



# The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies

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## Abstract

**Aims** Depression is a common co-morbidity in patients with type 2 diabetes mellitus (T2DM). Untreated depression in these patients adversely affects self-care activities and other diabetes complications. The aim of this study is to estimate the prevalence of depression among patients with T2DM by conducting a meta-analysis of observational studies.

**Methods** MEDLINE, Web of Science, Science Direct, and Google Scholar databases were searched for all observational studies that assessed depression in T2DM. Relevant articles were searched using the combination of Medical Subject Heading (MeSH) terms of “depression”, “depressive disorder”, and “diabetes mellitus” published between January 2007 and July 2018. Random effects model was used to estimate the weighted prevalence rates and 95% CI using “metaprop program in STATA 11”.

**Results** In total, the 248 included studies (with 273 reported prevalence) identified 83,020,812 participants; of them, 23,245,827 (28%; 95% CI 27, 29) suffered from different severity levels of depressive disorders. The prevalence of depression was separately reported in 137,372 males and 134,332 females. Of them, 31,396 males (23%, 95% CI: 20, 26) and 45,673 females (34%, 95% CI: 31, 38) were depressed. Compared with global estimate, depression prevalence was lower in Europe (24%) and Africa (27%), but higher in Australia (29%) and Asia (32%). The prevalence in America was equal to the estimated prevalence in the world (28%). Depression was more common in subjects younger than 65 compared with elderlies (31% vs. 21%).

**Conclusion** Our findings demonstrated that almost one in four adults with T2DM experienced depression. Given the high prevalence of depressive disorders in diabetic patients, screening these patients for co-morbid depression and its relevant risk factors is highly recommended.

**Keywords** Co-morbidity · Depression · Prevalence · Type 2 diabetes mellitus

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Managed by Antonio Secchi.

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## Introduction

In 2017, the International Diabetes Federation (IDF) estimated that 425 million individuals worldwide were suffering from diabetes mellitus (DM), and it is expected that the number rise to 629 million in 2045 [1]. Diabetes is one of the most relevant causes of economic loss, morbidity, and early

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mortality in the world [2]. The per capita cost burden associated with diabetes is 2–4-fold greater than non-diabetic patients [3] and it is estimated that managing of co-morbid conditions accounts for a substantial proportion of the costs [3]. Diabetes is associated with several complications such as mental health-related disorders, particularly depressive disorders, which can potentially decrease the quality of life in diabetic patients [4].

The global prevalence of depression increased by 17.8% between 2005 and 2015 [5]. According to reports by the World Health Organization (WHO), 322 million people were living with depression worldwide, with a prevalence rate as high as 4.4% in 2015 [6]. Depressive disorders are defined as a persistent condition for at least 2 weeks which is accompanied by losing interest or pleasure in activities that are normally enjoyable or uncomfortable or despairing and finally lead to inability to perform daily activities [7]. According to the severity of depression symptoms, it might be mild, moderate, or severe. The estimated prevalence of co-morbid depression by self-report tools is much higher than the reported prevalence of major depressive disorders in diabetic patients (31% vs. 11.4%), indicating that a large number of patients suffer from milder depressive disorders [8]. Patients with type 2 diabetes mellitus (T2DM) are almost treble as likely to be affected by depression as the general population [8]. A meta-analysis in 2006 revealed that the prevalence of depression in diabetic patients was considerably higher than non-diabetic subjects (17.6% vs. 9.8%, respectively) and patients had higher risk for affecting by depression (OR 1.6, 95% CI 1, 2.0) [9]. The great increase in the risk of co-morbid depression in diabetic patients might be attributed to the psychosocial burden of disease (e.g., having no current job), poor social support, awareness of having a chronic diseases or its related complications and disabilities, and their consequent psychological burden [10–13].

According to the Global Burden of Diseases (GBD) reports in 2015, both diabetes and depressive disorders are among the ten leading causes of disability and diabetes rose from position eight to six and depressive disorders are the fourth leading cause of disability [5]. Unrecognized and untreated depression in diabetic patients leads to higher prevalence of depression with probably greater severity which altogether causes poor glycemic control, lower adherence to medication, higher treatment cost, and higher mortality rate [14]. Determining the number of patients suffering from concurrence T2DM and depression would be relevant for the governments and health-care providers to plan appropriate treatment strategies and decrease economic burden of disease. The aim of this study was to estimate the prevalence of depression among patients with T2DM by conducting a meta-analysis of observational studies and update the results of earlier meta-analysis in this regard published in 2006 [9]. Due to differences in psychological and

physiological experiences in patients with type 1 and type 2 diabetes, the current systematic review and meta-analysis is confined to T2DM.

## Materials and methods

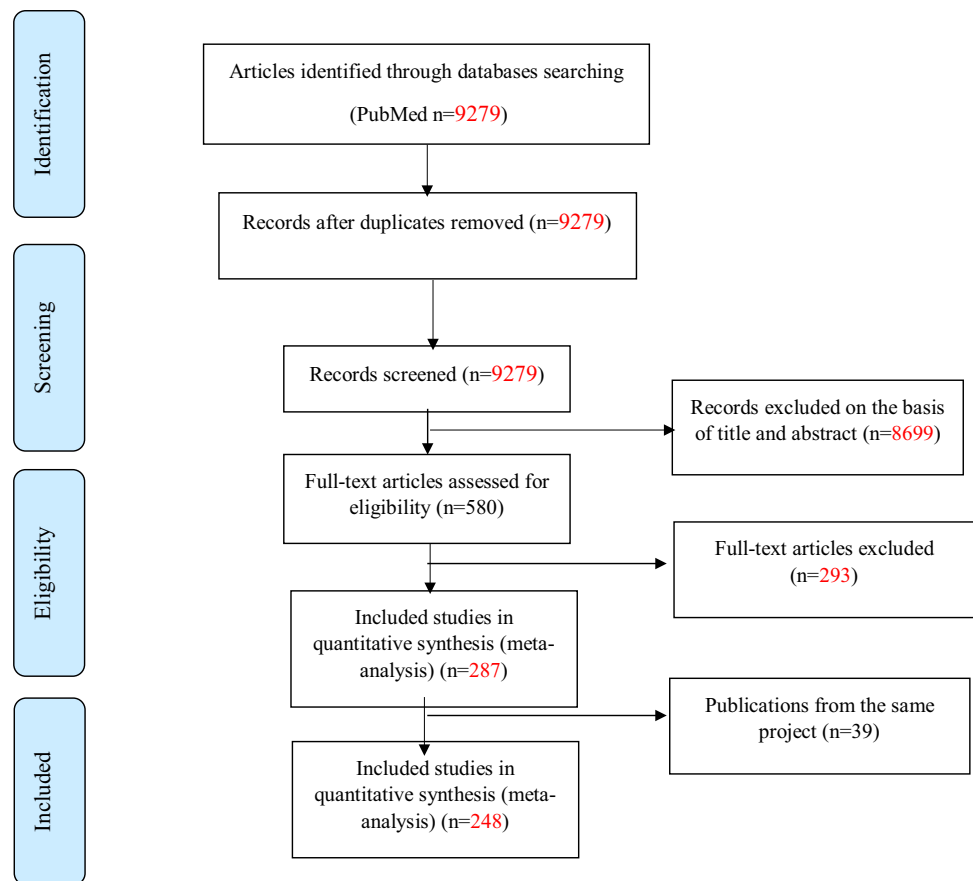
### Search strategy

This systematic review and meta-analysis was prepared and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [15]. To find potentially relevant published articles, a comprehensive search was conducted in PubMed/MEDLINE, Web of Science, Science Direct, and Google Scholar before April 2018. We did not include articles published before the year 2007, because a meta-analysis assessing the prevalence of depressive disorders in diabetic patient was published in 2006. All searches were updated using MEDLINE's alert system up to July 2018. The reference lists of relevant identified articles were reviewed for gray literature. Identified studies by our search strategies were imported into Endnote X7 (Thomson Reuters, Philadelphia, PA, USA) software and managed. Relevant articles were searched using the following combination of Medical Subject Heading (MeSH) terms and text words in PubMed: (“depression”[MeSH] OR “depression”[tiab] OR “depressions”[tiab] OR “depressive”[tiab] OR “depressive disorder”[MeSH] OR “depressive disorders”[tiab] OR “Melancholia”[tiab]) AND (“Diabetes Mellitus”[MeSH] OR “Diabetes Mellitus”[tiab] OR “diabetes”[tiab] OR “diabetic”[tiab] OR “prediabetic”[tiab] OR “glucose intolerance”[tiab]). The search terms were separated or combined using Boolean operators such as “OR” or “AND”. Totally, 8306 citations were retrieved using the search strategy (Fig. 1).

### Study selection and eligibility criteria

The process of study selection was performed by two independent reviewers (FH and MKH). Potentially, relevant articles were first determined using a preliminary evaluation of the titles and abstracts and then were further assessed using the full text of articles. Irrelevant citations were excluded applying the following criteria: (1) no original research (case reports, reviews, and letters); (2) failing to determine type of diabetes or provide prevalence of depression by type of diabetes, even if the prevalence of type 1 was very low in the study population; and (3) non-English articles when the prevalence rate of depressive disorder could not be extracted from the abstract. When there were different publications from a large observational study, only the study with the largest sample size was included.

**Fig. 1** Flow diagram of database searches and study selection



We included articles if they were original observational studies (cross section, case–control, and cohort) reporting the current or lifetime prevalence of depressive disorders identified through self-report or using validated instruments. In case–control studies, the prevalence of depressive disorders was extracted from the case group, and in cohort studies, data were extracted if the prevalence of depression was reported at baseline or other timepoints at the follow-up period. The method used to diagnosis of diabetes (self-report or medical record) was not considered as an eligibility criterion, since earlier studies have shown the reliability for self-reported diabetes as a medical record report [16]. When different articles were published from a same study, the article with the largest sample size was included in our analysis.

### Data extraction and quality assessment

Two independent reviewers extracted following information from the studies which met the inclusion criteria: the first author’s name, year of publication, country, sample size, number of depressed individuals, sex, number of male and female, mean or range of age, the instrument used to identify depression, number of depressed males and females (if available), and number of depressed cases in

different categories of depression severity (if available). In studies with no report regarding the number of depressed individuals, it was calculated manually via multiplying the prevalence of depressive disorders by the total number of study population. When the prevalence of depression was not reported in the whole population, but was separately reported in men and women, the overall prevalence was computed using weighted mean proportion. Three studies had assessed the prevalence of depression using two different validated instruments [17–19]. Since all applied instruments were highly valid and reliable, and they only varied in the classification of depression severity [20–22], which was not the aim of this study, the mean of two prevalence values was recorded as the prevalence rate for these studies. When the prevalence of depression was reported using both diagnostic method and self-reported questionnaire, values based on diagnostic method were recorded and included in analysis [213].

Two independent investigators assessed the quality of included studies. Investigators discussed their controversies and any disagreements were resolved finally by discussion and reevaluation and the decision from third investigator independently.

## Statistical analysis

To estimate pooled prevalence and corresponding 95% confidence interval (CI), weighted prevalence rates were calculated using “metaprop program” [23] in STATA version 14.0 (STATA, College Station, TX, USA). Heterogeneity of the included studies was assessed using Higgins’  $I^2$  statistic and Cochran  $Q$  test and expressed as percentage. Values of 25%, 50%, and 75% for  $I^2$  were considered as low, medium, and high levels of heterogeneity, respectively [24]. Data were pooled using random effects model due to high levels of heterogeneity among included studies [25].

Possible sources of heterogeneity were explored by sensitivity as well as subgroup analyses.

Publication bias was tested using Egger’s and Begg’s test and visual inspection of funnel plot [26]. In the existence of a bias, trim and fill analysis was conducted to detect the contribution of the bias to the overall effect.

## Results

### Search results and studies’ characteristics

The literature search (May 2005 to June 2018) identified 9279 articles. We limited our search strategy to this mentioned time, because Ali et al. have reported the prevalence of comorbid depression in patients with T2DM in their meta-analysis [9]. After excluding studies according to their title and abstract, 278 studies were retrieved for more evaluation using their full text and 248 studies met our inclusion criteria and included in the meta-analysis (Fig. 1) [10–12, 17–19, 27–271]. The characteristics of included studies and the extracted information are summarized in Supplementary Table 1. Sample size of studies ranged from 29 [101] to 82,232,151 [217]. Some eligible studies had reported more than one prevalence, and therefore, in overall, 273 reported prevalence were extracted from all 248 included studies. These studies comprised 83,020,812 participants; of them, 23,245,827 subjects suffered from different severity levels of depressive disorders. A variety of instruments were used to evaluate depression status. Most effect sizes were estimated using Personal Health Questionnaire (PHQ) ( $n=74$ ), whilst Beck’s Depression Inventory (BDI), Center for Epidemiologic Studies Depression Scale (CESD), and Hospital Anxiety and Depression Scale (HADS) were used in 44, 39, and 20 studies, respectively. Other studies assessed depression status using other validated questionnaires such as geriatric depression scale (GDS), Self-Rating Depression Scale (SDS), Kessler-10 Psychological Distress, Harvard Department of Psychiatry/National Depression Screening Day Scale (HANS), DSM IV or V, ICD, Mini-International Neuropsychiatric Interview, validated DASS-21

questionnaire (depression, anxiety and stress), Euro-D score, Major Depression Inventory (MDI), Short-CARE depression scale, Hamilton Depression Rating Scale, the Yesavage depression scale, MCS, Edinburgh Depression Scale (self-reported), Zung Self-rating Depression Scale, and WHO Five-Item Well-Being Index. Of the 273 reported prevalence, 105 reported prevalences were in Asia, 70 in Europe, 79 in America, 11 in Australia, and 7 in Africa. Three reported prevalences were extracted from abstract and the regions of studies were not identifiable [95, 183, 213]. Six studies enrolled only women [45, 108, 117, 154, 175, 197], whilst others enrolled both men and women.

### Meta-analysis and data synthesis

In the current meta-analysis, the lowest and highest prevalences were 2% (95% CI 1, 7) and 88% (95% CI 79, 93) reported in the studies by Maia et al. [158] and Czech et al. [105], respectively. The 273 included reported prevalence demonstrated that a pooled prevalence of depression among patients with T2DM in the world was 28.0% (95% CI 27, 29). To identify the potential sources of heterogeneity, subgroup analyses were done for estimating the prevalence of depression in the following categories: gender, the region of original study (based on the continent), age (<65 vs.  $\geq 65$  years), the method to assess depression status (clinical diagnosis vs. self-report), instruments used to estimate depression prevalence, in insulin- and non-insulin-dependent subjects. Nevertheless, none of these factors were identified to be statistically heterogeneity source.

The prevalence of depression was estimated to be 23%, 95% CI 20, 26% for male and 34%, 95% CI 31, 38% for female.

The prevalence of depression in Asia (prevalence = 32%; 95% CI 28, 37,  $I^2 = 99.4\%$ ) and Australia (prevalence = 29%; 95% CI 21, 39,  $I^2 = 98.8\%$ ) was higher than the world prevalence, whereas in Europe (prevalence = 24%; 95% CI 21, 26,  $I^2 = 99.8\%$ ) and Africa (prevalence = 27%; 95% CI 19, 36,  $I^2 = 99.8\%$ ), the prevalence rate was lower than the world-pooled prevalence (Fig. 2). In the USA, the prevalence of co-morbid depression was equal to the estimated prevalence in the world (prevalence = 28%; 95% CI 25, 31,  $I^2 = 99.7\%$ ). Co-morbid depression was more prevalent among diabetic females (prevalence = 34%; 95% CI 31, 38,  $I^2 = 99.3\%$ ) (Fig. 3) compared with males (prevalence = 23%; 95% CI 20, 26,  $I^2 = 98.9\%$ ) (Fig. 4). Subgroup analysis based on participants’ age demonstrated higher prevalence rate in patients younger than 65 years (prevalence = 31%; 95% CI 27, 34,  $I^2 = 99.5\%$ ) (Fig. 5) compared with those older than 65 years (prevalence = 21%; 95% CI 19, 24,  $I^2 = 99.9\%$ ) (Fig. 6). The estimated prevalence of depression was higher in studies which used self-reported methods (prevalence = 30%; 95% CI 28, 32,  $I^2 = 98.8\%$ ) in comparison with those used

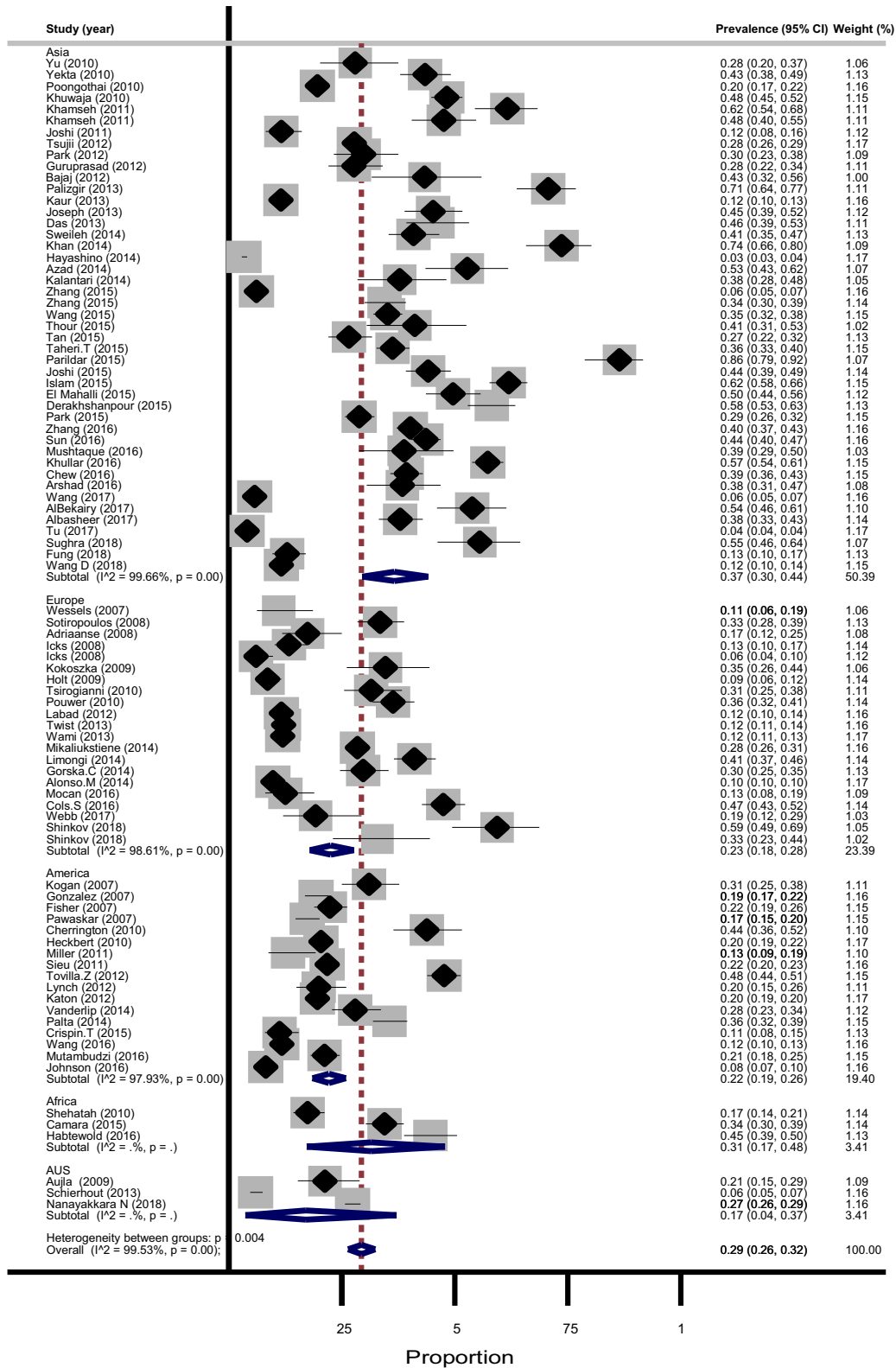


Fig. 2 Prevalence of comorbid depression in patients with type 2 diabetes stratified by the continents

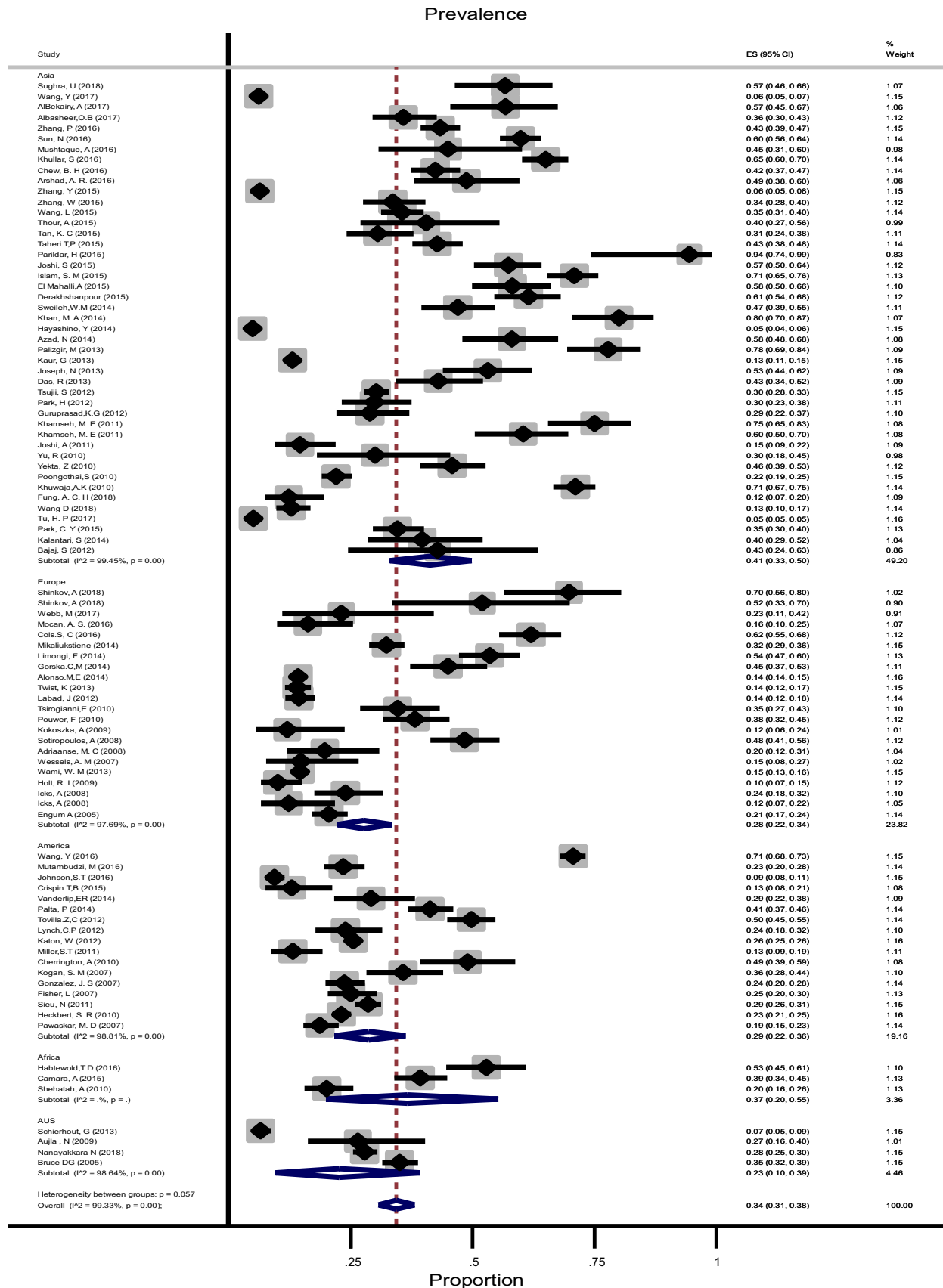


Fig. 3 Prevalence of comorbid depression in female patients with type 2 diabetes stratified by the continents

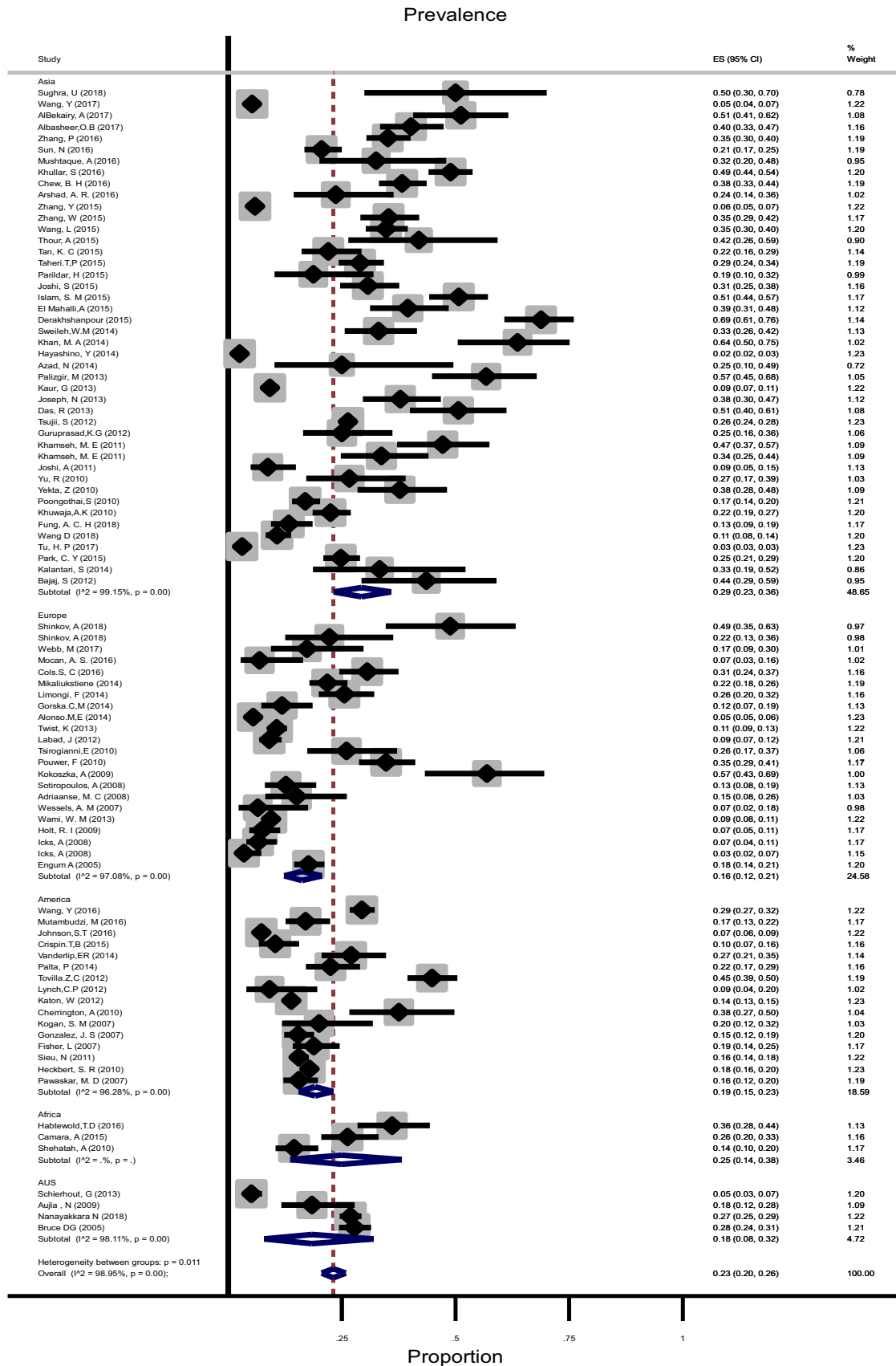


Fig. 4 Prevalence of comorbid depression in male patients with type 2 diabetes stratified by the continents

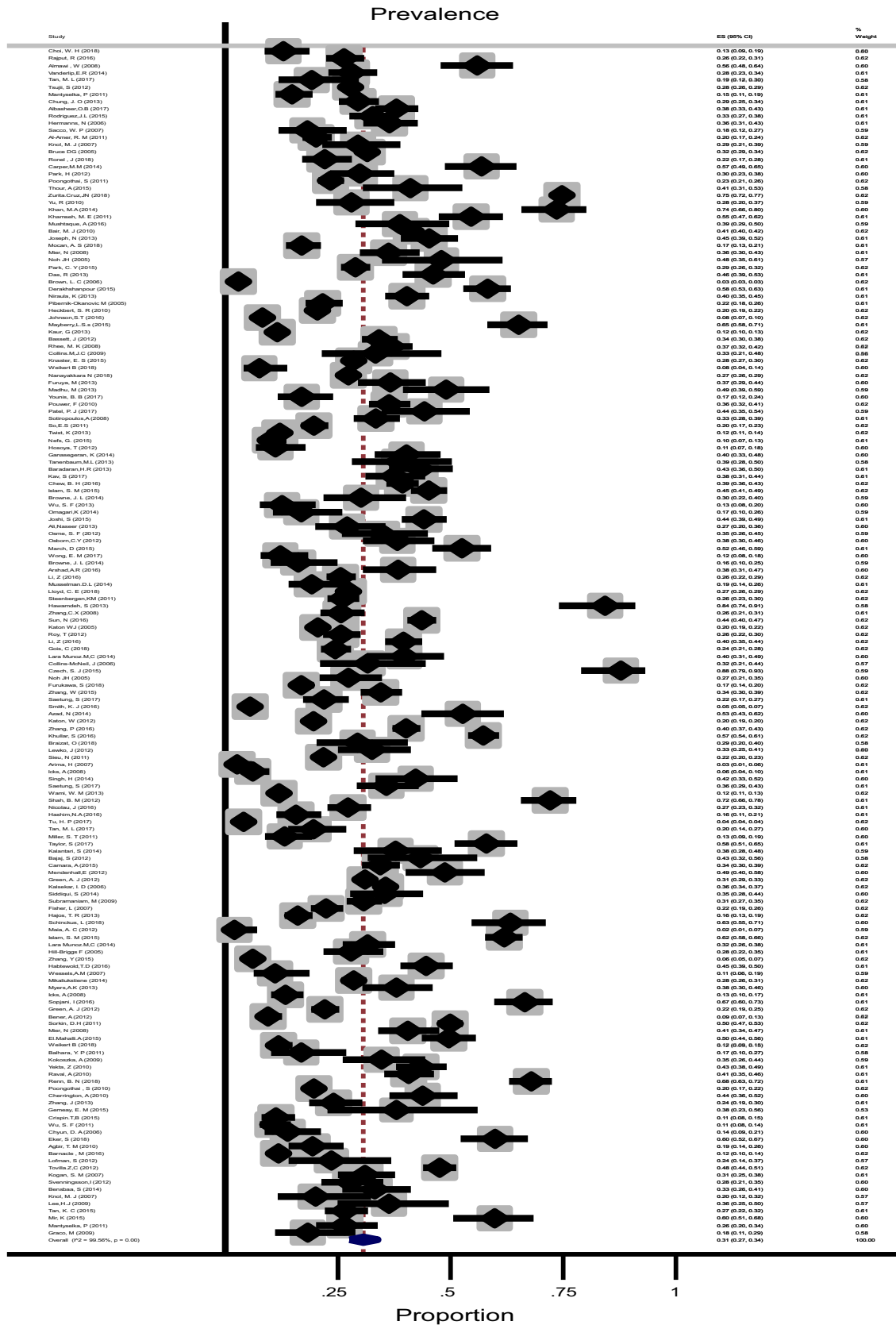


Fig. 5 Prevalence of comorbid depression in patients with type 2 diabetes younger than 65 years



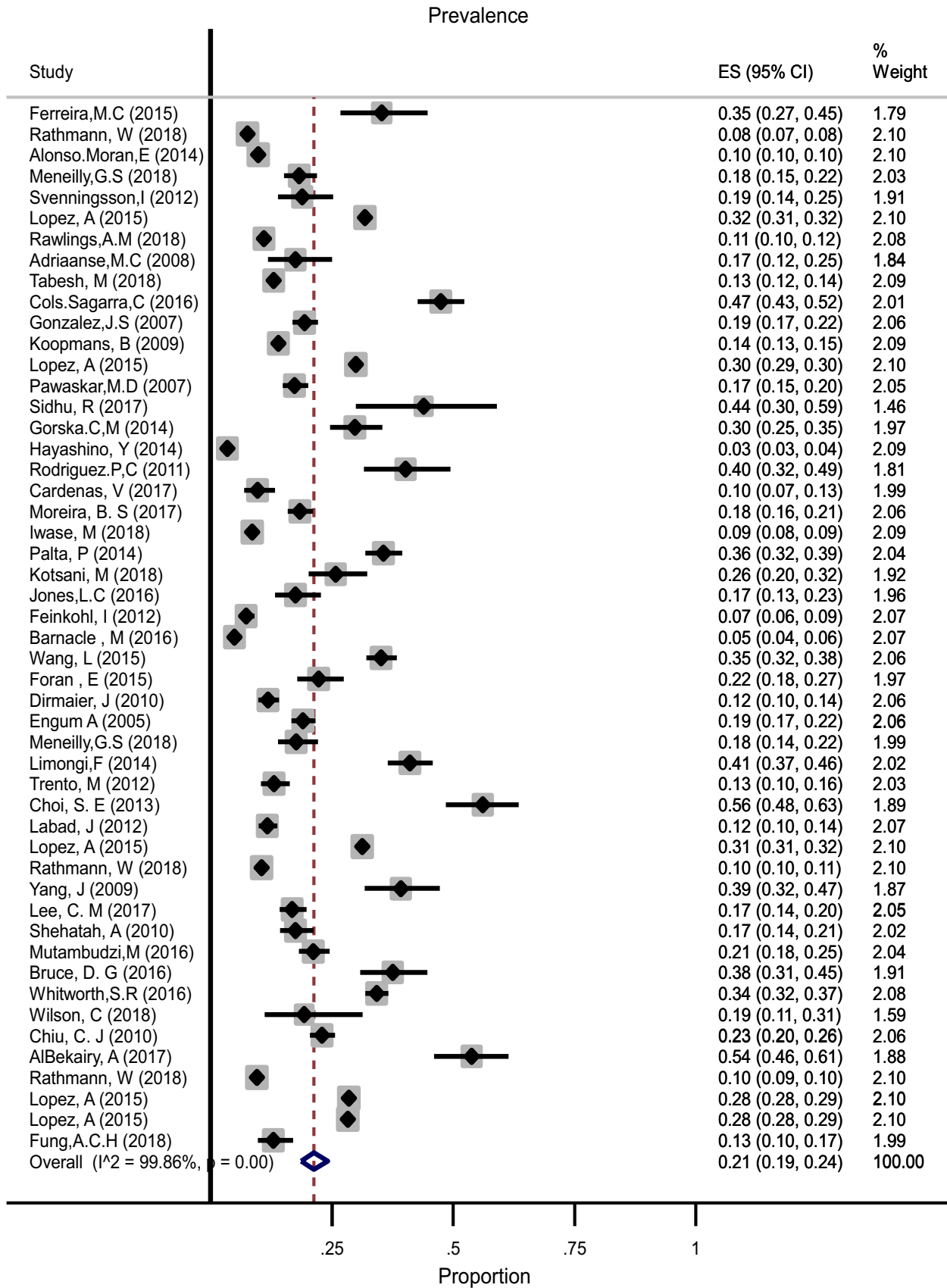


Fig. 6 Prevalence of comorbid depression in patients with type 2 diabetes older than 65 years

clinical diagnosis method (prevalence = 22%; 95% CI 19, 24,  $I^2 = 99.9\%$ ). Subgroup analysis based on instruments used to identify depressive disorders could not explain heterogeneity. The estimated pooled prevalence derived by PHQ, CESD, BDI, HADS, DSM, and other instruments was 25% (95% CI 22, 28), 28% (95% CI 24, 33), 40% (95% CI 34, 47), 28% (95% CI 23, 34), 12% (95% CI 6, 20), and 27% (95% CI 25, 29).

In the subgroup analyses based on regions and sex (Figs. 3, 4), both Asian males (prevalence = 29%; 95% CI 23, 36,  $I^2 = 99.1\%$ ) and females (prevalence = 41%; 95% CI 33, 50,  $I^2 = 99.4\%$ ) had the highest prevalence rate, whereas European men (prevalence = 16%; 95% CI 12, 21,  $I^2 = 97.1\%$ ) and Australian women (prevalence = 23%; 95% CI 10, 39,  $I^2 = 98.6\%$ ) had the lowest prevalence (Table 1). In subgroup analysis based on both age and continent, prevalence of depression was higher in younger patients than elderly in all continents; nevertheless, in Europe, the prevalence in both age categories was approximately the same (24% in young patients and 21% in elderly) (Table 1).

**Table 1** Subgroup analysis for the prevalence of comorbid depression based on sex and age in patients with type 2 diabetes in different continents

	No. of reported effect sizes	Prevalence	95% confidence interval
<i>Asia</i>	45	37	30, 44
Males	44	29	23, 36
Females	45	41	33, 50
< 65 years	75	32	27, 38
≥ 65 years	7	22	12, 33
<i>Europe</i>	21	23	18, 28
Males	22	16	12, 21
Females	22	28	22, 34
< 65 years	32	24	20, 28
≥ 65 years	23	21	17, 25
<i>America</i>	17	22	19, 26
Males	16	19	15, 23
Females	17	29	22, 36
< 65 years	49	32	26, 39
≥ 65 years	16	21	16, 27
<i>Australia</i>	3	17	4, 37
Males	4	18	8, 32
Females	3	23	10, 39
< 65 years	5	35	27, 44
≥ 65 years	3	27	11, 47
<i>Africa</i>	3	31	17, 48
Males	3	25	14, 38
Females	4	37	20, 55
< 65 years	4	33	24, 43
≥ 65 years	1	17	14, 21

In subgroup analysis based on insulin use, the prevalence of comorbid depression in insulin-dependent subjects was 11% (95% CI 8, 13,  $I^2 = 97.9\%$ ), whilst in non-insulin-dependent subjects was considerably higher (prevalence = 12%; 95% CI 9, 15,  $I^2 = 98.6\%$ ). Subgroup analysis among depressed subjects showed that 45% of depressed subjects were insulin-dependent (95% CI 40, 51%). Meta-regression on the mean duration of having diabetes was not related to the prevalence of depression ( $\beta$  coefficient =  $-0.0001594$ ,  $P = 0.971$ ), whilst on the number of insulin-dependent patients was slightly and inversely related ( $\beta$  coefficient =  $-0.0001577$ ,  $P = 0.003$ ).

### Publication bias and sensitivity analysis

Visual inspection of funnel plot suggests an asymmetrical distribution of articles. Consistently, the presence of publication bias was confirmed also by Egger's ( $P < 0.0001$ ) test. Results of trim and fill analysis showed that adjusted values (0.28, 95% CI 0.27, 0.29) did considerably differ with the original pooled estimates (0.20, 95% CI 0.19, 0.21). Excluding studies with the smallest sample size [101] and the highest prevalence of co-morbid depression [105] from analysis did not change the pooled estimate (prevalence = 28%, 95% CI 27, 29).

### Discussion

The current meta-analysis aimed to estimate the prevalence of depressive disorders in patients with T2DM. Our results indicate that nearly one in four diabetic patients suffer from co-morbid depression. This prevalence rate is higher than the values reported by Ali et al. in 2006, who showed that 17.6% patients with T2DM had depression [9]. Another meta-analysis summarized the prevalence of co-morbid depression among Bangladeshi outpatients with type 2 diabetes mellitus [18]. They identified that when the symptoms were assessed by PHQ and WHO-5, 34% and 36% of patients suffered from depression, respectively. In line with the earlier meta-analysis, our findings revealed higher prevalence rate of depression in female diabetic patients than males; however, a considerable increase was observed in the prevalence rate in both females and males compared with the estimates in 2006 [9]. Although there is numerous literature on this topic, we are aware of no update meta-analysis summarizing the overall prevalence rate of depression in patients with T2DM around the world, since such a review was performed by Ali et al. in 2006 [9].

In the previous meta-analysis, investigators aimed to compare the prevalence of co-morbid depression in patients with T2DM with non-diabetic patients and included only 12 studies in their review. Nevertheless, we did not do such

comparison and included all published studies which provided the prevalence of depressive disorders in their study sample either as the primary or secondary outcomes. In addition, the number of studies assessing depression prevalence separately in males and females was quite small in the earlier meta-analysis ( $n=4$ ), suggesting that publication bias may influence their results. Although the method of depression assessment could not explain the heterogeneity between studies and did not identify considerable differences between instruments, the potential bias suggested for different instruments cannot be totally eliminated. Further analysis based on instruments revealed that the prevalence of depression was higher in studies which have used self-report instruments compared with those which have used diagnostic criteria. Our pooled estimate for self-report prevalence of comorbid depression is similar to earlier report by Anderson in 2001, but the estimated prevalence based on diagnostic criteria in our study is considerably greater than theirs (23% vs. 11.4%) [8]. This finding may suggest an increase in the prevalence of major depression in patients with diabetes over the years. However, only a few studies have used diagnostic criteria and there is still need for future studies applying standardized diagnostic interviews for depression.

Although depression is highly treatable in diabetic patients [272], it remains unrecognized and untreated approximately in two-thirds of patients [273]. Untreated depressive disorders are associated with poor diabetes self-care activities such as regular physical activity and adherence to a healthy diet or medication regimens, and adversely affect diabetes complications such as retinopathy, nephropathy, neuropathy, sexual dysfunction, and coronary heart disease [273]. Moreover, it has been suggested when routine medical treatments fail to control glycemic status, depression should be taken into account as a possible cause [273]. Therefore, routine screening in terms of depression in patients with diabetes by trained health-care professionals is suggested [273].

There are several lines of evidence, indicating that the association between depression and diabetes might be bidirectional. Indeed, diagnosis of diabetes is associated with increased risk of developing depression and in contrast, and depressed subjects are at higher risk for diabetes [274]. Several mechanisms may explain the link between diabetes and depression. First, elevated levels of blood glucose and insulin resistance are associated with increased risk of diabetes *per se* [275, 276]. Second, depression is probably a somatic burden of diabetes, since it has been shown that psychological disorders are more common among diabetic patients rather than prediabetic and undiagnosed diabetic patients [277, 278]. In addition, there is evidence, suggesting that the increased risk of depression in prediabetic and undiagnosed diabetic patients might be attributed to cardiovascular diseases; nevertheless, depression–diabetes association

in previously diagnosed T2DM was slightly influenced by cardiovascular diseases which indicates the potential role of other risk factors [279]. Third, elevated serum concentrations of some common inflammatory biomarkers such as the C-reactive protein (CRP) and interleukin (IL)-6 have been implicated in the pathogenesis of both diseases [278]. Fourth, depression is associated with activation of the hypothalamic–pituitary–adrenal (HPA) axis and causes increased levels of cortisol and catecholamine hormones which lead to insulin resistance [274, 280].

Some limitations should be taken into account when interpreting the findings of the current study. Due to using secondary data of a study assessing a different primary outcome, measurement bias and residual confounding will inevitably influence the results of this meta-analysis. Almost in all studies, the reported prevalence of depression was not adjusted for various relevant confounders such as age, socioeconomic status, and comorbid conditions such as cardiovascular diseases which may mediate the relationship between diabetes and depressive disorders [211, 281]. Furthermore, included studies in the current meta-analysis used a large variety of self-rating instruments to assess depression status rather than the clinical diagnostic criteria which may cause between studies heterogeneity. In addition, the prevalence of “elevated depressive symptoms” is estimated higher based on self-rating instruments that may suggest that milder depressive disorder is prevalent among a large number of diabetic patients. Nevertheless, we ran a subgroup analysis based on the depression scales used as well as self-report vs. clinical-interview methods, to reduce the heterogeneity and potential bias. The main strengths of our meta-analysis were that we included a large sample of diabetic patients with different age ranges through the world in our analysis and conducted subgroup analysis based on some relevant factors. In addition, like other systematic reviews, a comprehensive review of available literatures provides a systematic identification of gaps and limitations which can lead to improved designs of future research. Although based on  $I^2$  test, there was considerable heterogeneity between studies, this might not be clinically relevant when the number of studies and sample size is large [282].

In summary, our current meta-analysis revealed that more than one in four (28%) adults with T2DM experienced depression. The corresponding value in diabetic females is 34%, whilst in males is 23%. The greatest prevalence was observed in Asian countries, whereas the lowest prevalence was found in Europe. Increasing level of information and knowledge of diabetic patients in terms of controlling their diseases can delay progression or prevent depression in patients with T2DM. In addition, given the high prevalence of depressive disorders in diabetic patients, it is suggested screening these patients for co-morbid depression and its relevant risk factors. Conversely, due to bidirectional link

between depression and diabetes, and considering that diabetes is an age-related chronic disease, screening depressed elderly for diabetes is suggested.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interests.

**Statement of human and animal rights** This study is a meta-analysis of other studies where all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

**Informed consent** For this type of study consent form is not required.

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