics
15 of depression questionnaires, measurement of diabetes-specific emotional problems
16 and standard clinical assessment. *Diabetologia* 2006;49:469-77.
17
18
19

20
21 41 Stankovic Z, Jasovic-Gasic M, Zamaklar M. Psycho-social and clinical variables
22 associated with depression in patients with type 2 diabetes. *Psychiatr Danub*
23 2011;23:34-44.
24
25
26

27
28 42 Zuberi SI, Syed EU, Bhatti JA. Association of depression with treatment
29 outcomes in Type 2 Diabetes Mellitus: a cross-sectional study from Karachi, Pakistan.
30 *BMC Psychiatry* 2011;11:27.
31
32
33

34
35 43 Lynch CP, Hernandez-Tejada MA, Strom JL, et al. Association between
36 spirituality and depression in adults with type 2 diabetes. *Diabetes Educ*
37 2012;38:427-35.
38
39
40

41 44 Osme SF, Ferreira L, Jorge MT, et al. Difference between the prevalence of
42 symptoms of depression and anxiety in non-diabetic smokers and in patients with type
43 2 diabetes with and without nicotine dependence. *Diabetol Metab Syndr* 2012;4:39.
44
45
46

47 45 Trento M, Raballo M, Trevisan M, et al. A cross-sectional survey of depression,
48 anxiety, and cognitive function in patients with type 2 diabetes. *Acta Diabetol*
49 2012;49:199-203.
50
51
52

53 46 Joseph N, Unnikrishnan B, Raghavendra Babu YP, et al. Proportion of depression
54 and its determinants among type 2 diabetes mellitus patients in various tertiary care
55
56
57

1
2
3 hospitals in Mangalore city of South India. *Indian J Endocrinol Metab*
4 2013;17:681-8.

5
6
7 47 Hayashino Y, Mashitani T, Tsujii S, et al. Elevated Levels of hs-CRP Are
8 Associated With High Prevalence of Depression in Japanese Patients With Type 2
9 Diabetes: The Diabetes Distress and Care Registry at Tenri (DDCRT 6). *Diabetes*
10 *Care* 2014;37:2459-65.

11
12
13 48 Sweileh WM, Abu-Hadeed HM, Al-Jabi SW, et al. Prevalence of depression
14 among people with type 2 diabetes mellitus: a cross sectional study in Palestine. *BMC*
15 *Public Health* 2014;14:163.

16
17
18 49 Kikuchi Y, Iwase M, Fujii H, et al. Association of severe hypoglycemia with
19 depressive symptoms in patients with type 2 diabetes: the Fukuoka Diabetes Registry.
20 *BMJ Open Diabetes Res Care* 2015;3:e000063.

21
22
23 50 Luca A, Luca M, Di Mauro M, et al. Alexithymia, more than depression,
24 influences glycaemic control of type 2 diabetic patients. *J Endocrinol Invest*
25 2015;38:653-60.

26
27
28 51 Rodríguez Calvín JL, Zapatero Gaviria A, Martín Ríos MD. Prevalence of
29 depression in type 2 diabetes mellitus. *Revista Clínica Española (English Edition)*
30 2015;215:156-64.

31
32
33 52 Zhang Y, Ting RZ, Yang W, et al. Depression in Chinese patients with type 2
34 diabetes: associations with hyperglycemia, hypoglycemia, and poor treatment
35 adherence. *J Diabetes* 2015;7:800-8.

36
37
38 53 Cols-Sagarra C, Lopez-Simarro F, Alonso-Fernandez M, et al. Prevalence of
39 depression in patients with type 2 diabetes attended in primary care in Spain. *Prim*
40 *Care Diabetes* 2016.

41
42
43 54 Habtewold TD, Alemu SM, Haile YG. Sociodemographic, clinical, and
44 psychosocial factors associated with depression among type 2 diabetic outpatients in

1
2
3 Black Lion General Specialized Hospital, Addis Ababa, Ethiopia: a cross-sectional
4 study. *BMC Psychiatry* 2016;16:103.

5
6
7 55 Harris PA. The impact of age, gender, race, and ethnicity on the diagnosis and
8 treatment of depression. *J Manag Care Pharm* 2004;10:S2-7.

9
10
11 56 Skinner TC, Carey ME, Cradock S, et al. Depressive symptoms in the first year
12 from diagnosis of Type 2 diabetes: results from the DESMOND trial. *Diabet Med*
13 2010;27:965-7.

14
15
16 57 Thoolen BJ, de Ridder DT, Bensing JM, et al. Psychological outcomes of patients
17 with screen-detected type 2 diabetes: the influence of time since diagnosis and
18 treatment intensity. *Diabetes Care* 2006;29:2257-62.

19
20
21 58 Petrak F, Stridde E, Leverkus F, et al. Development and validation of a new
22 measure to evaluate psychological resistance to insulin treatment. *Diabetes Care*
23 2007;30:2199-204.

24
25
26 59 Brod M, Kongso JH, Lessard S, et al. Psychological insulin resistance: patient
27 beliefs and implications for diabetes management. *Qual Life Res* 2009;18:23-32.

28
29
30 60 Polonsky WH, Hajos TR, Dain MP, et al. Are patients with type 2 diabetes
31 reluctant to start insulin therapy? An examination of the scope and underpinnings of
32 psychological insulin resistance in a large, international population. *Curr Med Res*
33 *Opin* 2011;27:1169-74.

34
35
36 61 Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality
37 of evidence--imprecision. *J Clin Epidemiol* 2011;64:1283-93.

38
39
40 62 Anderson RJ, Freedland KE, Clouse RE, et al. The prevalence of comorbid
41 depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24:1069-78.

Figure legends

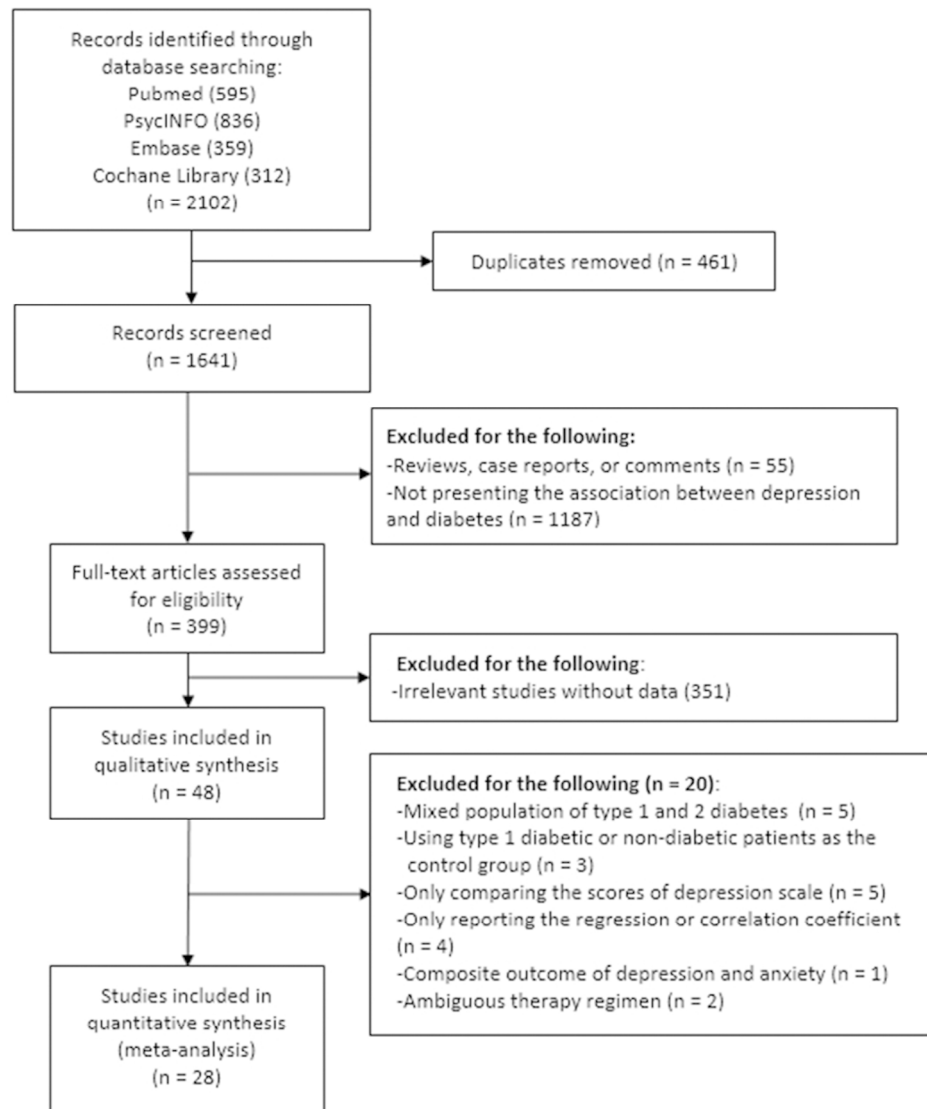
Figure 1. The selection process for eligible studies.

Figure 2. The pooled adjusted odds ratio for the risk of depression in insulin-prescribed patients compared with those without insulin therapy.

Figure 3. The pooled crude odds ratio for the risk of depression in insulin-prescribed patients compared with those without insulin therapy.

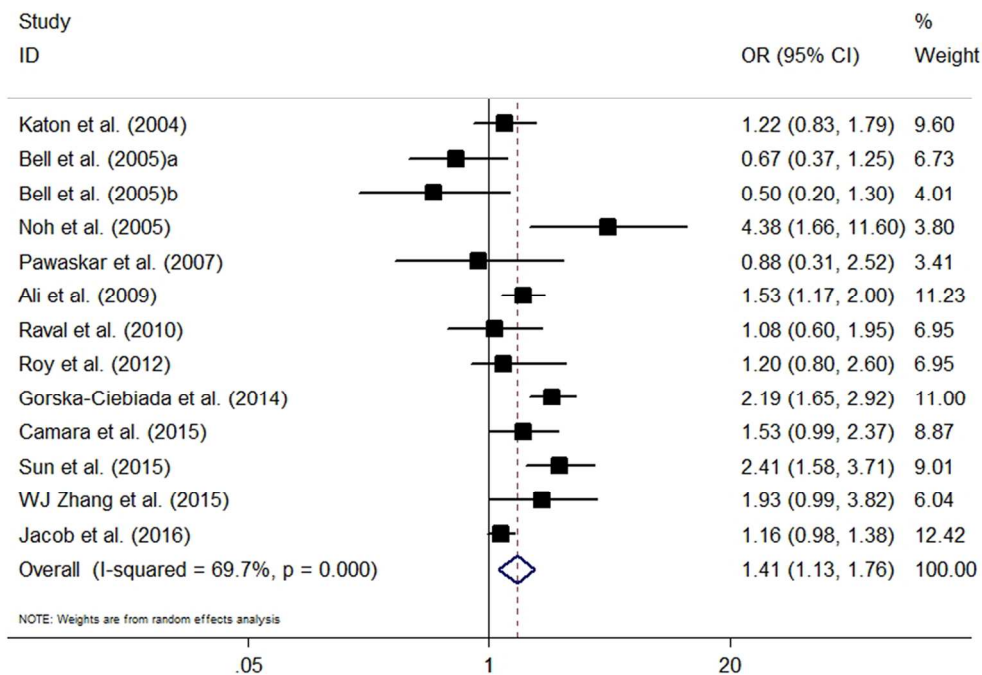
Figure 4. The funnel plot for the studies reporting adjusted odds ratios.

Figure 5. The funnel plot for the studies presenting crude odds ratios.



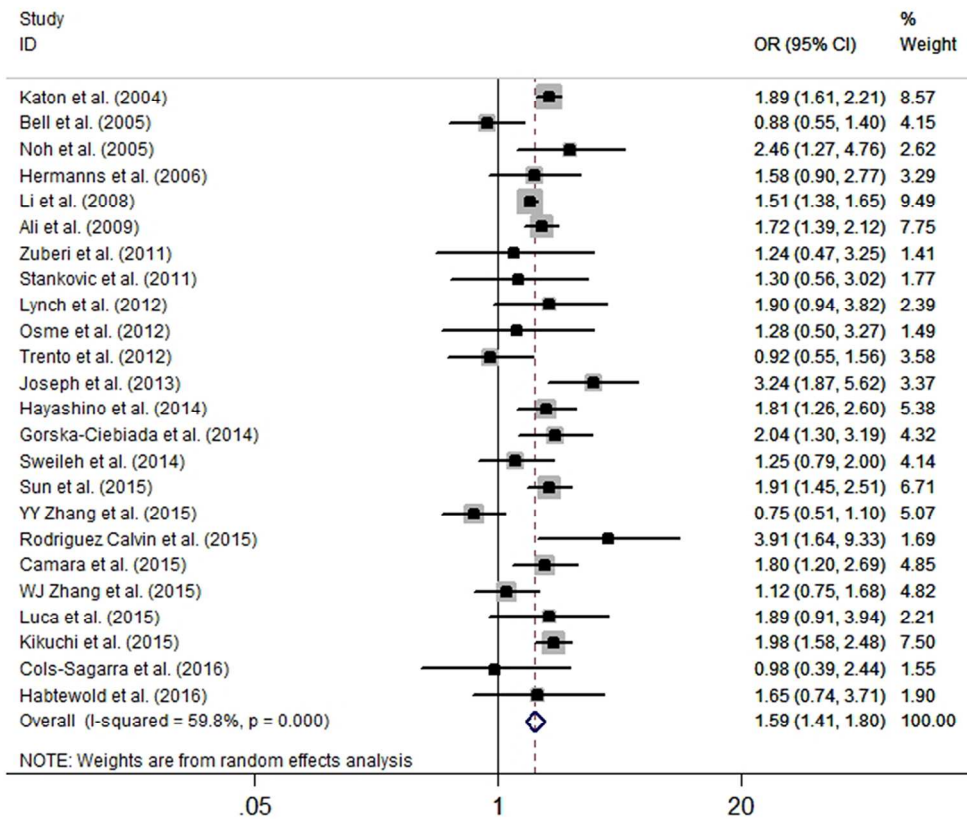
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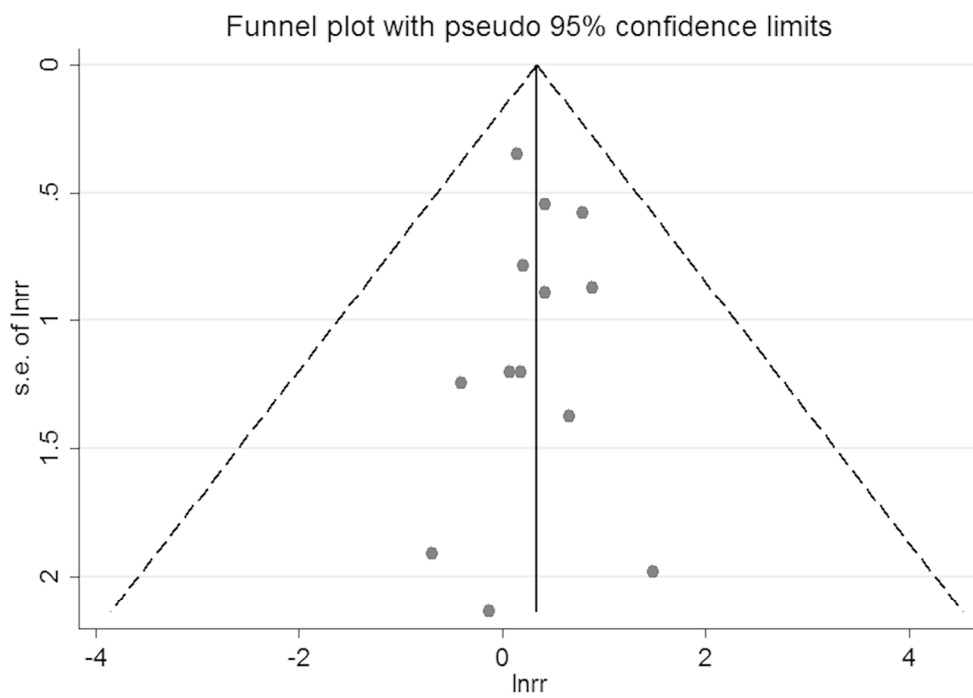
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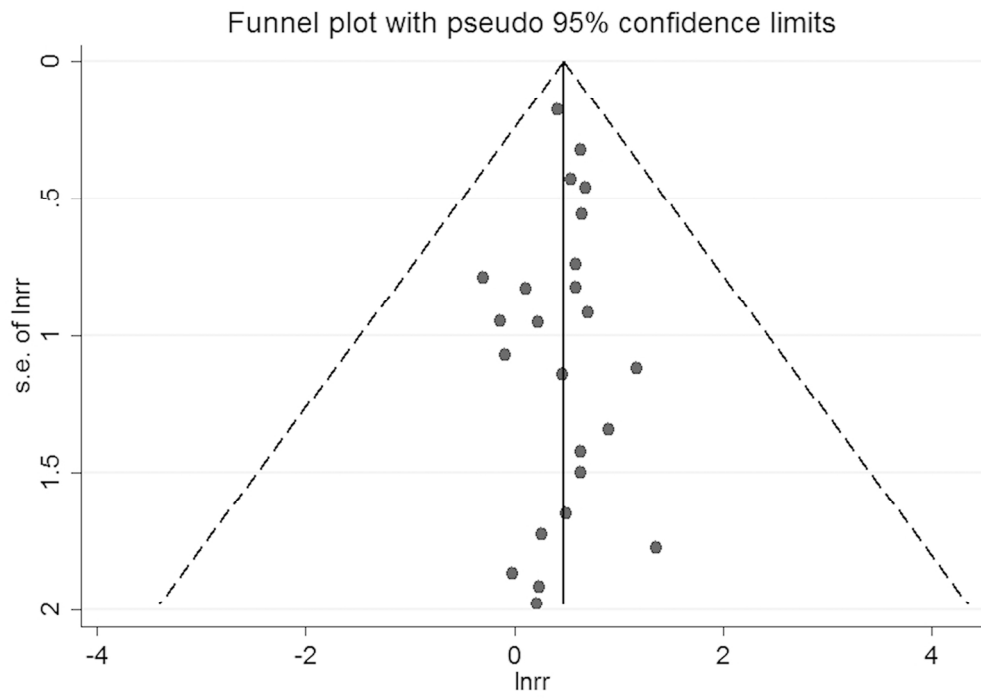
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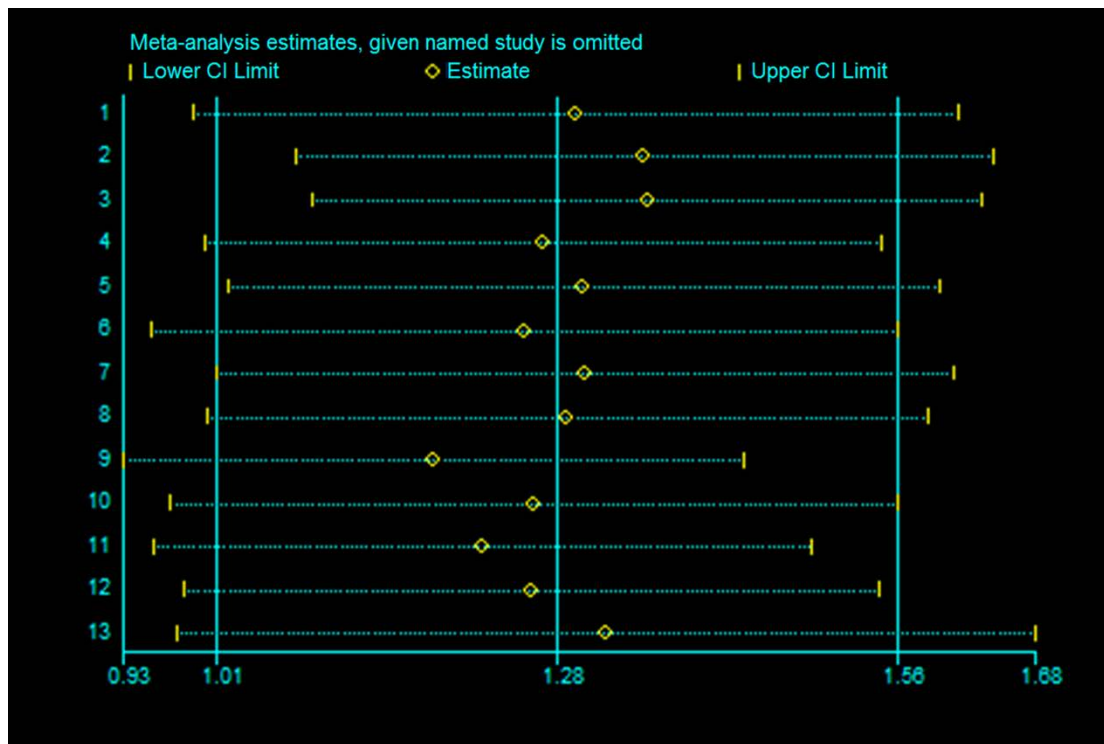
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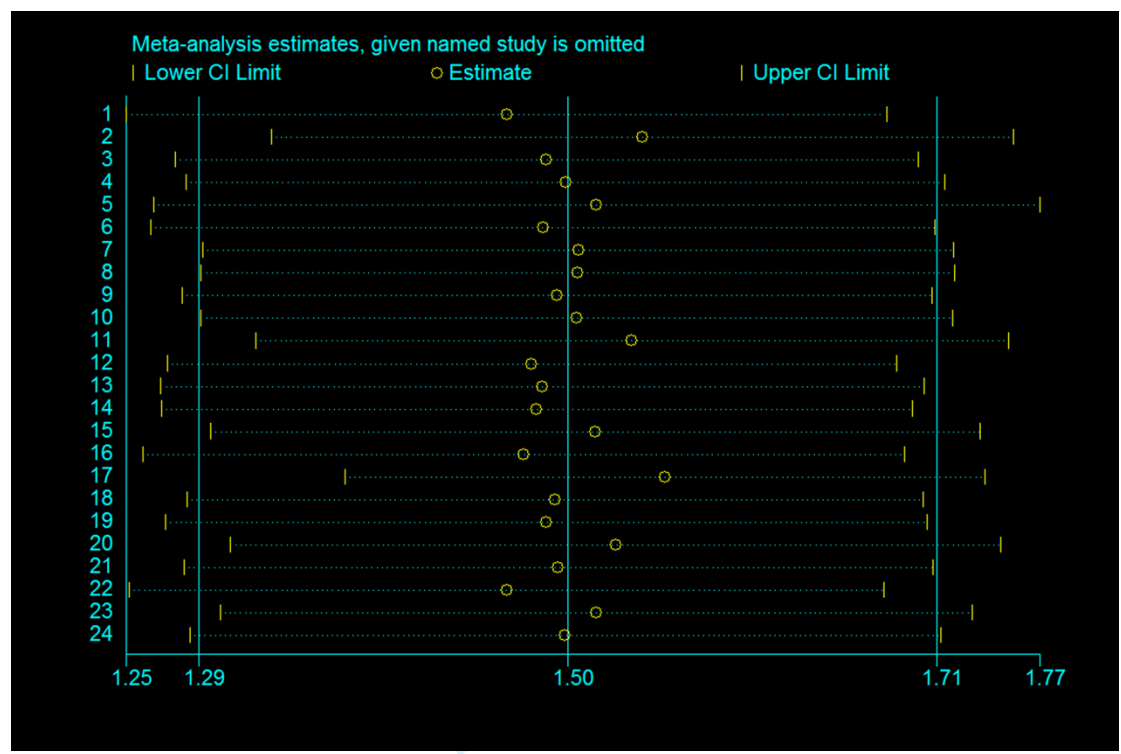
Supplementary Figure S1. Sensitivity analysis for adjusted data



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Supplementary Figure S2. Sensitivity analysis for crude data



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Search strategy in Pubmed

1. Depression [Mesh]
2. Depressive Disorder
3. Depressive Disorder, Major
4. Dysthymic Disorder
5. dysthym*.mp.
6. depress*.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. random* controlled trial.mp.
9. cross-sectional.mp.
10. case-control.mp.
11. cohort.mp.
12. Randomized Controlled Trial
13. Cross-Sectional Studies
14. Case-Control Studies
15. Cohort Studies
16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. Diabetes mellitus [Mesh]
18. Diabetes
19. diabetic. mp
20. Blood Glucose
21. 17 or 18 or 19 or 20
22. insulin [Mesh]
23. Insulin, Lente
24. Insulin Aspart
25. Insulin Lispro
26. Insulin, Short-Acting
27. Insulin, Long-Acting
28. 22 or 23 or 24 or 25 or 26 or 27
29. 7 and 16 and 21 and 28

MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Reporting Criteria	Reported (Yes/No)	Reported on Page
Reporting of background should include		
Problem definition	Yes	4
Hypothesis statement	Yes	4
Description of study outcomes	Yes	4
Type of exposure or intervention used	Yes	4
Type of study designs used	Yes	4
Study population	Yes	4
Reporting of search strategy should include		
Qualifications of searchers (eg librarians and investigators)	Yes	5
Search strategy, including time period used in the synthesis and key words	Yes	5
Effort to include all available studies, including contact with authors	Yes	5
Databases and registries searched	Yes	5
Search software used, name and version, including special features used (eg explosion)	Yes	5
Use of hand searching (eg reference lists of obtained articles)	Yes	5
List of citations located and those excluded, including justification	Yes	7
Method of addressing articles published in languages other than English	Yes	5
Method of handling abstracts and unpublished studies	Yes	5
Description of any contact with authors	No	NA
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	No	NA
Rationale for the selection and coding of data (eg sound clinical principles or convenience)	Yes	5
Documentation of how data were classified and coded (eg multiple raters, blinding and interrater reliability)	Yes	6
Assessment of confounding (eg comparability of cases and controls in studies where appropriate)	Yes	6
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Yes	6

Assessment of heterogeneity	Yes	6
Description of statistical methods (eg complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	6
Provision of appropriate tables and graphics	Yes	6
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Yes	9-15
Table giving descriptive information for each study included	Yes	9-15
Results of sensitivity testing (eg subgroup analysis)	Yes	19-22
Indication of statistical uncertainty of findings	Yes	19-22
Reporting of discussion should include		
Quantitative assessment of bias (eg publication bias)	Yes	23
Justification for exclusion (eg exclusion of non-English language citations)	No	23
Assessment of quality of included studies	Yes	Table 2
Strengths and weaknesses	Yes	24-25
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	Yes	23-24
Generalization of the conclusions (eg appropriate for the data presented and within the domain of the literature review)	Yes	25
Guidelines for future research	Yes	25
Disclosure of funding source	Yes	26

NA: Not Applicable