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

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ABSTRACT

Objectives Several patients with type 2 diabetes mellitus (T2DM) 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. A random-effects model was used for meta-analysis. The adjusted and crude data were analysed.

Results Twenty-eight studies were included. Of these, 12 studies presented with adjusted ORs. Insulin therapy was significantly associated with increased risk of depression (OR=1.41, 95% CI 1.13 to 1.76, p=0.003). Twenty-four studies provided crude data. Insulin therapy was also associated with an odds for developing depression (OR=1.59, 95% CI 1.41 to 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 to 1.86, p=0.008) and crude (OR=1.61, 95% CI 1.35 to 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.

Strengths and limitations of this study

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

INTRODUCTION

Diabetes and depression are major global public health problems, and both of these are likely to be among the five leading causes of disease burden by 2030.[1] Approximately 90% of diabetic patients was type 2 diabetes (T2DM).[2] Recently, a bidirectional link between T2DM and depression has been recognised.[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's quality of life.[6 7] Growing evidence has shown that T2DM and depression may share similar lifestyle factors and biological origins.[3]

T2DM is a chronic and progressive disease characterised by insulin resistance and dysfunction of pancreatic islet β cells.[8 9] For patients with T2DM, insulin is the cornerstone of treatment for lowering glucose and glycated hemoglobin (HbA1c) concentrations.[10] Although the optimal timing and indications for insulin therapy remain controversial,[11–13] most of the patients inevitably require insulin therapy to attain adequate glycaemic control in the natural history of T2DM.[11 14]

However, insulin treatment seems to be less popular than oral hypoglycaemic medications. Approximately 25% of the patients with T2DM are reluctant to take insulin as the 'last-resort' option.[15] Some patients may experience considerable psychological disorders with the transition from oral antidiabetic drugs to insulin. Additionally, depressive symptoms were more commonly seen in patients who undergo more frequent insulin injections per day.[16] However, the correlations between insulin use and depression among previous studies were inconsistent. Several studies have demonstrated a positive correlation,[17–19] whereas other studies have the opposite result.[20–22] Besides, these

studies varied in the 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 patients with T2DM.

METHODS

Patient and public involvement

No patients were involved in the 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 computerised 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 online 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 antidiabetic drug, diet or no treatment) among patients with T2DM. (2) Reported adjusted/unadjusted 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 and the Centre for Epidemiologic Studies–Depression Scale were used.[24] The diagnostic interviews were based on the criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (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 patients with T2DM and patients without T2DM. (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 that reported only mean and SD 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 men, depression diagnostic criteria, compared groups and adjustment of effect estimates. The unadjusted and adjusted effect estimates and 95% CIs were directly extracted or indirectly calculated. The degree of adjustment for confounders were categorised as: '+' for age and/or sex only; '++' for those with further adjusted for more than two standard sociobehavioural risk factors (ie, education, race, marital status, insurance, exercise, occupation, smoking status, alcohol consumption, family history of diabetes and body mass index); '+++' for those with +2 or more clinical factors, including dyslipidaemia, 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 8 points to each study, with ≤6 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 patients with T2DM, 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 Cochran's Q statistics and I^2 values. A value of $p<0.05$ 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 low, moderate and high heterogeneity, respectively.[28] To weigh up the relative influence of each individual study, sensitivity analysis was performed by excluding one study at a time and assessing 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 antidiabetic 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 (7/8 or <7). Publication bias was assessed by Egger's and Begg's 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 (V.12.0; StataCorp, College Station, Texas, USA). A p value < 0.05 was considered to be statistically significant.

RESULTS

Study selection

A total of 2102 records were identified including 595 articles from Pubmed, 836 articles from PsycINFO, 359 articles from Embase and 312 articles from Cochrane

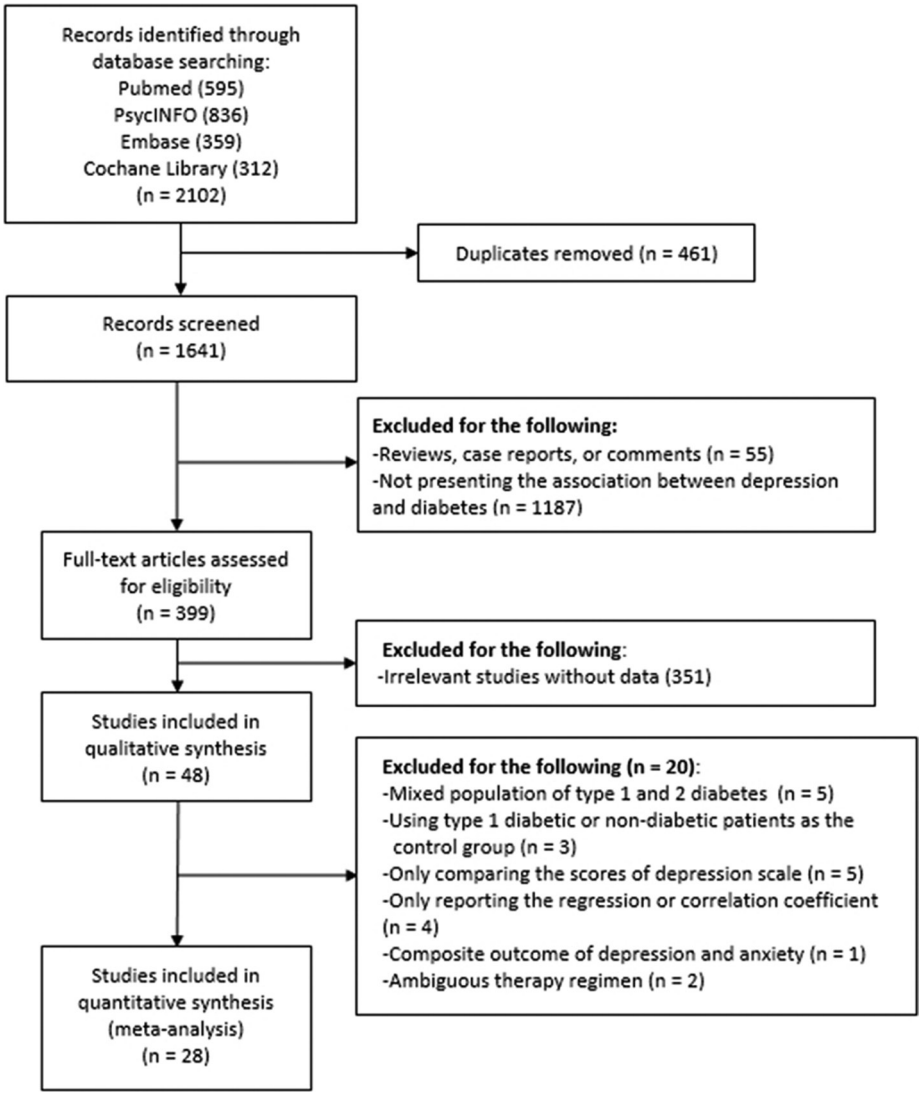

Figure 1 The selection process for eligible studies.

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 five studies enrolling mixed patients with type 1 diabetes and patients with T2DM, three studies comparing depression between DM and non-DM patients, four studies comparing the mean or median scores of depression questionnaire, four studies reporting the regression or correlation coefficient, one study presenting a mixed outcome of depression and anxiety, and two 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

Except for 1 prospective cohort study,[31] most of the 28 studies pooled in the meta-analysis were cross-sectional. A worldwide distribution was displayed, including 5 US studies, 8 European studies, 10 Asian studies, 2 African studies, 1 South-American study, and 1 study of a mixed 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] five studies reported adjusted ORs,[31 36–39] and unadjusted ORs were retrieved from 16 studies.[18 40–54] Descriptive data of the included studies are summarised in table 1. In quality assessment, all studies had low to moderate risk of bias, with scores ranging from 6 to 8. The items least satisfied were the control of confounding factors (12/28) and the report of response rates or follow-up data (10/28), (table 2).

Meta-analysis of adjusted data

The adjusted ORs for comparison of depression between insulin-treated 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 to 1.76, p=0.003). Significantly high heterogeneity was revealed (I^2=69.7%, p<0.001) (figure 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*[21]	Cross-sectional	Community	4193	65	USA	51	20.5	PHQ-9	Insulin versus 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*[20]	Cross-sectional	Community	696	74	USA	50.7	15.8	CES-D	Insulin versus oral medication; insulin versus non-drug	Adjusted	Age, sex, ethnicity, education, marital status, income, diabetes duration, number of medications, BMI, HbA1c, chronic conditions, PCS Score
Noh *et al*[17]	Hospital-based	Hospital	204	53	Korean	53	32.4	BDI	Insulin versus 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*[40]	Cross-sectional	Hospital	236	52.2	Germany	60.6	33	BDI; CES-D	Insulin versus non-insulin	Unadjusted	NA
Pawaskar *et al*[31]	Prospective cohort	Medicare Health Maintenance Organisation	792	72	USA	44	17.3	CES	Insulin versus sulfonylurea	Adjusted	Age, sex, number of prescriptions, antidiabetic medication, perceived health status, health-related quality of life, number of hospitalisations, ER visits
Li *et al*[18]	Cross-sectional	Surveillance Programme	16 651	≥18	USA	42	14.4	PHQ	Insulin versus non-insulin	Unadjusted	NA
Ali *et al*[33]	Cross-sectional	Hospital	3845	NA	Mixed (South Asia and UK)	52.8	9.3	Medical records	Insulin versus non-insulin	Adjusted	Age, gender, comorbidities, complications, insulin and oral anti-diabetic medication use, BMI, HbA1c, duration of diabetes and deprivation

Continued

Table 1 Continued

Author (year)	Design	Study setting	No. of patients	Mean age, years	Country	Male, %	Depression prevalence, %	Depression assessment	Compared groups	Source of estimates	Adjusted factors
Raval *et al*[36]	Cross-sectional	Hospital	300	54	India	49	41	PHQ-9	Insulin versus non-insulin	Adjusted	Age, gender, obesity, diabetic complications, blood pressure, duration of disease, income, education, BMI, HbA1c, diabetic complications, dyslipidaemia, number of medicines
Zuberi *et al*[42]	Cross-sectional	Hospital	286	52	Pakistan	39.2	50	HADS	Insulin versus oral medication	Unadjusted	NA
Stanković *et al*[41]	Cross-sectional	Hospital	90	55.5	Serbia	34.4	51.1	PHQ, BDI or interview	Insulin versus oral medication	Unadjusted	NA
Lynch *et al*[43]	Cross-sectional	Hospital	201	NA	USA	27.4	19.9	CES-D	Insulin versus non-insulin	Unadjusted	NA
Osme *et al*[44]	Cross-sectional	Outpatient clinic	138	≥30	Brazil	27.5	44.6	HAD	Insulin versus non-insulin	Unadjusted	NA
Trento *et al*[45]	Cross-sectional	Outpatient clinic	498	67.6	Italy	52.6	14.2	ZSDS	Insulin versus non-insulin	Unadjusted	NA
Roy *et al*[37]	Cross-sectional	Outpatient clinic	417	53.2	Bangladesh	50.6	34	PHQ-9	Insulin versus oral medication+diet; insulin+oral medication versus oral medication+diet	Adjusted	Age, gender, education, income, region, CVD, hypertension, diabetic complications, BMI, HbA1c
Joseph *et al*[46]	Cross-sectional	Hospital	230	53.6	India	51.7	45.2	PHQ-9	Insulin versus oral medication	Unadjusted	NA
Hayashino *et al*[47]	Cross-sectional	Hospital	3573	66	Japan	61.1	3.4	PHQ-9	Insulin versus oral medication or diet	Unadjusted	NA
Gorska-Ciebiada *et al*[34]	Cross-sectional	Outpatient clinic	276	74	Poland	46	29.7	GDS	Insulin versus oral medication	Adjusted	Age, sex, education, marital status, smoking, physical activity, duration of diabetes, BMI, HbA1c, lipid levels, diabetic complications, previous HA or use of HA drugs, hyperlipidaemia, number of comorbid conditions, hypoglycaemia
Sweileh *et al*[48]	Cross-sectional	Hospital	294	60	Palestine	44.2	40.2	BDI	Insulin versus non-insulin	Unadjusted	NA
YY Zhang *et al*[52]	Cross-sectional	Hospital	2538	56.4	China	53	6.1	PHQ-9	Insulin versus oral drugs	Unadjusted	NA

Continued

Table 1 Continued

Author (year)	Design	Study setting	No. of patients	Mean age, years	Country	Male, %	Depression prevalence, %	Depression assessment	Compared groups	Source of estimates	Adjusted factors
Rodriguez Calvin *et al*[51]	Cross-sectional	Hospital	275	64.5	Spain	56.4	32.7	BDI	Insulin versus oral medication	Unadjusted	NA
Camara *et al*[35]	Cross-sectional	Outpatient clinic	491	58	Guinea	37	34.4	HADS	Insulin versus oral medication	Adjusted	Age, HbA1c, hypertension, BMI, residence zone, socioeconomic status
Sun *et al*[39]	Cross-sectional	Community	229 047	57.4	China	34.4	5.9	PHQ-9	Insulin versus oral medication or diet	Adjusted	Age, sex, BMI, HbA1c, smoking, alcohol, physical activity, education, occupation, marital status, self-report cardiometabolic disorders, diabetes treatment, diabetes duration
WJ Zhang *et al*[32]	Cross-sectional	Hospital	412	59.8	China	50.2	5.7	BDI	Insulin versus 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*[50]	Cross-sectional	Hospital	128	64.7	Italy	58.6	50.8	HAM-D	Insulin versus oral medication or diet	Unadjusted	NA
Kikuchi *et al*[49]	Cross-sectional	Community	4218	65.5	Japan	57.1	10.6	CES-D	Insulin versus non-insulin	Unadjusted	NA
Jacob *et al*[38]	Cross-sectional	Community	90 412	65.5	Germany	50.2	30.3	Medical records	Insulin versus non-insulin	Adjusted	Age, gender, insurance, diabetic complications, CVD, HbA1c
Cols-Sagarra *et al*[53]	Cross-sectional	Community	411	70.8	Spain	46.2	29.2	PHQ-9	Insulin versus oral medications or diet	Unadjusted	NA
Habtewold *et al*[54]	Cross-sectional	Hospital	276	44	Ethiopia	47	44.7	PHQ-9	Insulin versus oral medication	Unadjusted	NA

BDI, Beck Depression Inventory; BMI, body mass index; CES-D, Centre for Epidemiologic Studies-Depression; CVD, cardiovascular disease; DM, diabetes mellitus; ER, emergency room; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; IHD, ischaemic heart disease; PCS, Physical Component Summary Score; PHQ, Patient Health Questionnaire; 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*[21]	1	1	1	1	1	1	1	1	8
Bell *et al*[20]	1	1	1	1	1	1	1	0	7
Noh *et al*[17]	1	0	1	1	1	1	1	0	6
Hermanns *et al*[40]	1	1	1	1	1	0	1	0	6
Pawaskar *et al*[31]	1	1	1	1	1	1	1	1	7
Li *et al*[18]	1	1	1	1	1	0	1	0	6
Ali *et al*[33]	1	1	1	1	1	1	1	0	7
Raval *et al*[36]	1	1	1	1	1	1	1	0	7
Zuberi *et al*[42]	1	1	1	1	1	0	1	1	7
Stanković *et al*[41]	1	1	1	1	1	0	1	0	6
Lynch *et al*[43]	1	1	1	1	1	0	1	1	7
Osme *et al*[44]	1	1	1	1	1	0	1	0	6
Trento *et al*[45]	1	1	1	1	1	0	1	0	6
Roy *et al*[37]	1	1	1	1	1	1	1	1	8
Joseph *et al*[46]	1	1	1	1	1	0	1	0	6
Hayashino *et al*[47]	1	1	1	1	1	0	1	0	6
Gorska-Ciebiada *et al*[34]	0	1	1	1	1	1	1	0	6
Sweileh *et al*[48]	1	1	1	1	1	0	1	1	7
YY Zhang *et al*[52]	1	1	1	1	1	0	1	1	7
Rodriguez Calvin *et al*[51]	1	1	1	1	1	0	1	1	7
Camara *et al*[35]	1	1	1	1	1	0	1	0	6
Sun *et al*[39]	1	1	1	1	1	1	1	0	7
WJ Zhang *et al*[32]	1	1	1	1	1	1	1	1	8
Luca *et al*[50]	1	1	1	1	1	0	1	0	6
Kikuchi *et al*[49]	1	1	1	1	1	0	1	0	6
Jacob *et al*[38]	1	1	1	1	1	0	1	0	6
Cols-Sagarra *et al*[53]	1	1	1	1	1	0	1	0	6
Habtewold *et al*[54]	1	1	1	1	1	0	1	1	7

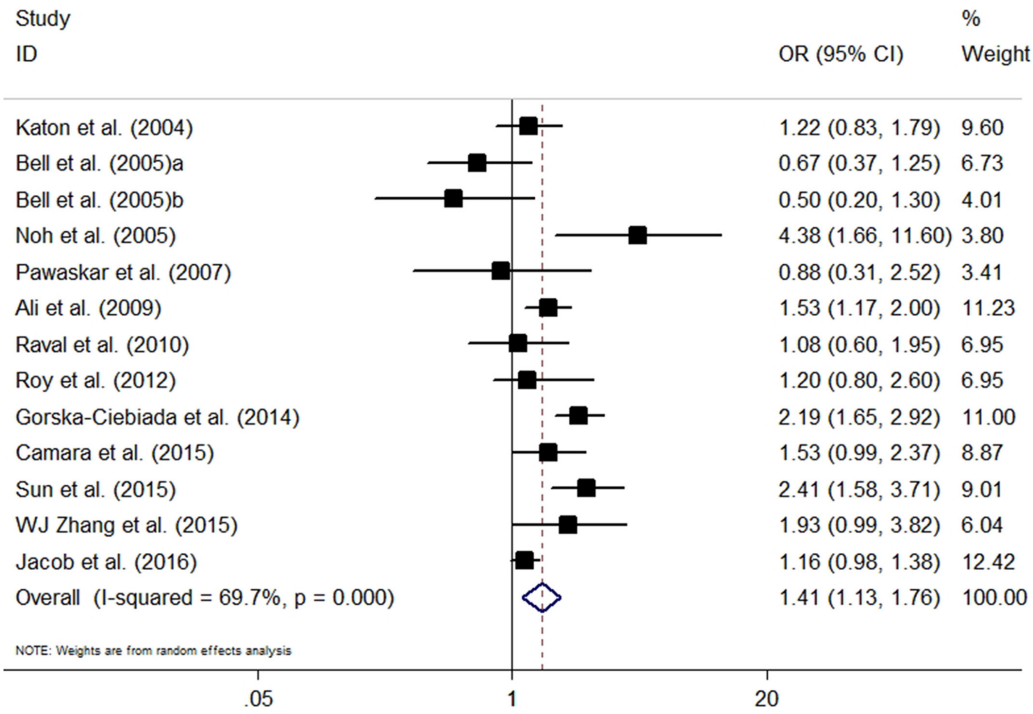

Figure 2 The pooled adjusted OR for the risk of depression in insulin-prescribed patients compared with those without insulin therapy.

The results of the sensitivity analysis, which was done by excluding studies one by one, might vary when several included studies were excluded (online supplementary figure S1). To identify the sources of heterogeneity, we performed subgroup analyses based on several important confounding factors. Six studies, in particular, compared insulin with oral antidiabetic drugs and showed that insulin therapy was significantly associated with increased risk of depression (OR=1.42, 95% CI 1.08 to 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 to 2.03, p=0.745). 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. The association was significant for the subgroups of full adjustment (+++), Asian studies, self-report questionnaires, sample size ≥1000, mean age <60.0 years, percentage male <50.0%, prevalence of depression over 20% and NOS <6 (table 3). Meta-regression analyses indicated a lack of effect measures modification by sample size (p=0.93), mean age (p=0.17), percentage male (p=0.28) or prevalence of depression (p=0.75).

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 antidiabetic drugs, and insulin vs non-insulin treatment). Data that compared insulin and non-insulin therapies were preferred. The pooled results showed that patients with T2DM on insulin therapy were associated with an increased risk of depression compared with those on non-insulin treatment (OR=1.59, 95% CI 1.41 to 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 (online supplementary figure S2).

Seventeen studies compared insulin with oral antidiabetic drugs and showed a significant association for the risk of depression (OR=1.61, 95% CI 1.35 to 1.93, p<0.001). For six 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 to 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, there was a significant association between insulin use and depression among all subgroups except in 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.

Publication bias

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

DISCUSSION

This is the first meta-analysis that estimated the magnitude of association between insulin therapy and depression.

Table 3 Subgroup analyses for 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 versus oral drugs	6	1.42 (1.08 to 1.86)	<0.05	71.3%	<0.05	0.28
Insulin versus non-drugs	2	0.87 (0.37 to 2.03)	>0.05	66.5%	0.08	
Degree of adjustment						
+++	10	1.43 (1.08 to 1.89)	<0.05	68.9%	<0.05	0.44
++	2	1.24 (0.98 to 1.55)	>0.05	25.3%	0.25	
Region						
USA	4	0.86 (0.57 to 1.31)	>0.05	36.4%	0.19	0.12
Asia	5	1.81 (1.18 to 2.79)	<0.05	59%	0.05	
Europe	2	1.58 (0.85 to 2.94)	>0.05	92.9%	<0.05	
Africa	1	1.53 (0.99 to 2.37)	>0.05	–	–	
Identification of depression						
Self-report questionnaire	10	1.42 (1.06 to 1.91)	<0.05	68.9%	<0.05	0.69
Medical records	2	1.31 (1.00 to 1.71)	>0.05	65.6%	0.09	
Sample size						
≥1000	4	1.46 (1.10 to 1.94)	<0.05	73.1%	<0.05	0.72
<1000	8	1.34 (0.93 to 1.93)	>0.05	70%	<0.05	
Mean age, years						
≥60.0	5	1.12 (0.77 to 1.62)	>0.05	78.8%	<0.05	0.08
<60.0	6	1.74 (1.24 to 2.43)	<0.05	50.8%	0.07	
Percentage male (%)						
≥50.0	7	1.26 (0.97 to 1.63)	>0.05	62.4%	<0.05	0.14
<50.0	5	1.71 (1.25 to 2.35)	<0.05	53.9%	0.07	
Prevalence of depression						
≥20%	7	1.48 (1.12 to 1.96)	<0.05	71.3%	<0.05	0.53
<20%	5	1.25 (0.80 to 1.95)	>0.05	72.7%	<0.05	
NOS						
7 or 8	8	1.25 (0.94 to 1.66)	>0.05	60.0%	<0.05	0.19
<7	4	1.79 (1.14 to 2.80)	<0.05	84.6%	<0.05	

NOS, Newcastle-Ottawa Scale.

The pooled data of adjusted ORs proved that patients with T2DM on insulin treatment were associated with the prevalence of depressive syndromes compared with 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. The adjusted (OR=1.42) and unadjusted data (OR=1.61) showed that insulin users were associated to a 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 homogeneity of the pooled effect estimates. The prevalence of depression could differ based on different ethnicities.[55] In subgroup analyses of adjusted data, we found significant results for Asian studies. Non-significant results were shown for studies with a sample size below 1000, suggesting that the results were unstable for a 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 a 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 because younger patients were associated

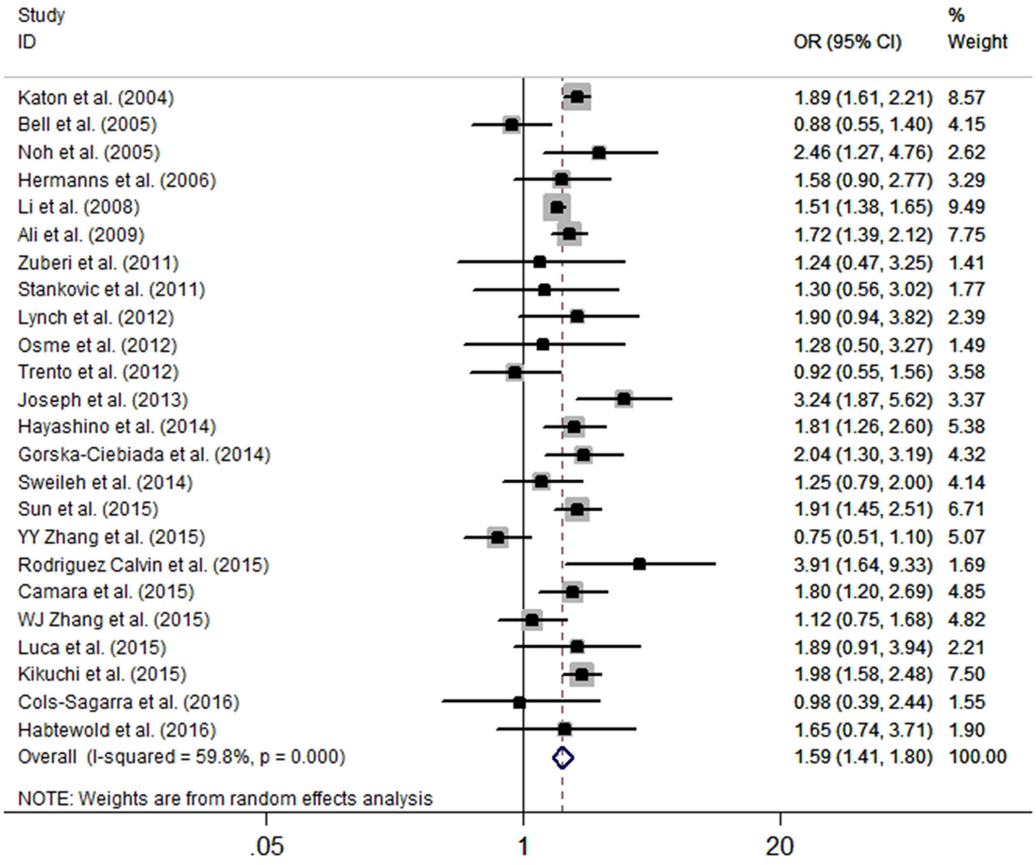

Figure 3 The pooled crude OR for the risk of depression in insulin-prescribed patients compared with those without insulin therapy.

with a higher prevalence of depression, and women receiving insulin therapy might be under greater risk of depression compared with men.

The mechanisms that link diabetes and depression were complex and are still unclear. Depression and T2DM could develop in parallel through shared biological processes. The involved pathways include the innate inflammatory response, the hypothalamic-pituitary-adrenal axis, circadian rhythms and insulin resistance.[3] Although the overall prevalence of depression is high in patients with diabetes, the Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND) Trial reported that it was not so in patients with 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 12-month follow-up period.[57] In accordance with these findings, we confirmed that insulin therapy was associated with increased prevalence of depression. Patients on insulin therapy had less endogenous insulin and were therefore more susceptible 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 T2DM. The negative attitude of patients towards insulin therapy may contribute to the delay in insulin initiation, prolonged duration of hyperglycaemia and increased risk of diabetic complications.[58] Psychological insulin resistance has been defined as psychological opposition towards insulin treatment in both patients with diabetes and their prescribers. They may display fear of insulin injection and self-testing, complex regimen, hypoglycaemia 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 psychological 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 minimised the risk of missing data. The meta-analysis identified 28 studies that enrolled participants distributed worldwide. Both the adjusted and crude effect estimates were analysed and demonstrated consistent results. The CIs 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 analysed 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.

Table 4 Subgroup analyses for studies reporting 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 versus oral drugs	17	1.61 (1.35 to 1.93)	<0.05	62.6%	<0.05	0.49
Insulin versus non-drugs	6	1.89 (1.25 to 2.88)	<0.05	68.2%	<0.05	
Region						
USA	4	1.53 (1.21 to 1.93)	<0.05	75.4%	<0.05	0.31
Asia	9	1.60 (1.22 to 2.10)	<0.05	75.4%	0.05	
Europe	7	1.59 (1.13 to 2.22)	<0.05	45.3%	<0.05	
Africa	2	1.77 (1.23 to 2.54)	<0.05	0.0	0.85	
South America	1	1.28 (0.50 to 3.27)	>0.05	–	–	
Sample size						
≥1000	7	1.64 (1.39 to 1.93)	<0.05	77.5%	<0.05	0.71
<1000	17	1.56 (1.27 to 1.91)	<0.05	46.7%	<0.05	
Mean age						
≥60.0	10	1.60 (1.30 to 1.97)	<0.05	61.8%	<0.05	0.92
<60.0	10	1.57 (1.18 to 2.09)	<0.05	68.0%	<0.05	
Percentage male (%)						
≥50.0	13	1.59 (1.29 to 1.96)	<0.05	75.1%	<0.05	0.82
<50.0	11	1.55 (1.43 to 1.68)	<0.05	0.0	0.71	
Prevalence of depression						
≥20%	14	1.84 (1.59 to 2.12)	<0.05	11.7%	0.33	<0.05
<20%	10	1.43 (1.19 to 1.70)	<0.05	74.0%	<0.05	
Newcastle-Ottawa Scale						
7 or 8	11	1.45 (1.16 to 1.82)	<0.05	72.3%	<0.05	0.22
<7	13	1.72 (1.47 to 2.00)	<0.05	42.8%	0.05	

Some studies have a small sample size, which may influence the statistical power. Several studies have reported the response rates. The unmeasured differences between respondents and non-respondents may potentially influence the pooled results. Most of the studies used self-reported scales rather than clinical interview-based

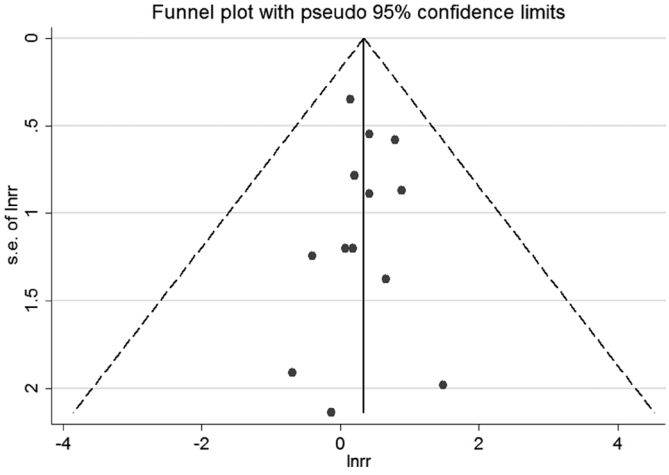

Figure 4 The funnel plot for studies reporting adjusted ORs. s.e. of lnrr, standard error of lnrr.

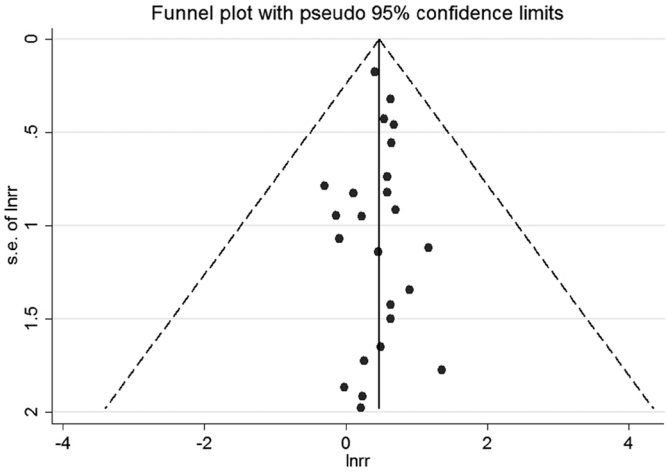

Figure 5 The funnel plot for studies presenting crude ORs.

assessments to identify depression. Prevalence of depression was generally much higher using the self-reported scales than standardised 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 antidiabetic drug uses in the insulin group might affect the association of insulin use with the risk of depressive syndromes, although 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 a few studies, and these presented as potential confounders in patients who received insulin therapy and with progression of depression.

CONCLUSIONS

In conclusion, patients with T2DM who were prescribed insulin were associated with depressive syndromes. For insulin users, careful monitoring of depressive symptoms should be incorporated in the management of the disease. Intensified psychological and education programmes should be carried out to prevent depressive illness after insulin initiation in primary care settings.

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