BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020062
Article Type:	Research
Date Submitted by the Author:	11-Oct-2017
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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

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

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Word count: 2791

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.

• 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.

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,

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

Statistical analysis

As most included studies were cross-sectional, effect sizes had to be expressed as odds ratios (ORs). Given the low prevalence of depression in T2DM patients, the risk ratio (RR) reported by prospective study approximated the OR. Where available, the fully adjusted OR was pooled into meta-analysis to avoid the bias caused by confounding factors. However, the degree of adjustment and the variables entering into regression models varied between included studies. Thus, we additionally pooled the unadjusted ORs for data homogeneity. When only raw data were available, the crude ORs were calculated by using a random Mantel-Haenszel method. The random-effects model was used for meta-analysis. Heterogeneity was assessed by the Cochrane Q statistics and I^2 values. $P < 0.05$ was regarded as significant heterogeneity for the Q test. I^2 ranged between 0% (no heterogeneity) and 100% (high heterogeneity), with values around 25, 50, and 75% suggesting low, moderate, and high heterogeneity.[28] To weigh up the relative influence of each individual study, sensitivity analysis was performed by excluding one study at a time and assessing alteration in pooled results. Subgroup analyses and meta-regression analyses were performed using the following variables: compared groups (insulin vs. non-drug therapy or insulin vs. oral anti-diabetic drugs), degree of adjustment of confounders (+, ++ or +++), region (USA, Asia, Europe, or Africa), identification of depression

(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

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

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

											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
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 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-s	Outpatient	138	≥30	Brazil	27.5	44.6	HAD	Insulin	Unadjusted	NA

(2012)	ectional	clinic							vs.non-insulin		
Trento et al. (2012)	Cross-sectional	Outpatient clinic	498	67.6	Italy	52.6	14.2	ZSDS	Insulin vs.non-insulin	Unadjusted	NA
Roy et al. (2012)	Cross-sectional	Outpatient clinic	417	53.2	Bangladesh	50.6	34	PHQ-9	Insulin vs. oral medication +diet; insulin+oral medication vs. oral medication +diet	Adjusted	Age, gender, education, income, region, CVD, hypertension, diabetic complications, BMI, HbA1c
Joseph et al. (2013)	Cross-sectional	Hospital	230	53.6	India	51.7	45.2	PHQ-9	Insulin vs. oral medication	Unadjusted	NA

Hayashino et al. (2014)	Cross-sectional	Hospital	3573	66	Japan	61.1	3.4	PHQ-9	Insulin vs. oral medication or diet	Unadjusted	NA
Górska-Ciebiada 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
YY Zhang et al. (2015)	Cross-sectional	Hospital	2538	56.4	China	53	6.1	PHQ-9	Insulin vs. oral drugs	Unadjustd	NA

Rodriguez 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. (2015)	Cross-sectional	Outpatient clinic	491	58	Guinea	37	34.4	HADS	Insulin vs. oral medication	Adjusted	Age, HbA1c, hypertension, BMI, residence zone, socioeconomic status
Sun et al. (2015)	Cross-sectional	Community	22947	57.4	China	34.4	5.9	PHQ-9	Insulin vs. oral medication or diet	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 vs. oral medication	Adjusted	Age, gender, education, marital status, occupation, insurance, HbA1c, BMI, DM history, diabetic complications, duration of DM, smoking, alcohol, exercise,

											sleeping hours
Luca et al. (2015)	Cross-sectional	Hospital	128	64.7	Italy	58.6	50.8	HAM-D	Insulin vs. oral medication or diet	Unadjusted	NA
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-Sagarra et al. (2016)	Cross-sectional	Community	411	70.8	Spain	46.2	29.2	PHQ-9	Insulin vs. oral medications or diet	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, emergence 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 Questionnaire; SBP, systolic blood pressure; ZSDS, Zung Self-Rating Depression Scale.

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 insulin initiation	Control of confounding factors	Assessment of depression	Report response rates 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
Zuberi et al. (2011)	1	1	1	1	1	0	1	1	7
Stanković et al. (2011)	1	1	1	1	1	0	1	0	6
Lynch et al. (2012)	1	1	1	1	1	0	1	1	7
Osme et al. (2012)	1	1	1	1	1	0	1	0	6

Trento et al. (2012)	1	1	1	1	1	0	1	0	6
Roy et al. (2012)	1	1	1	1	1	1	1	1	8
Joseph et al. (2013)	1	1	1	1	1	0	1	0	6
Hayashino et al. (2014)	1	1	1	1	1	0	1	0	6
Gorska-Ciebiada et al. (2014)	0	1	1	1	1	1	1	0	6
Sweileh et al. (2014)	1	1	1	1	1	0	1	1	7
YY Zhang et al. (2015)	1	1	1	1	1	0	1	1	7
Rodriguez Calvin et al. (2015)	1	1	1	1	1	0	1	1	7
Camara et al. (2015)	1	1	1	1	1	0	1	0	6
Sun et al. (2015)	1	1	1	1	1	1	1	0	7
WJ Zhang et al. (2015)	1	1	1	1	1	1	1	1	8
Luca et al. (2015)	1	1	1	1	1	0	1	0	6
Kikuchi et al. (2015)	1	1	1	1	1	0	1	0	6
Jacob et al. (2016)	1	1	1	1	1	0	1	0	6
Cols-Sagarra et al. (2016)	1	1	1	1	1	0	1	0	6
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 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 questionaire	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

patients on insulin treatment had a 41% increased prevalence of depressive syndromes compared to those without insulin therapy. When pooling crude ORs, the increased prevalence attained to 59%. 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 had increased occurrence 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 treatment effect 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. The involved pathways include the innate inflammatory response, the hypothalamicpituitary-adrenal axis, circadian rhythms, and insulin resistance.[3] Although the overall prevalence of depression is high in diabetic patients, the DESMOND trial reported that it was not so in newly diagnosed T2DM.[56] Screen-detected patients with T2DM showed low distress and anxiety at the time of diagnosis, with a significant increase during the following 12 months.[57] In

accordance with these findings, we confirmed that insulin therapy was associated with increased prevalence of depression. For patients on insulin therapy, they had less endogenous insulin and were therefore more susceptive to metabolic dysregulation than patients who might have some residual insulin secretory activity. Especially, patients who are more metabolically labile are more vulnerable to depression.[16] Besides, insulin therapy is always a symbol of more advanced type 2 diabetes. The patients' negative attitudes toward insulin therapy may contribute to delays for insulin initiation, prolonged duration of hyperglycemia, and increased risk of diabetic complications.[58] Psychological insulin resistance (PIR) has been defined as psychological opposition towards insulin treatment in both diabetic patients and their prescribers. They may display fear of insulin injection and self-testing, complex regimen, hypoglycemia, and weight gain; a perceived loss of control over one's life; poor self-efficacy concerning insulin treatment; and perceived lack of positive outcomes related to insulin.[58-60] These psycological aspects may explain for the increased risk of depression when insulin was prescribed.

The primary strength of this study was the systematic and expansive search of multiple databases, which minimized the risk of missing data. The meta-analysis identified 28 studies enrolling worldwide-distributed participants. Both of the adjusted and crude effect estimates were analyzed and demonstrated consistent results. The confidential intervals were narrow, suggesting the precision of pooled results.[61] For adjusted data, most studies had full adjustment for confounders. The subtypes of non-insulin therapy, including oral drug and non-drug treatment, were analyzed separately. The between-study heterogeneity was intensively explored by sensitivity, subgroup, and meta-regression analyses. Besides, no publication bias was detected among the selected studies.

We were aware of the limitations of this meta-analysis. Our findings mainly relied on cross-sectional data; as such, the causal and temporal relationship between insulin use and depression could not be established. Some studies had a small sample size which may influence the statistical power. The response rate was only reported by several studies. The unmeasured differences between respondents and nonrespondents

may potentially influence the pooled results. Most of the studies used self-reported scales rather than clinical interview-based assessments to identify depression. Prevalence of depression was generally much higher using the self-reported scales than standardized diagnostic interviews.[20, 62] Furthermore, 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. Finally, the impact of the total number of daily insulin injections with depression development was included only in few studies, and these contributed as potential confounders in patients who received insulin therapy and the progression of depression.

CONCLUSIONS

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

Acknowledgments

None.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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.

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Figure legends

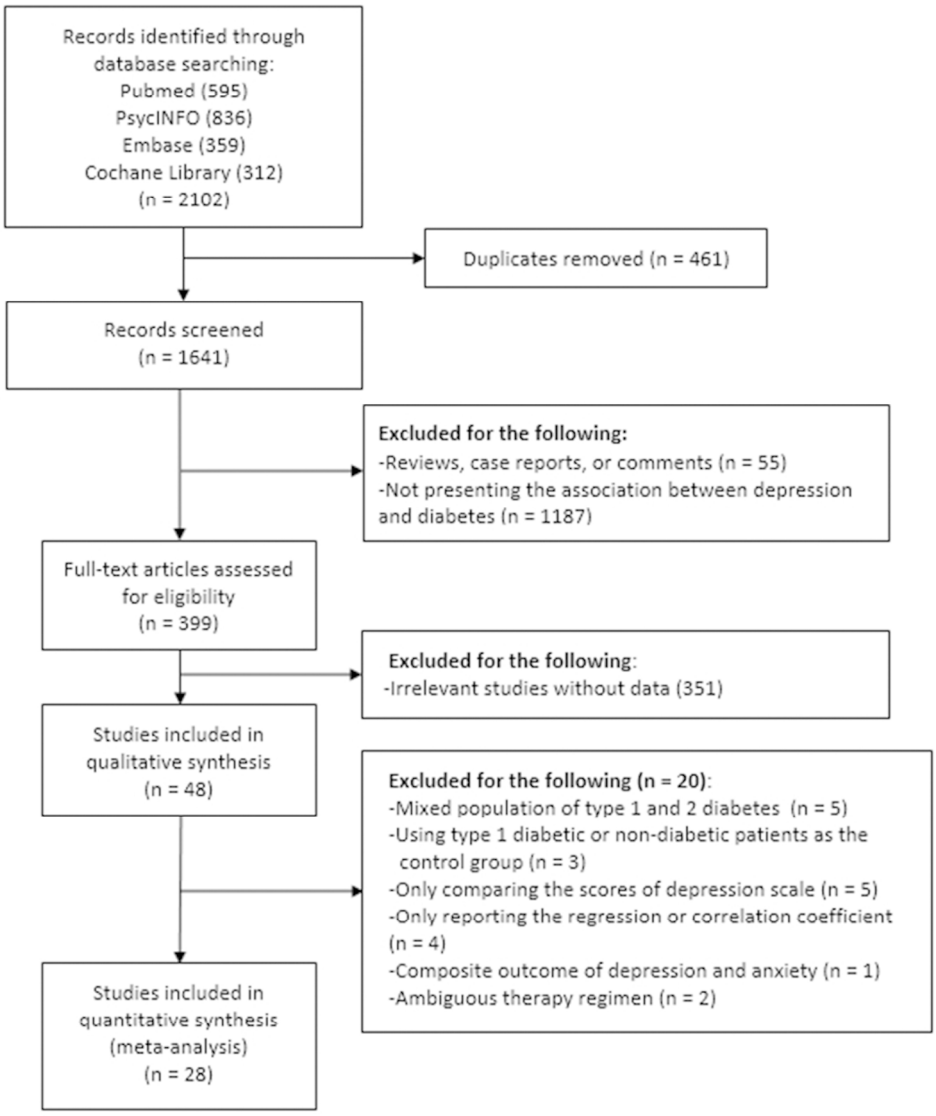
Figure 1. The selection process for eligible studies.

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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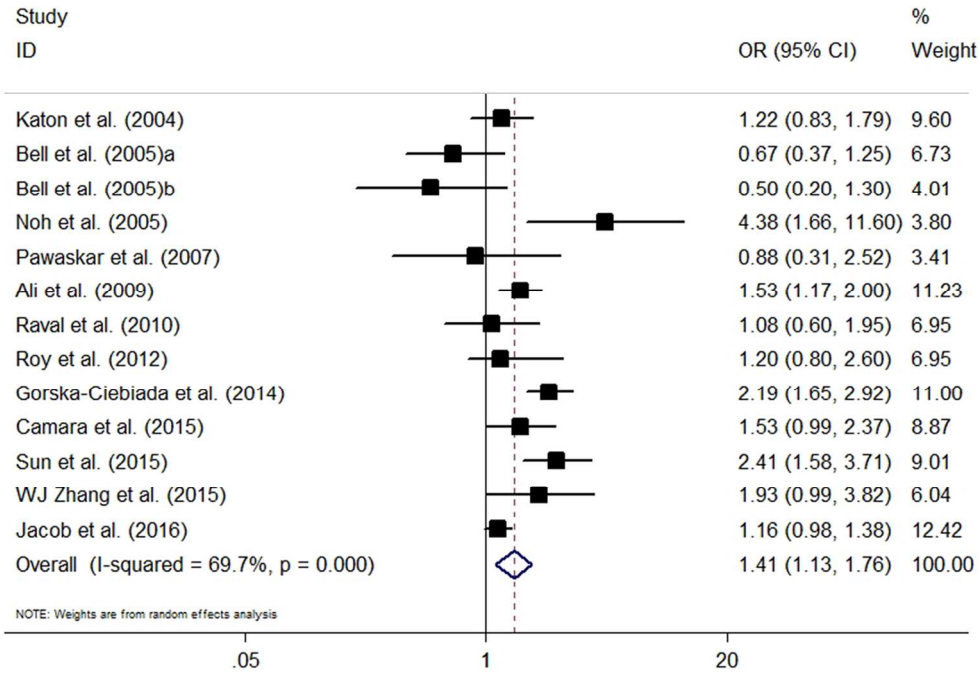

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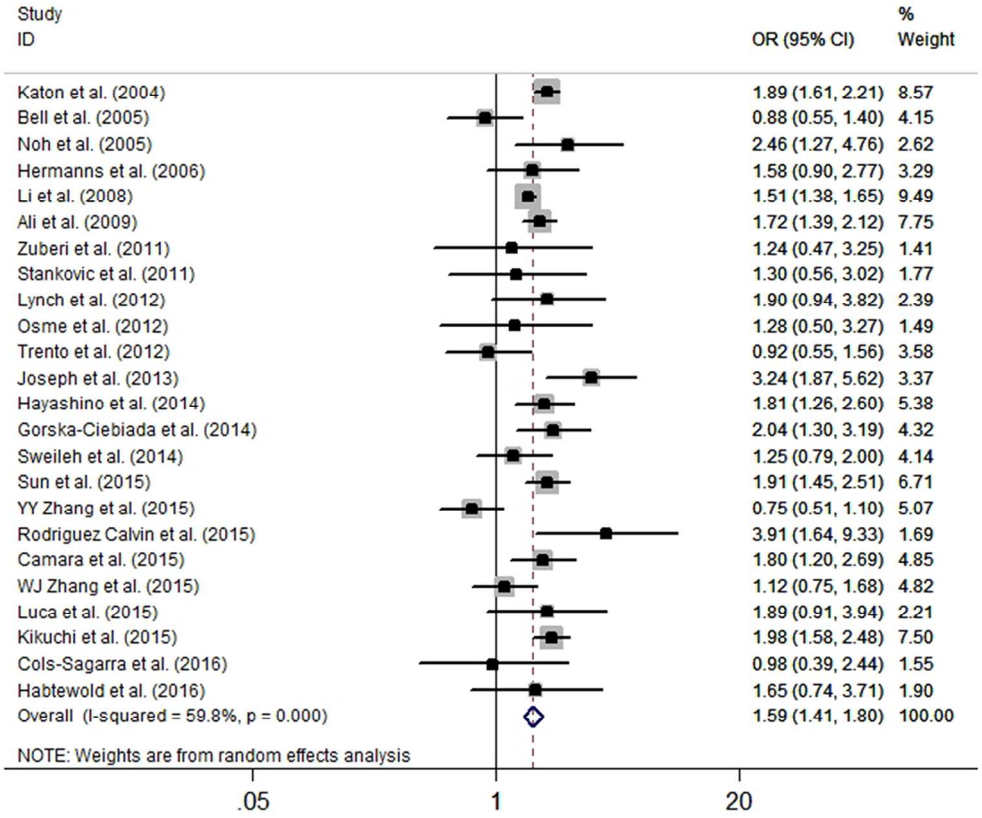

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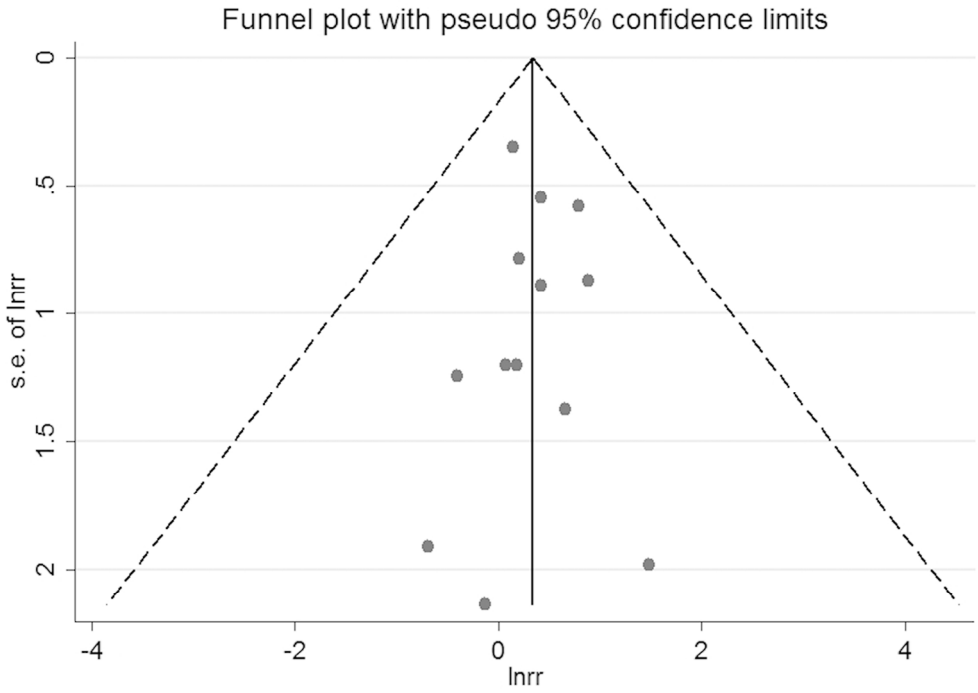

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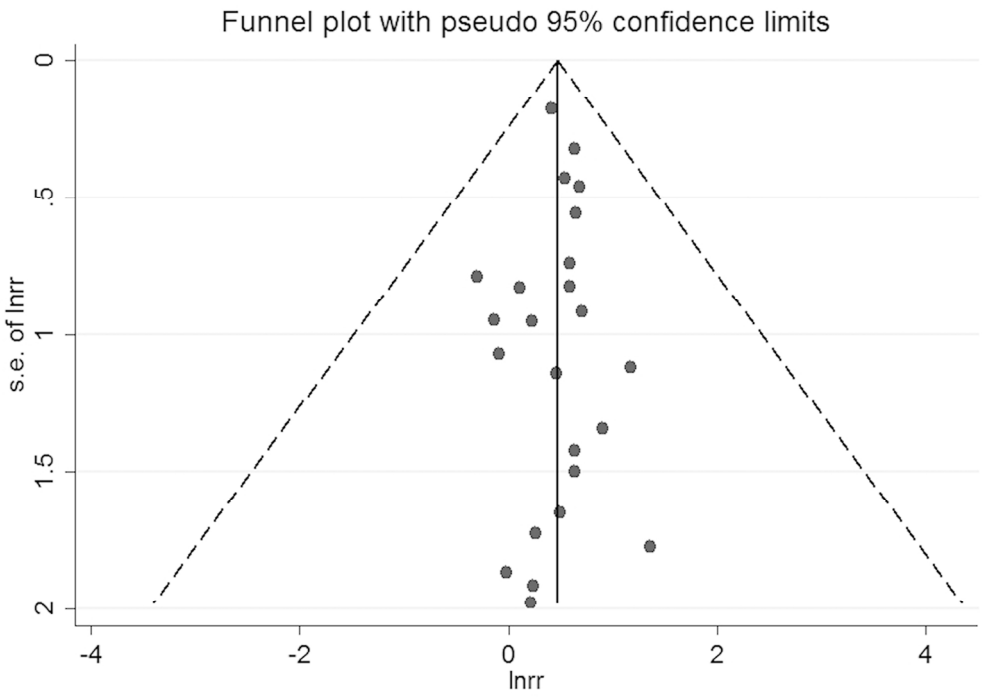

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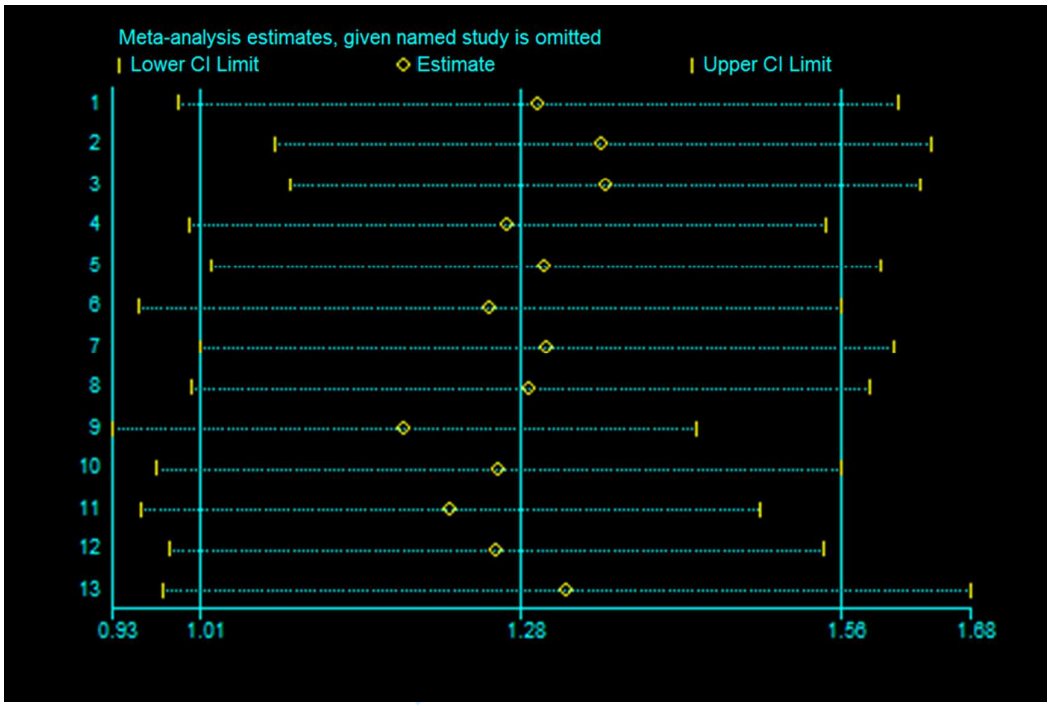
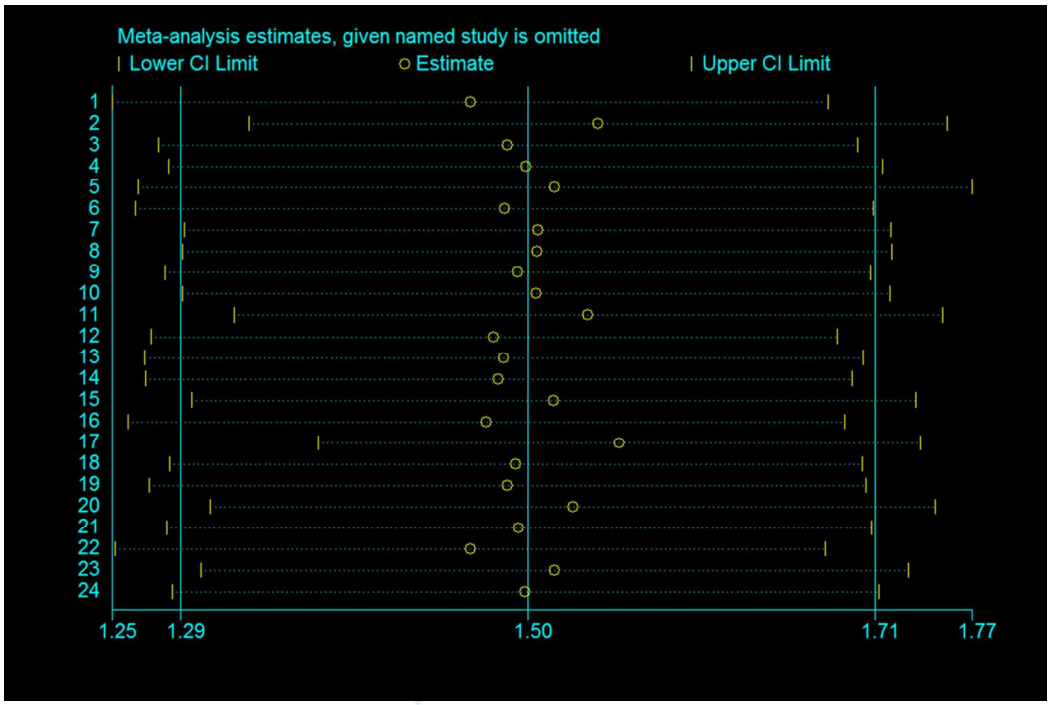
Supplementary Figure S1. Sensitivity analysis for adjusted data



Supplementary Figure S2. Sensitivity analysis for crude data



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

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

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BMJ Open

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

Journal:	*BMJ Open*
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

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

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Word count: 2791

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

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.

• 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.

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;

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

Statistical analysis

As most included studies were cross-sectional, effect sizes had to be expressed as odds ratios (ORs). Given the low prevalence of depression in T2DM patients, the risk ratio (RR) reported by prospective study approximated the OR. Where available, the fully adjusted OR was pooled into meta-analysis to avoid the bias caused by confounding factors. However, the degree of adjustment and the variables entering into regression models varied between included studies. Thus, we additionally pooled the unadjusted ORs for data homogeneity. The random-effects model was used for meta-analysis. Heterogeneity was assessed by the Cochrane Q statistics and I^2 values.

P < 0.05 was regarded as significant heterogeneity for the Q test. I^2 ranged between 0% (no heterogeneity) and 100% (high heterogeneity), with values around 25, 50, and 75% suggesting low, moderate, and high heterogeneity.[28] To weigh up the relative influence of each individual study, sensitivity analysis was performed by excluding one study at a time and assessing alteration in pooled results. Subgroup analyses and meta-regression analyses were performed using the following variables: compared groups (insulin vs. non-drug therapy or insulin vs. oral anti-diabetic drugs), degree of adjustment of confounders (+, ++ or +++), region (USA, Asia, Europe, or Africa), identification of depression (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 2,102 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 of the included studies were summarized in Table 1. In quality assessment, all studies had low to moderate risk of bias, with the scores ranging from 6 to 8. The items satisfied least were the control of confounding factors (12/28) and the report of response rates or follow-up data (10/28) (Table 2).

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
Ell 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.	Hospita	Hospital	204	53	Korean	53	32.4	BDI	Insulin vs.	Adjusted	Age, sex, BMI, duration of

(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

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-s	Hospital	90	55.5	Serbia	34.4	51.1	PHQ, BDI,	Insulin vs.	Unadjusted	NA

et al. (2011)	ectional							or interview	oral medication		
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. (2012)	Cross-sectional	Outpatient clinic	138	≥30	Brazil	27.5	44.6	HAD	Insulin vs.non-insulin	Unadjusted	NA
Tranto et al. (2012)	Cross-sectional	Outpatient clinic	498	67.6	Italy	52.6	14.2	ZSDS	Insulin vs.non-insulin	Unadjusted	NA
Roy et al. (2012)	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

									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. oral medication	Unadjusted	NA
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-Ciebiada 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
Yx Zhang et al. (2015)	Cross-sectional	Hospital	2538	56.4	China	53	6.1	PHQ-9	Insulin vs. oral drugs	Unadjustd	NA
Rodriguez Calvin et al. (2015)	Cross-sectional	Hospital	275	64.5	Spain	56.4	32.7	BDI	Insulin vs. oral medication	Unadjusted	NA
Câmara et	Cross-s	Outpatient	491	58	Guinea	37	34.4	HADS	Insulin vs. oral	Adjusted	Age, HbA1c, hypertension, BMI, residence zone, socioeconomic

al. (2015)	ectional	clinic							medication		status
Sun et al. (2015)	Cross-sectional	Community	229047	57.4	China	34.4	5.9	PHQ-9	Insulin vs. oral medication or diet	Adjusted	Age, sex, BMI, HbA1c, smoking, alcohol, physical activity, education, occupation, marital status, selfreport cardio-metabolic disorders, diabetes treatment, diabetes duration
WJ Zhang et al. (2015)	Cross-sectional	Hospital	412	59.8	China	50.2	5.7	BDI	Insulin vs. oral medication	Adjusted	Age, gender, education, marital status, occupation, insurance, HbA1c, BMI, DM history, diabetic complications, duration of DM, smoking, alcohol, exercise, sleeping hours
Luca et al. (2015)	Cross-sectional	Hospital	128	64.7	Italy	58.6	50.8	HAM-D	Insulin vs. oral medication	Unadjusted	NA

									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
Cols-Sagarra et al. (2016)	Cross-sectional	Community	411	70.8	Spain	46.2	29.2	PHQ-9	Insulin vs. oral medications or diet	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, emergence 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

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

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 insulin initiation	Control of confounding factors	Assessment of depression	Report response rates 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

Zuberi et al. (2011)	1	1	1	1	1	0	1	1	7
Stanković et al. (2011)	1	1	1	1	1	0	1	0	6
Lynch et al. (2012)	1	1	1	1	1	0	1	1	7
Osme et al. (2012)	1	1	1	1	1	0	1	0	6
Trento et al. (2012)	1	1	1	1	1	0	1	0	6
Roy et al. (2012)	1	1	1	1	1	1	1	1	8
Joseph et al. (2013)	1	1	1	1	1	0	1	0	6
Hayashino et al. (2014)	1	1	1	1	1	0	1	0	6
Gorska-Ciebiada et al. (2014)	0	1	1	1	1	1	1	0	6
Sweileh et al. (2014)	1	1	1	1	1	0	1	1	7
YY Zhang et al. (2015)	1	1	1	1	1	0	1	1	7
Rodriguez Calvin et al. (2015)	1	1	1	1	1	0	1	1	7

Camara et al. (2015)	1	1	1	1	1	0	1	0	6
Sun et al. (2015)	1	1	1	1	1	1	1	0	7
WJ Zhang et al. (2015)	1	1	1	1	1	1	1	1	8
Luca et al. (2015)	1	1	1	1	1	0	1	0	6
Kikuchi et al. (2015)	1	1	1	1	1	0	1	0	6
Jacob et al. (2016)	1	1	1	1	1	0	1	0	6
Cols-Sagarra et al. (2016)	1	1	1	1	1	0	1	0	6
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 questionaire	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 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 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						

≥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). 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.

The involved pathways include the innate inflammatory response, the hypothalamicpituitary-adrenal axis, circadian rhythms, and insulin resistance.[3] Although the overall prevalence of depression is high in diabetic patients, the DESMOND trial reported that it was not so in newly diagnosed T2DM.[56] Screen-detected patients with T2DM showed low distress and anxiety at the time of diagnosis, with a significant increase during the following 12 months.[57] In accordance with these findings, we confirmed that insulin therapy was associated with increased prevalence of depression. For patients on insulin therapy, they had less endogenous insulin and were therefore more susceptive to metabolic dysregulation than patients who might have some residual insulin secretory activity. Especially, patients who are more metabolically labile are more vulnerable to depression.[16] Besides, insulin therapy is always a symbol of more advanced type 2 diabetes. The patients' negative attitudes toward insulin therapy may contribute to delays for insulin initiation, prolonged duration of hyperglycemia, and increased risk of diabetic complications.[58] Psychological insulin resistance (PIR) has been defined as psychological opposition towards insulin treatment in both diabetic patients and their prescribers. They may display fear of insulin injection and self-testing, complex regimen, hypoglycemia, and weight gain; a perceived loss of control over one's life; poor self-efficacy concerning insulin treatment; and perceived lack of positive outcomes related to insulin.[58-60] These psycological aspects may explain for the increased risk of depression when insulin was prescribed.

The primary strength of this study was the systematic and expansive search of multiple databases, which minimized the risk of missing data. The meta-analysis identified 28 studies enrolling worldwide-distributed participants. Both of the adjusted and crude effect estimates were analyzed and demonstrated consistent results. The confidential intervals were narrow, suggesting the precision of pooled results.[61] For adjusted data, most studies had full adjustment for confounders. The subtypes of non-insulin therapy, including oral drug and non-drug treatment, were analyzed separately. The between-study heterogeneity was intensively explored by sensitivity,

subgroup, and meta-regression analyses. Besides, no publication bias was detected among the selected studies.

We were aware of the limitations of this meta-analysis. Our findings mainly relied on cross-sectional data; as such, the causal and temporal relationship between insulin use and depression could not be established. Some studies had a small sample size which may influence the statistical power. The response rate was only reported by several studies. The unmeasured differences between respondents and nonrespondents may potentially influence the pooled results. Most of the studies used self-reported scales rather than clinical interview-based assessments to identify depression. Prevalence of depression was generally much higher using the self-reported scales than standardized diagnostic interviews.[20, 62] Furthermore, 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. Moreover, background oral anti-diabetic drug uses in insulin group might affect the associations of insulin use with the risk of depressive syndromes, while these information was not available in mostly included studies. In addition, althugh subgroup analyses based on several factors were conducted, while substantial residual heterogeneity were observed in numerous subsets. These results were restricted by uncontrolled baseline characteristics of included patients and studies. Finally, the impact of the total number of daily insulin injections with depression development was included only in few studies, and these contributed as potential confounders in patients who received insulin therapy and the progression of depression.

CONCLUSIONS

In conclusion, we noted type 2 diabetic patients who were prescribed insulin was relation to depressive syndromes. For insulin-users, careful monitoring of depressive symptoms should be incorporated into the disease management. Intensified

psychological and education programs should be carried out to prevent depressive illness after insulin initiation in the primary care settings.

Acknowledgments

None.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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.

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Figure legends

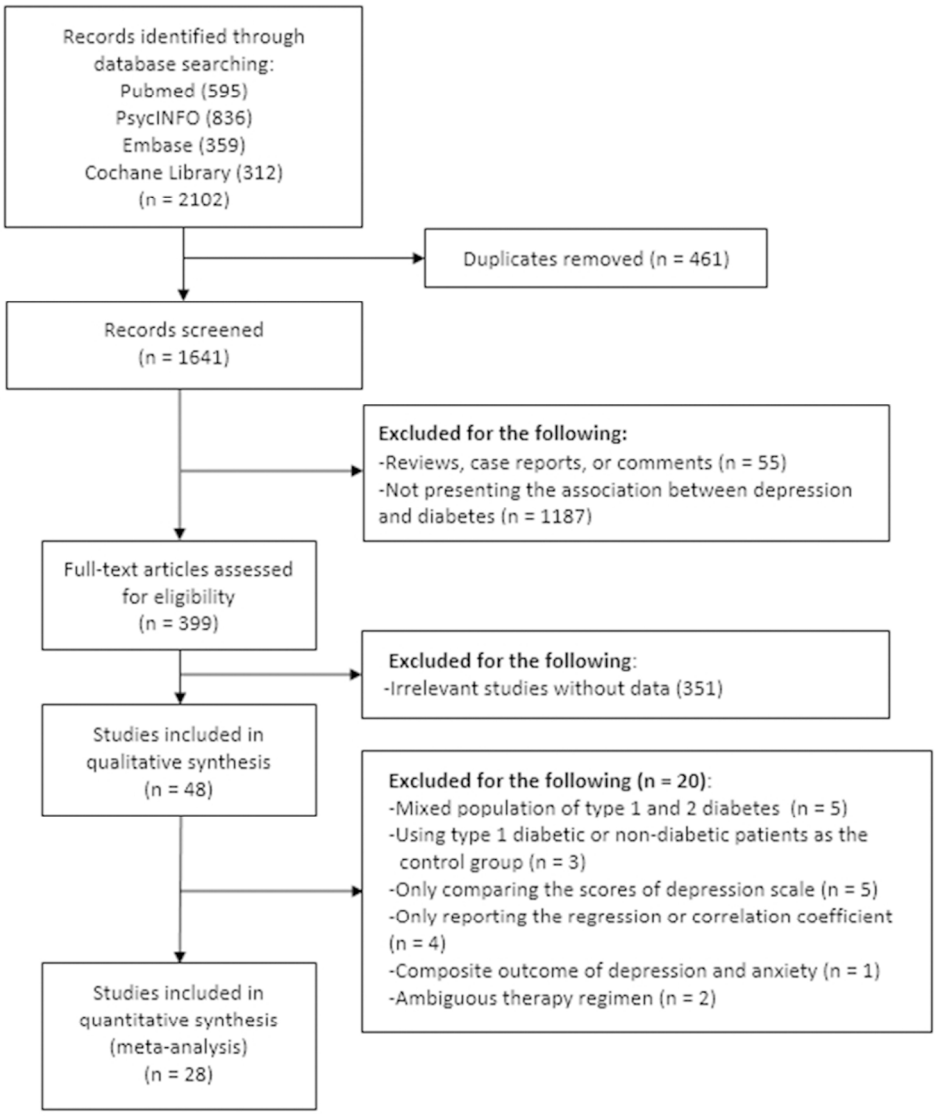
Figure 1. The selection process for eligible studies.

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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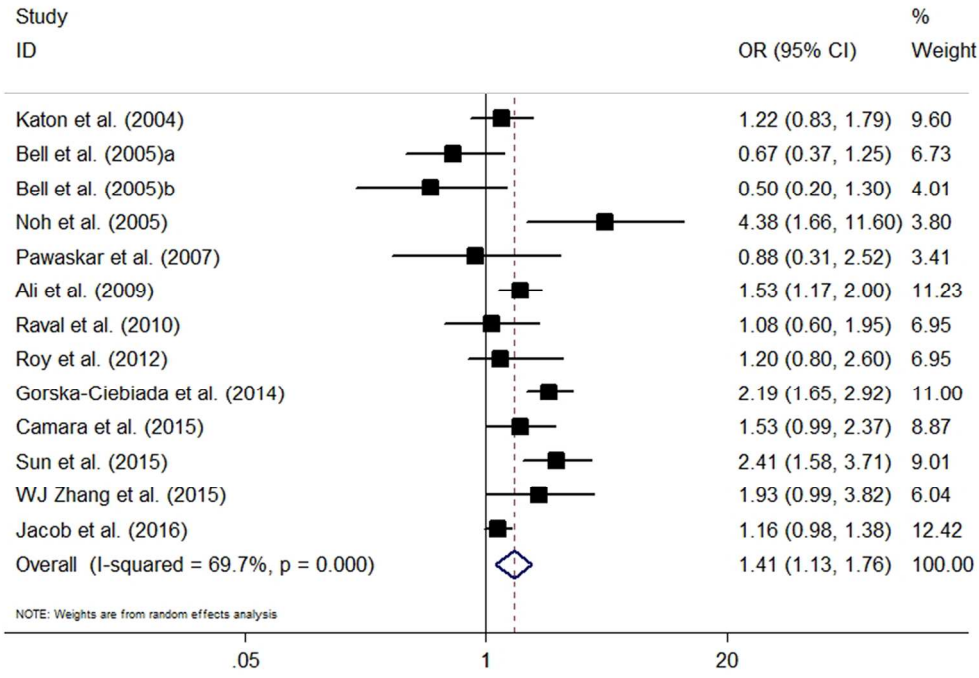

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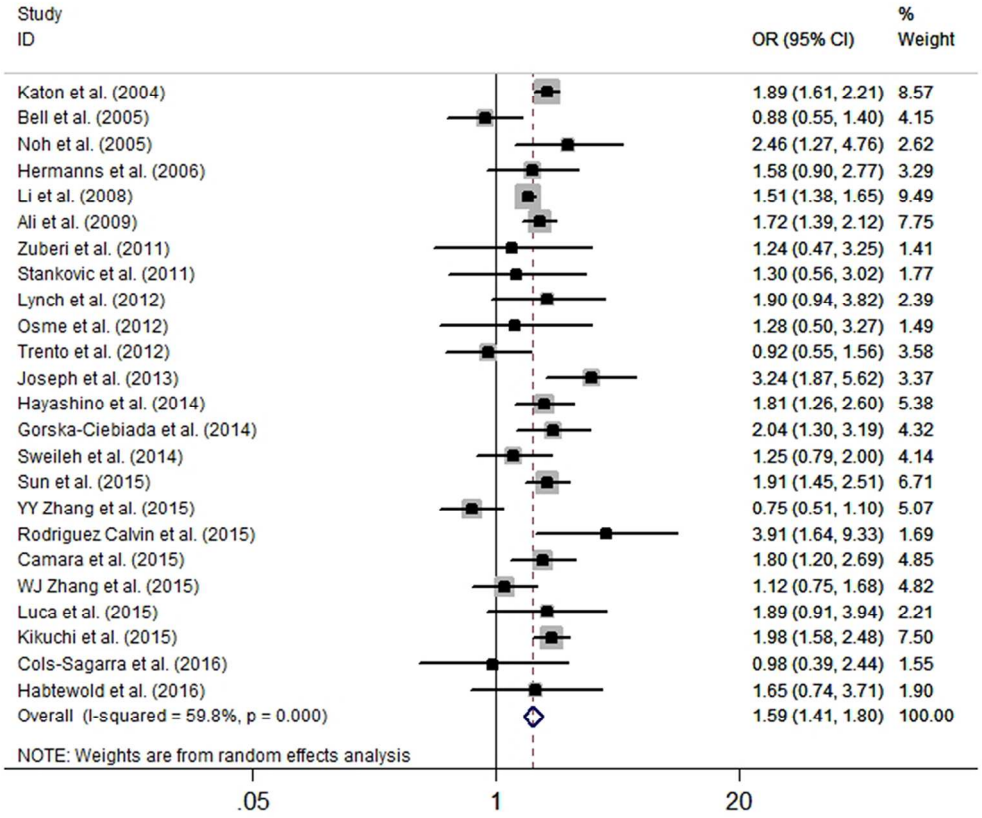

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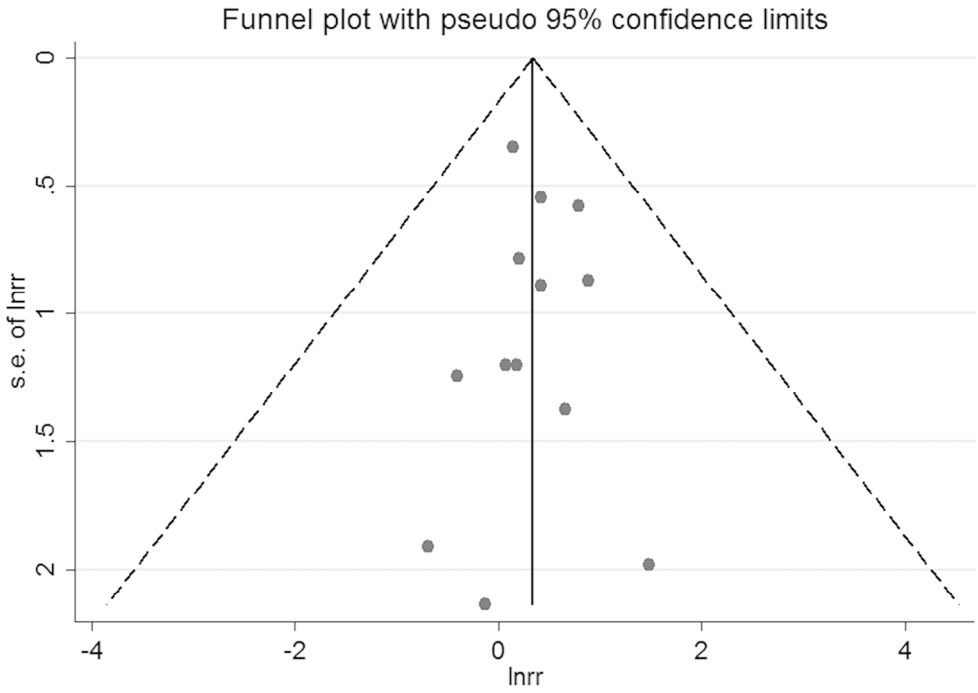

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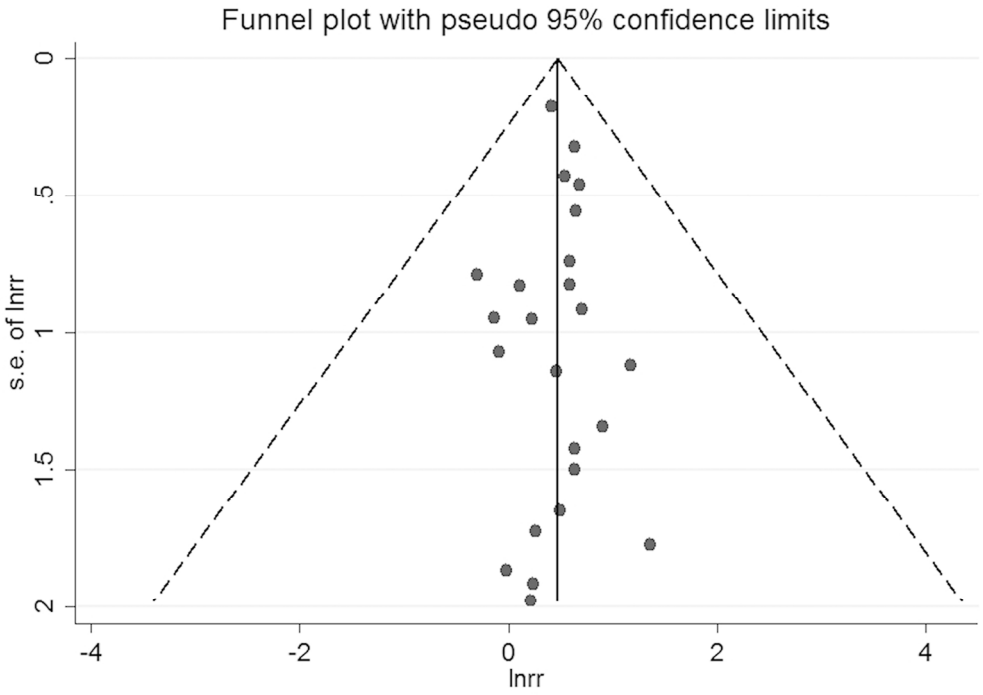

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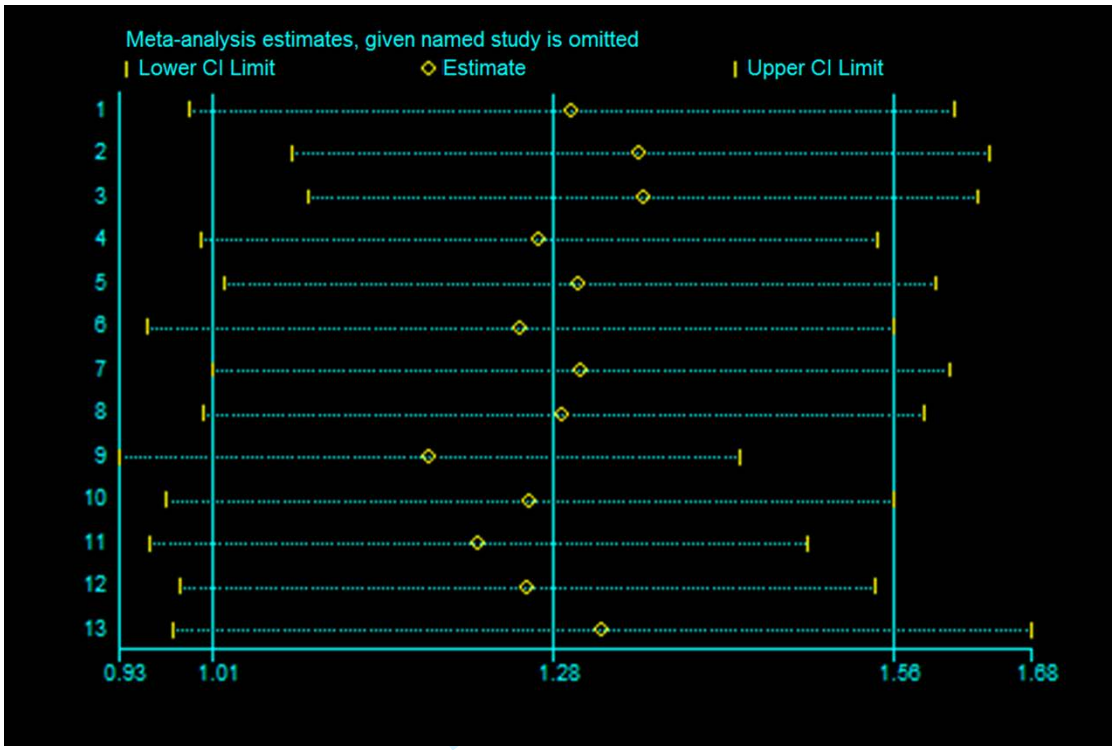
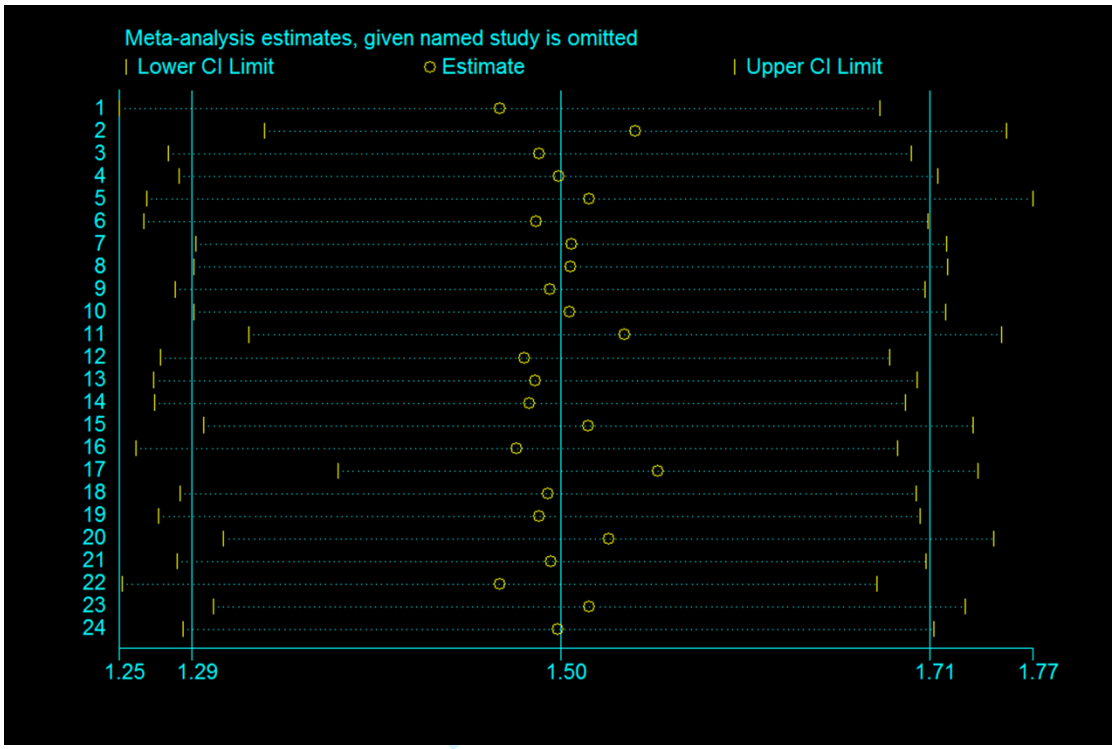
Supplementary Figure S1. Sensitivity analysis for adjusted data



Supplementary Figure S2. Sensitivity analysis for crude data



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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020062.R2
Article Type:	Research
Date Submitted by the Author:	12-Sep-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

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

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Word count: 2791

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 ave 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

T2DM patients.

METHODS

Patient and Public Involvement

No patients were involved in study design or conduct of the study.

Search strategy

This study is reported in accordance with 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 used for the search: (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 full search strategy for Pubmed is shown in Supplementary file. The language was restricted to English. We also manually screened the reference lists of selected studies to obtain 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 that 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 were used [24]. The diagnostic interviews were based on the criteria of 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) comparison was conducted between T2DM and non-T2DM patients; (3) depression could not be distinguished from anxiety or distress; (4) odds ratios (ORs) or risk ratios (RRs) could not be obtained or calculated, for example, we excluded studies that reported only mean and standard deviations of outcome measures.

Data collection and quality assessment

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

Statistical analysis

As most of the included studies were cross-sectional, effect sizes were expressed as ORs. Given the low prevalence of depression in T2DM patients, the RR reported by prospective study approximated the OR. Where available, the fully adjusted OR was pooled into meta-analysis to avoid the bias caused by confounding factors. However, the degree of adjustment and the variables entering into regression models varied

between the included studies. Thus, we additionally pooled the unadjusted ORs for data homogeneity. The random-effects model was used for meta-analysis. Heterogeneity was assessed by Cochrane Q statistics and I^2 values. $P < 0.05$ was regarded as significant heterogeneity for Q test. I^2 ranged between 0% (no heterogeneity) and 100% (high heterogeneity), with values around 25, 50, and 75% suggesting as low, moderate, and high heterogeneity [28]. To weigh up the relative influence of each individual study, sensitivity analysis was performed by excluding one study at a time and assessed the alteration in pooled results. Subgroup analyses and meta-regression analyses were performed using the following variables: compared groups (insulin vs. non-drug therapy or insulin vs. oral anti-diabetic drugs), degree of adjustment of confounders (+, ++ or +++), region (USA, Asia, Europe, or Africa), identification of depression (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 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 to be significant.

RESULTS

Study selection

A total of 2,102 records were identified including 595 articles from Pubmed, 836 articles from PsycINFO, 359 articles from Embase, and 312 articles from Cochrane Library. 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 comparing the mean or median scores of depression

questionnaire, 4 studies 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 the meta-analysis. The flow diagram was shown in Figure 1.

Study characteristics and quality assessment

Among the 28 studies pooled in the meta-analysis, except 1 prospective cohort [31], most of them 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 the adjusted and unadjusted ORs [17, 20, 21, 32-35], 5 studies reported the adjusted ORs [31, 36-39], and unadjusted ORs were retrieved from 16 studies [18, 40-54]. Descriptive data of the included studies were summarized in Table 1. In quality assessment, all studies had low to moderate risk of bias, with scores ranging from 6 to 8. The items satisfied least were the control of confounding factors (12/28) and the report of response rates or follow-up data (10/28), (Table 2).

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
Ball 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.	Hospita	Hospital	204	53	Korean	53	32.4	BDI	Insulin vs.	Adjusted	Age, sex, BMI, duration of

(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

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 et	Cross-s	Hospital	90	55.5	Serbia	34.4	51.1	PHQ, BDI,	Insulin vs.	Unadjusted	NA

t al. (2011)	ectional							or interview	oral medication		
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. (2012)	Cross-sectional	Outpatient clinic	138	≥30	Brazil	27.5	44.6	HAD	Insulin vs.non-insulin	Unadjusted	NA
Tranto et al. (2012)	Cross-sectional	Outpatient clinic	498	67.6	Italy	52.6	14.2	ZSDS	Insulin vs.non-insulin	Unadjusted	NA
Roy et al. (2012)	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

									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. oral medication	Unadjusted	NA
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-Ciebiada 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
Y.Y Zhang et al. (2015)	Cross-sectional	Hospital	2538	56.4	China	53	6.1	PHQ-9	Insulin vs. oral drugs	Unadjustd	NA
Rodriguez Calvin et al. (2015)	Cross-sectional	Hospital	275	64.5	Spain	56.4	32.7	BDI	Insulin vs. oral medication	Unadjusted	NA
Camara et	Cross-s	Outpatient	491	58	Guinea	37	34.4	HADS	Insulin vs. oral	Adjusted	Age, HbA1c, hypertension, BMI, residence zone, socioeconomic

al. (2015)	ectional	clinic							medication		status
Sun et al. (2015)	Cross-sectional	Community	22947	57.4	China	34.4	5.9	PHQ-9	Insulin vs. oral medication or diet	Adjusted	Age, sex, BMI, HbA1c, smoking, alcohol, physical activity, education, occupation, marital status, selfreport cardio-metabolic disorders, diabetes treatment, diabetes duration
WJ Zhang et al. (2015)	Cross-sectional	Hospital	412	59.8	China	50.2	5.7	BDI	Insulin vs. oral medication	Adjusted	Age, gender, education, marital status, occupation, insurance, HbA1c, BMI, DM history, diabetic complications, duration of DM, smoking, alcohol, exercise, sleeping hours
Luca et al. (2015)	Cross-sectional	Hospital	128	64.7	Italy	58.6	50.8	HAM-D	Insulin vs. oral medication	Unadjusted	NA

									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
Cols-Sagarra et al. (2016)	Cross-sectional	Community	411	70.8	Spain	46.2	29.2	PHQ-9	Insulin vs. oral medications or diet	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, emergence 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

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

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

Author (year)	Adequate definitionof cases using insulin	Representativenessof cases using insulin	Selection of the non-insulin users	Ascertainmentof insulin use	Depression was not present before insulin initiation	Control of confounding factors	Assessmentof depression	Report response rates 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

Zuberi et al. (2011)	1	1	1	1	1	0	1	1	7
Stanković et al. (2011)	1	1	1	1	1	0	1	0	6
Lynch et al. (2012)	1	1	1	1	1	0	1	1	7
Osme et al. (2012)	1	1	1	1	1	0	1	0	6
Trento et al. (2012)	1	1	1	1	1	0	1	0	6
Roy et al. (2012)	1	1	1	1	1	1	1	1	8
Joseph et al. (2013)	1	1	1	1	1	0	1	0	6
Hayashino et al. (2014)	1	1	1	1	1	0	1	0	6
Gorska-Ciebiada et al. (2014)	0	1	1	1	1	1	1	0	6
Sweileh et al. (2014)	1	1	1	1	1	0	1	1	7
YY Zhang et al. (2015)	1	1	1	1	1	0	1	1	7
Rodriguez Calvin et al. (2015)	1	1	1	1	1	0	1	1	7

Camara et al. (2015)	1	1	1	1	1	0	1	0	6
Sun et al. (2015)	1	1	1	1	1	1	1	0	7
WJ Zhang et al. (2015)	1	1	1	1	1	1	1	1	8
Luca et al. (2015)	1	1	1	1	1	0	1	0	6
Kikuchi et al. (2015)	1	1	1	1	1	0	1	0	6
Jacob et al. (2016)	1	1	1	1	1	0	1	0	6
Cols-Sagarra et al. (2016)	1	1	1	1	1	0	1	0	6
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 questionaire	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).

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 test (P = 0.94).

DISCUSSION

This is the first meta-analysis that estimated the magnitude of association between insulin therapy and depression. The pooled data of adjusted ORs proved that T2DM patients on insulin treatment were associated with the prevalence of depressive syndromes compared to those without insulin therapy. When pooling the crude ORs, the results showed a permanent and significant association. 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 related 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 different ethnicities [55]. In subgroup analyses of adjusted data, we found significant results for Asian studies. Non-significant results were shown for studies with sample size below 1000, suggesting that the results were unstable for small sample size. Substantial change of heterogeneity was also detected for 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 with the prevalence of depression below 20%, substantial change in the effect estimates was observed for adjusted data, and obvious change in heterogeneity for crude data. Thus, this may partly account for the heterogeneity. Finally, 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 the 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 that link diabetes and depression were complex and still unclear. Depression and T2DM could develop in parallel through shared biological processes. The involved pathways include the innate inflammatory response, the hypothalamicpituitary-adrenal axis, circadian rhythms, and insulin resistance [3]. Although the overall prevalence of depression is high in diabetic patients, the DESMOND trial reported that it was not so in the newly diagnosed T2DM patients [56]. Screen-detected patients with T2DM showed low distress and anxiety at the time of diagnosis, with a significant increase during the 12 months follow-up period [57]. In accordance with these findings, we confirmed that insulin therapy was associated with increased prevalence of depression. For patients on insulin therapy, they had less endogenous insulin and were therefore more susceptive to metabolic dysregulation than patients who might have some residual insulin secretory activity. Especially, patients who are more metabolically labile are more vulnerable to depression [16]. Besides, insulin therapy is always a symbol of more advanced type 2 diabetes. The patients' negative attitude towards insulin therapy may contribute to the delay for insulin initiation, prolonged duration of hyperglycemia, and increased risk of diabetic complications [58]. Psychological insulin resistance (PIR) has been defined as psychological opposition towards insulin treatment in both diabetic patients and their prescribers. They may display fear of insulin injection and self-testing, complex regimen, hypoglycemia, and weight gain; a perceived loss of control over one's life; poor self-efficacy concerning insulin treatment; and lack of positive outcomes related to insulin [58-60]. These psycological aspects may explain the increased risk of depression when insulin was prescribed.

The primary strength of this study was the systematic and expansive search of multiple databases, which minimized the risk of missing data. The meta-analysis identified 28 studies that enrolled worldwide-distributed participants. Both the adjusted and crude effect estimates were analyzed and demonstrated consistent results.

The confidential intervals were narrow, suggesting the precision of pooled results [61]. For adjusted data, most of the studies had full adjustment for confounders. The subtypes of non-insulin therapy, including oral drug and non-drug treatment, were analyzed separately. The between-study heterogeneity was intensively explored by sensitivity, subgroup, and meta-regression analyses. Besides, no publication bias was detected among the selected studies.

We were aware of the limitations of this meta-analysis. Our findings mainly relied on cross-sectional data; and as such, the causal and temporal relationship between insulin use and depression could not be established. Some studies have small sample size, which may influence the statistical power. Several studies have reported the response rates. The unmeasured differences between respondents and nonrespondents may potentially influence the pooled results. Most of the studies used self-reported scales rather than clinical interview-based assessments to identify depression. Prevalence of depression was generally much higher using the self-reported scales than standardized diagnostic interviews [20, 62]. Furthermore, 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. Moreover, background oral anti-diabetic drug uses in insulin group might affect the association of insulin use with the risk of depressive syndromes, while this information was not available in most of the included studies. In addition, although subgroup analyses based on several factors were conducted, substantial residual heterogeneity was observed in numerous subsets. These results were restricted due to uncontrolled baseline characteristics of included patients and studies. Finally, the impact of the total number of daily insulin injections with depression development was included only in few studies, and these contributed as potential confounders in patients who received insulin therapy and with progression of depression.

CONCLUSIONS

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

Acknowledgments

None.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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.

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Figure legends

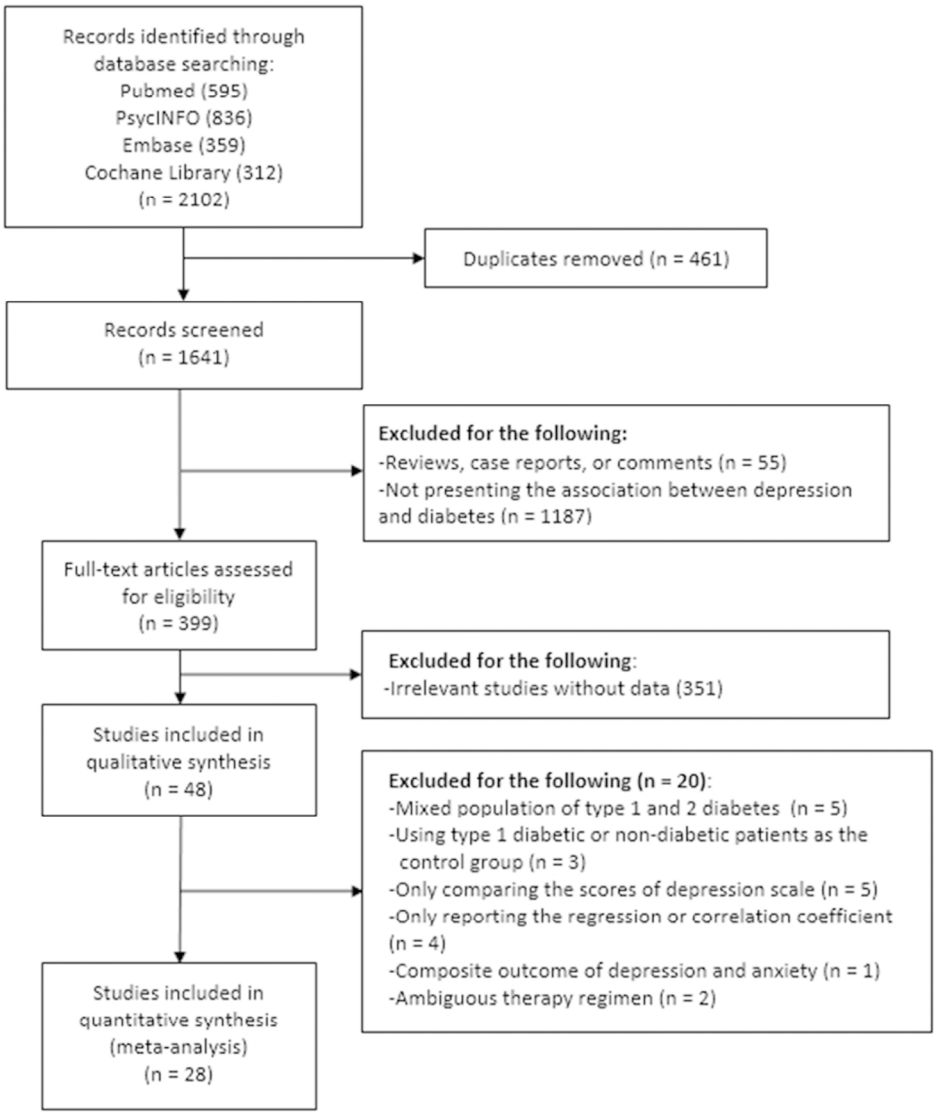
Figure 1. The selection process for eligible studies.

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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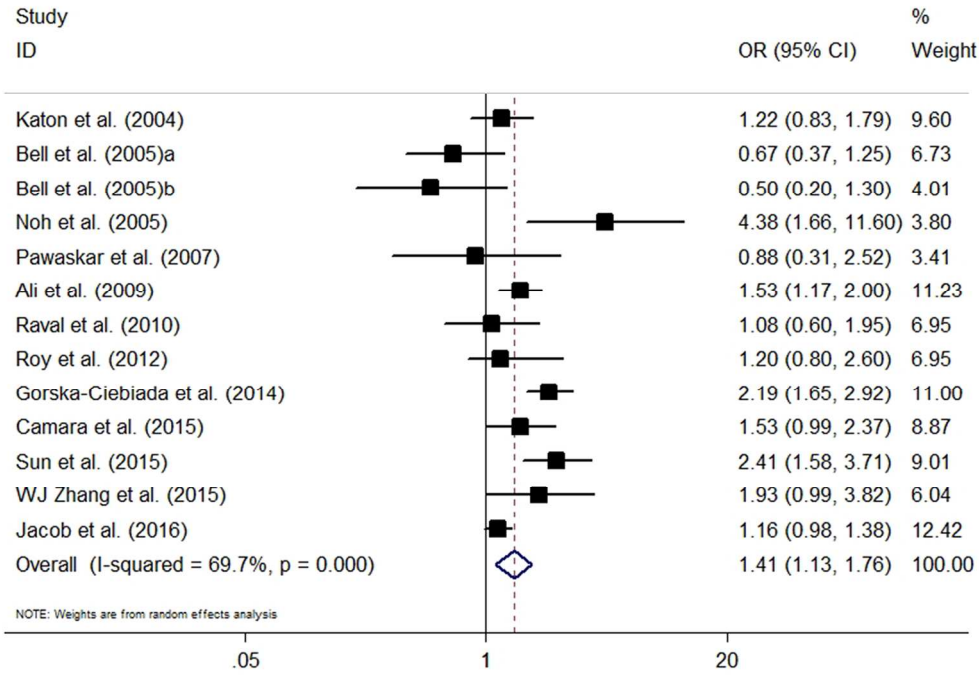

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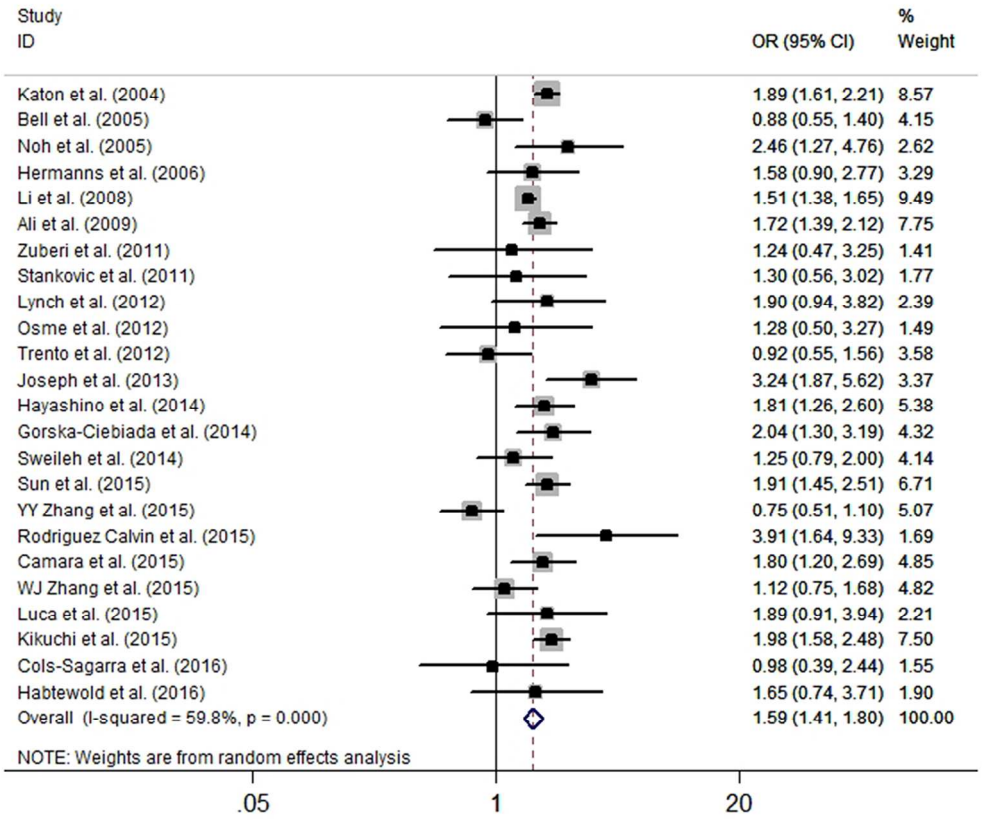

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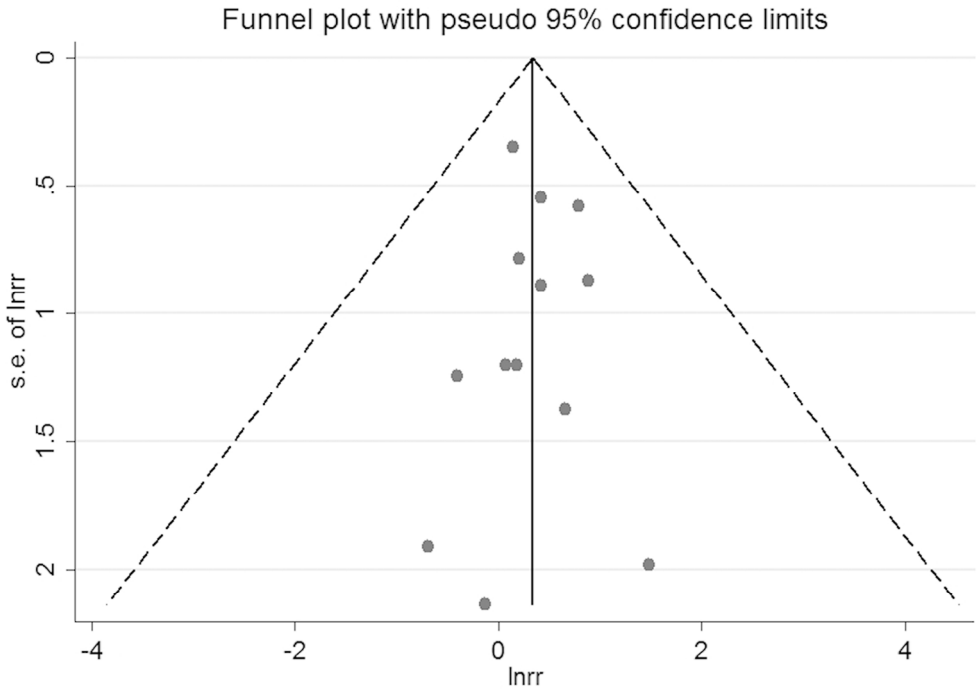

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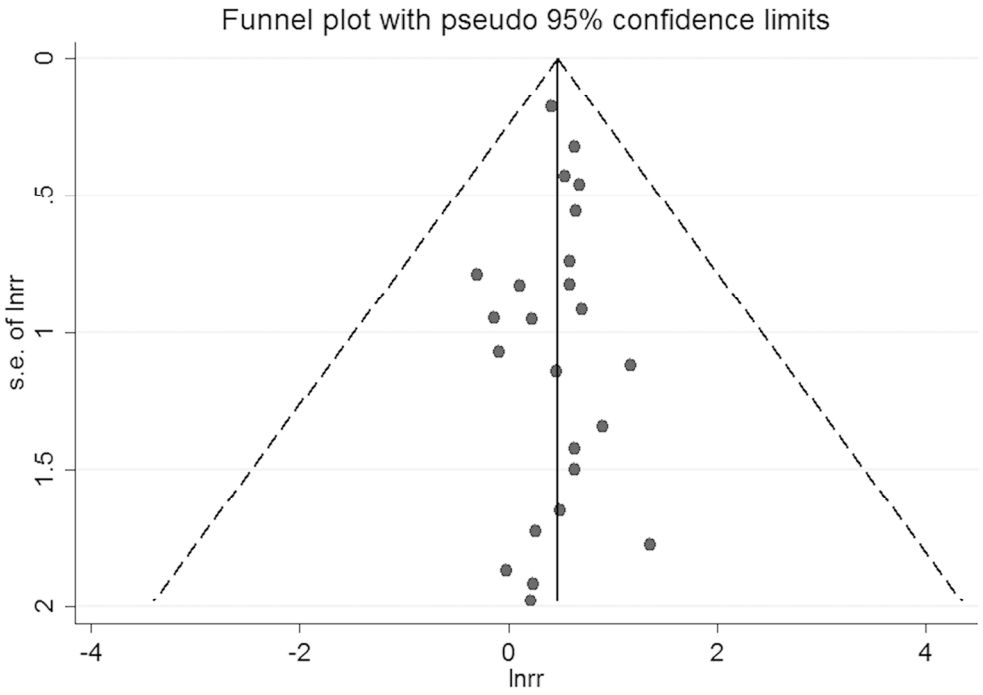

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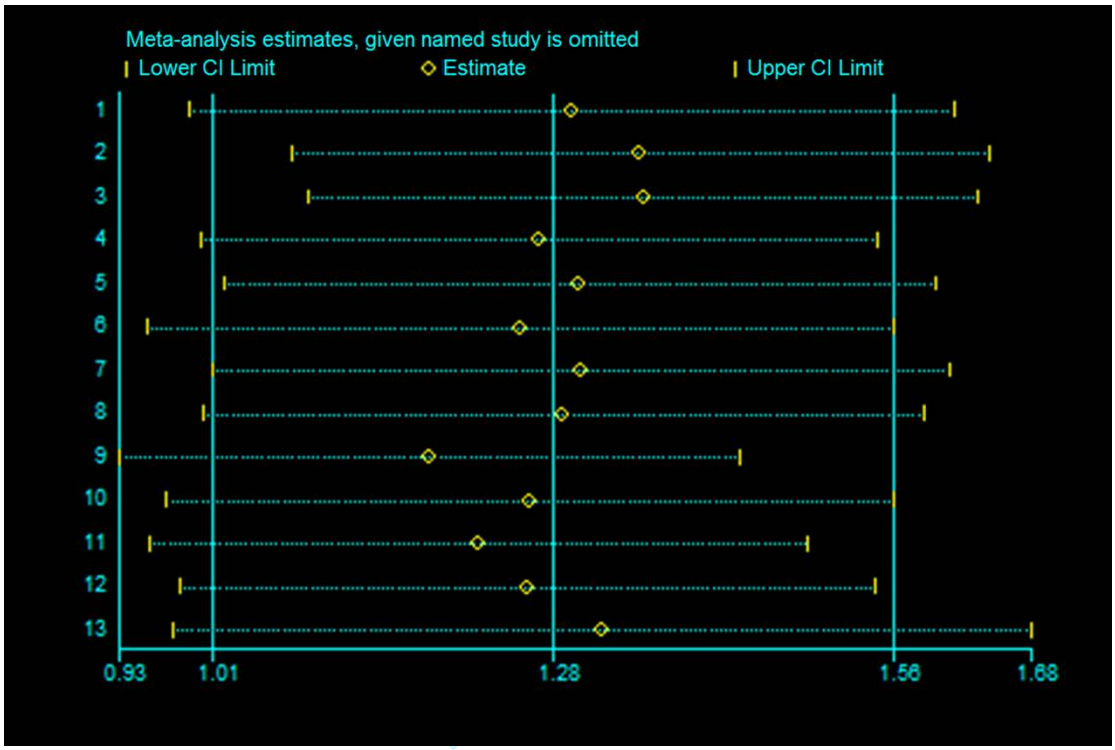
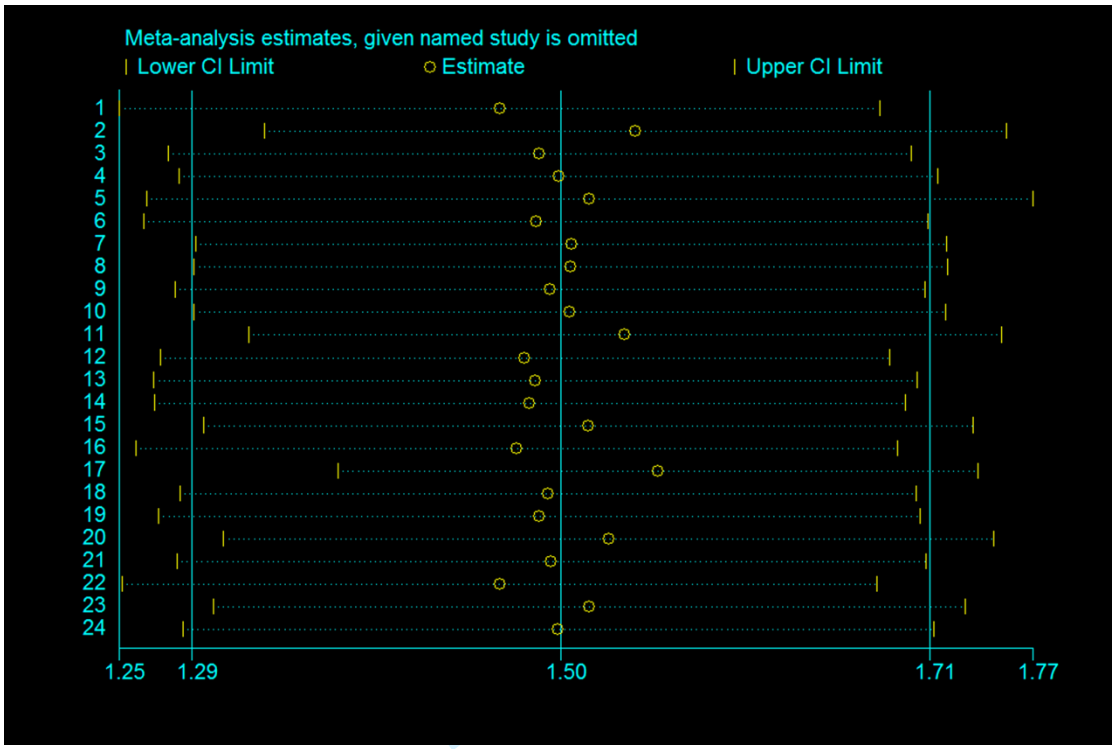
Supplementary Figure S1. Sensitivity analysis for adjusted data



Supplementary Figure S2. Sensitivity analysis for crude data



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