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## EDITED BY

Panagiotis Ferentinos,  
National and Kapodistrian University of  
Athens, Greece

## REVIEWED BY

Konstantinos Tsamakis,  
King's College London, United Kingdom  
Christos Theleritis,  
King's College London, United Kingdom

## \*CORRESPONDENCE

Yi Yu

✉ yuyi8797@126.com

<sup>†</sup>These authors have contributed  
equally to this work and share  
first authorship

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# Association between the triglyceride glucose index and depression: a meta-analysis

Weitao Wan<sup>1†</sup> and Yi Yu<sup>2\*†</sup>

<sup>1</sup>Department of Psychiatry, Tianyou Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, Hubei, China, <sup>2</sup>Department of Psychiatry, Wuchang Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, Hubei, China

**Background:** Obesity and diabetes have been associated with depressive symptoms. The aim of this systematic review and meta-analysis was to evaluate the association between the triglyceride glucose index (TyG index) a novel indicator of insulin resistance (IR) and depression in the adult population.

**Methods:** Relevant observational studies were acquired through comprehensive searches of the Medline, Web of Science, Embase, Wanfang, and China National Knowledge Internet databases. To account for heterogeneity, a random-effects model was employed to combine the findings. Additionally, multiple subgroup analyses were conducted to assess the impact of various study characteristics on the outcome.

**Results:** The meta-analysis comprised eight datasets from six cross-sectional studies, encompassing a total of 28,973 adults. The pooled findings suggested that subjects with a high TyG index, compared to those with a low TyG index, were associated with a higher prevalence of depression (odds ratio [OR]: 1.41, 95% confidence interval (CI): 1.28–1.56,  $p < 0.001$ ;  $I^2 = 19\%$ ). Sensitivity analyses, by omitting one dataset at a time, showed consistent results (OR: 1.39–1.45,  $p < 0.05$ ). Further subgroup analyses showed consistent results in participants aged  $< 50$  years old and in those aged  $\geq 50$  years old, in men and in women, in studies with different cutoff values for the TyG index, and in studies with different methods for the diagnosis of depression (for each subgroup difference,  $p > 0.05$ ).

**Conclusion:** A high TyG index may be associated with a higher prevalence of depression in the adult population.

## KEYWORDS

depression, triglyceride glucose index, insulin resistance, risk factor, meta-analysis

**Abbreviations:** IR, insulin resistance; TG, triglyceride; FPG, fasting plasma glucose; TyG index, triglyceride glucose index; HOMA-IR, homeostasis model assessment of insulin resistance; OR, odds ratio; CIs, confidence intervals; NHANES, National Health and Nutrition Examination Survey.

## Introduction

Depression is a severe and common affective disorder that adversely affects the quality of life of individuals (1, 2). Moreover, depression is associated with suicidal ideation, which may expose those affected to fatal events (3, 4). The pathogenesis of depression is complicated and far from clarified, but it is considered to involve a variety of genetic and environmental factors (5–7). Among them, metabolic disorders such as obesity (8) and type 2 diabetes (9) are both related to depression. The key component underlying obesity and type 2 diabetes is insulin resistance (IR) (10). Conventionally, the extent of IR can be accurately measured by the use of a hyperinsulinemic euglycemic clamp (11). However, this method is time-consuming, thus limiting its use in real-world clinical practice (11, 12). Recently, a novel indicator of IR based on the serum triglyceride (TG) and fasting plasma glucose (FPG) values has been proposed; this indicator is named the triglyceride glucose index (TyG index) and calculated on the basis of the equation:  $TyG\ index = \ln [TG\ (mg/dL) \times FPG\ (mg/dL)/2]$  (13, 14). It has been shown that the TyG index correlates well with IR as measured by a hyperinsulinemic euglycemic clamp (15–17). Moreover, compared to the conventional homeostasis model assessment of insulin resistance (HOMA-IR), the TyG index may more effectively predict the adverse events related to IR, such as early atherosclerosis (18), metabolic syndrome (19), and renal dysfunction (20). In view of the important association between IR and depression (21), it is necessary to evaluate the relationship between the TyG index and depression. However, previous studies evaluating the association between the TyG index and depression in the adult population have shown inconsistent results (22–27). Accordingly, a systematic review and meta-analysis was performed in this study to comprehensively address this issue.

## Methods

The present meta-analysis adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) (28, 29) and the Cochrane Handbook for Systematic Reviews and Meta-analyses (30) throughout the process of study design, data collection, statistical analysis, and interpretation of results.

### Literature search

To identify studies relevant to the aim of this meta-analysis, we searched the Medline, Web of Science, Embase, Wanfang, and China National Knowledge Internet databases utilizing comprehensive search terms involving (1) “TyG index” OR “triglyceride-glucose index” OR “triglyceride and glucose index” OR “triglyceride glucose index” OR “triacylglycerol glucose index” OR “TyGI;” and (2) “depression” OR “depressive.” The search was restricted to human studies, specifically focusing on full-length

articles published in peer-reviewed journals in English or Chinese. Additionally, the references of relevant original or review articles were manually examined to identify potentially pertinent studies. The literature encompassing the period from the establishment of the databases to December 6, 2023 was thoroughly screened.

### Inclusion and exclusion criteria

The eligibility criteria for the potentially included studies encompassed the following aspects, according to the PICOS criteria: The participants (P) included adults aged 18 years or older, without a diagnosis of a specific somatic disease. For the intervention/exposure (I), the TyG index was measured and the participants with the highest-category TyG index were considered as exposure. The TyG index was calculated as  $TyG\ index = \ln [TG\ (mg/dL) \times FPG\ (mg/dL)/2]$ . The cutoff for defining a high versus low TyG index was in accordance with the value used among the original studies. The participants with the lowest-category TyG index were considered as comparisons (C). To determine the outcomes (O), the incidence and/or prevalence of depression was compared between participants with the highest- versus the lowest-category TyG index. The study design (S) included observational studies, including case–control studies, cross-sectional studies, and cohort studies.

The exclusion criteria were as follows: (1) studies including children or adolescents; (2) studies including a patient population with a specific somatic disease; (3) studies that did not evaluate the TyG index or report the outcome of depression; or (4) preclinical studies, reviews, or editorials. If studies with an overlapping population were retrieved, the one with the largest sample size was included in the meta-analysis.

### Study quality evaluation and data extraction

The literature search, study identification, study quality evaluation, and data collection were carried out independently by two authors. In the event of any disagreement, consultation with the corresponding author was sought to resolve the matter. The Newcastle-Ottawa Scale (31) was employed to assess the quality of the studies included. This scale encompasses three dimensions, namely the selection of the study population, comparability between groups, and measurement of exposure. The score of NOS varied between 0–9, with a higher score indicating a better study quality. The NOS of 7–9 was defined as of good study quality. The data extracted from each study included various elements for subsequent analysis, such as the study information (including authors, year, country, and design), participant characteristics (including population characteristics, sample size, age, and sex), cutoff values for the TyG index analysis, methods for the diagnosis of depression, numbers of participants with depression, and variables adjusted when the association between the TyG index and depression was estimated.

## Statistical analysis

The relationship between the TyG index and depression in the adult population was summarized as the odds ratio (OR) and the corresponding 95% confidence intervals (CIs) comparing the prevalence of depression between participants with the highest-versus the lowest-category TyG index. ORs and standard errors were determined using 95% CIs or  $p$ -values, with a subsequent logarithmical transformation applied to stabilize and normalize the variance. Study heterogeneity was evaluated using the Cochrane Q test and  $I^2$  statistics, with an  $I^2$  value greater than 50% indicating significant heterogeneity (32). A random-effects model was employed to combine the results, taking into account the influence of heterogeneity (30). Sensitivity analyses, by omitting one study at a time, were conducted to further examine the findings. The study conducted predefined subgroup analyses to assess the impact of the study characteristics on the outcome. The medians of the continuous variables were utilized as thresholds to define the subgroups. To estimate publication bias in the meta-analysis, funnel plots were constructed and visually inspected for symmetry (33). Additionally, an Egger's regression test was conducted (33). The statistical analysis was performed using RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata software (version 12.0; Stata Corporation, College

Station, TX, USA). A two-sided  $p < 0.05$  indicates statistical significance.

## Results

### Study inclusion

The process of study inclusion is presented in Figure 1. In brief, 67 potentially relevant records were obtained after comprehensively searching the five databases, and 15 of them were excluded due to duplication. Subsequently, screening of the titles and abstracts of the remaining records further excluded 42 studies, mostly because they were not related to the aim of the meta-analysis. Accordingly, the full texts of the ten resulting records were read by two independent authors, and four of them were further removed for the reasons listed in Figure 1. Finally, six observational studies were considered to be suitable for the subsequent quantitative analyses.

### Overview of study characteristics

Table 1 presents the summarized characteristics of the included studies. Overall, six cross-sectional studies (22–27) were included in

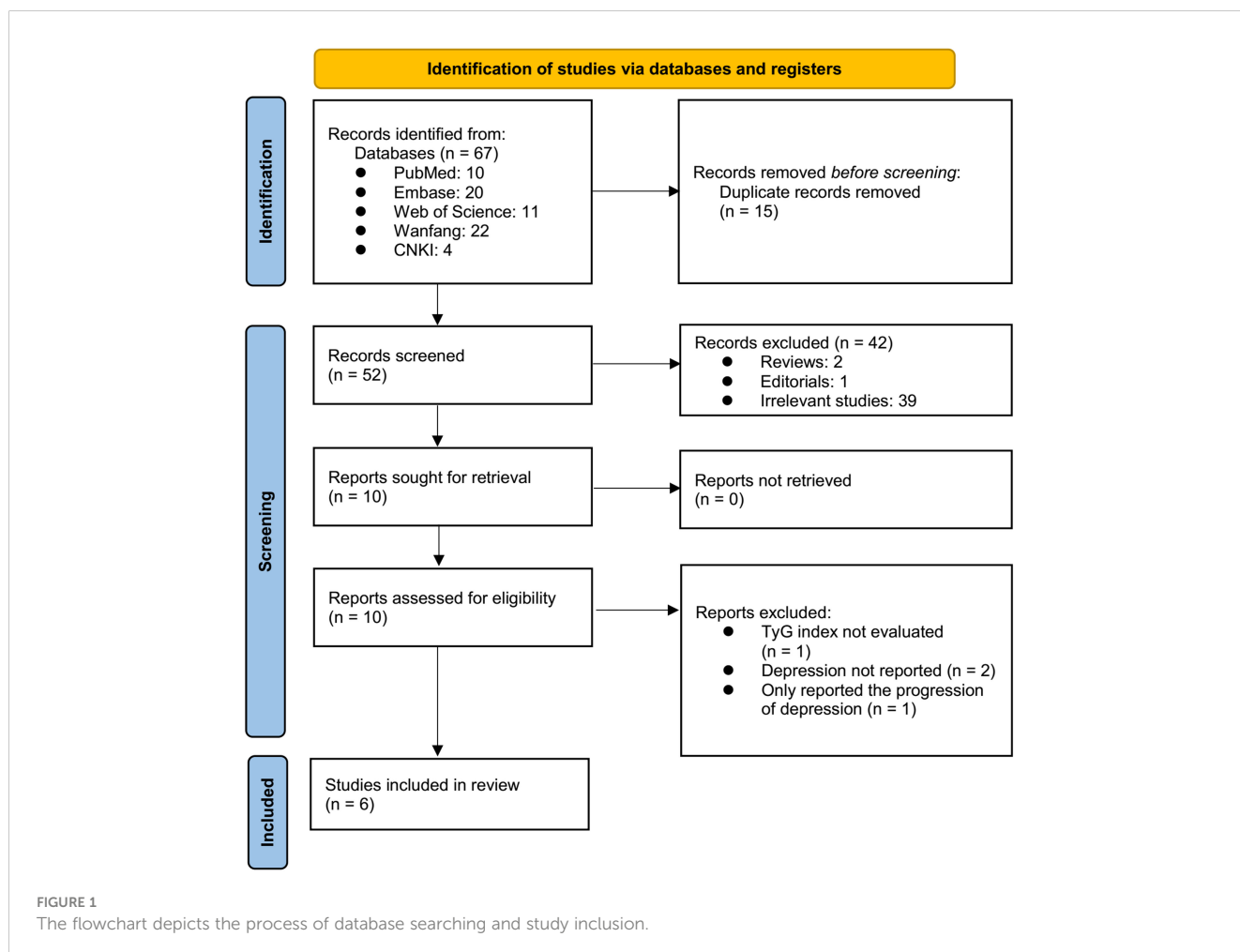


TABLE 1 Characteristics of the included studies.

Study	Location	Design	Population	No. of participants	Mean age (years)	Male (%)	TyG index analysis	Methods for depression diagnosis	Number of patients with depression	Adjusted variables
Shi 2021 (23)	USA	CS	Community population aged 20 years or older	13350	45.5	51.5	Q4:Q1	PHQ-9	1001	Age, race, sex, education, income, BMI, smoking, alcohol drinking, CHF, CAD, liver function, cancer, DM, and HDL-C
Lee 2021 (22)	Korea	CS	Community population aged 19 years or older	4688	46.8	54.2	Median	PHQ-9	422	Age, sex, marital status, personal income, smoking, DM, HTN, and CVD
Wang 2023 (26)	China	CS	Community population aged 45 years or older	8942	59.1	46.4	Median	CES-D-10	4345	Age, sex, education, marital status, live place, smoking, alcohol drinking, activities, exercises, and chronic diseases
Jiao 2023 (24)	China	CS	Community population aged 45 years or older	960	58.3	17	Q4:Q1	CES-D-10	NR	Age, sex, marital status, alcohol drinking, sleep duration, and chronic diseases
Jin 2023 (25)	China	CS	Participants receiving a health examination aged 18 years or older	646	44	42.7	T3:T1	ICD-10	321	Age, sex, BMI, marital status, family history of psychiatric disorders, education levels, hypertension, cardiovascular disease, stroke, cancer, and hypothyroidism
Zhang 2023 (27)	China	CS	Participants receiving a health examination aged 45 years or older	387	58.1	47.8	T3:T1	ICD-10	198	Age, sex, BMI, smoking, alcohol drinking, family history of depression, TC, HDL-C, and LDL-C

CS, cross-sectional; TyG index, triglyceride-glucose index; Q, quartile; T, tertile; PHQ-9, Patient Health Questionnaire-9; CES-D-10, the Center for Epidemiological Research Depression Scale 10; ICD-10, International Classification of Diseases 10; BMI, body mass index; CHF, congestive heart failure; CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not reported.

the meta-analysis. These studies were published between 2021 and 2023, and conducted in the United States, Korea, and China. Four studies included a community-derived adult population (22–24, 26), while the other two studies included adult participants who received a health examination (25, 27). The mean age of the participants was 44–59.1 years old, and the proportion of men was 17–54.2%. Medians (22, 26), tertiles (25, 27), and quartiles (23, 24) of the TyG index were selected as the cutoffs for the analyses of the TyG index in two studies each. Different methods were used to diagnose depression, including the Patient Health Questionnaire-9 (22, 23), the Center for Epidemiological Research Depression Scale 10 (24, 26), and the International Classification of Diseases 10 codes (25, 27). The assessment of patients that were diagnosed with depression was performed by trained medical personnel among all the included studies. Multivariate analyses were used to estimate the association between the TyG index and depression in all of the included studies, which adjusted potential confounding factors such as age, sex, body mass index, socioeconomic status, and comorbidities to a varying degree. The NOS of the included studies were summarized in Table 2. All of the included studies were of good study quality, with NOS between 7 and 9.

### Results of the meta-analysis

Two (25, 26) of the included studies reported the outcome according to the sex of the participants, and these datasets were included in the meta-analysis independently. Overall, the meta-analysis comprised eight datasets from six cross-sectional studies (22–27). The pooled findings suggested that the subjects with a high TyG index, compared to those with a low TyG index, were associated with a higher prevalence of depression (OR: 1.41, 95% CI: 1.28–1.56,  $p < 0.001$ ; Figure 2) with mild between-study heterogeneity ( $I^2 = 19\%$ ). Sensitivity analyses, by omitting one dataset at a time, showed consistent results (OR: 1.39–1.45,  $p < 0.05$ ). Further subgroup analyses showed consistent results in participants aged  $< 50$  years old and in those aged  $\geq 50$  years old ( $p = 0.32$ ; Figure 3A), in men and in women ( $p = 0.12$ ; Figure 3B), in studies with different cutoff values for the TyG index ( $p = 0.10$ ; Figure 4A), and in studies with different methods for the diagnosis of depression ( $p = 0.08$ ; Figure 4B).

### Publication bias evaluation

The symmetrical nature of the funnel plots observed for the meta-analysis investigating the relationship between the TyG index and depression in the adult population suggests the absence of publication bias (Figure 5). This finding is further supported by the nonsignificant findings of Egger’s regression test ( $p = 0.25$ ), which also suggested a low risk of publication bias.

### Discussion

This systematic review and meta-analysis synthesized the results of eight datasets from six cross-sectional studies and showed that in

TABLE 2 Study quality evaluation via the Newcastle-Ottawa Scale.

Cross-sectional study	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for age and sex	Control for other confounders	Exposure ascertainment	Same methods for events ascertainment	Non-response rates	Total
Shi 2021 (23)	1	0	1	1	1	1	1	1	0	7
Lee 2021 (22)	1	0	1	1	1	1	1	1	1	8
Wang 2023 (26)	1	1	1	1	1	1	1	1	1	9
Jiao 2023 (24)	1	0	1	1	1	1	1	1	1	8
Jin 2023 (25)	1	0	1	1	1	1	1	1	1	8
Zhang 2023 (27)	1	0	1	1	1	1	1	1	1	8

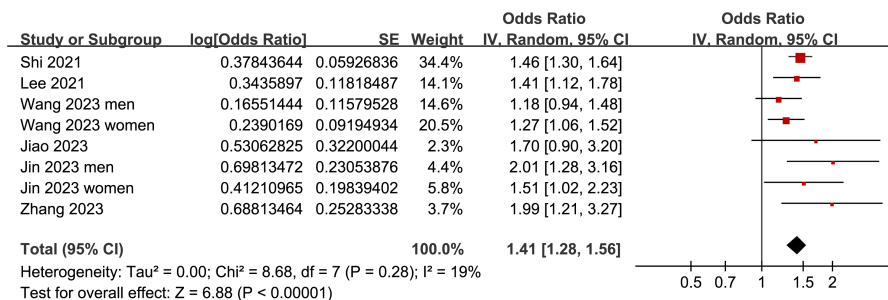


FIGURE 2 Forest plots for the meta-analysis of the association between the TyG index and depression in the adult population.

the adult population, a high TyG index was associated with a higher prevalence of depression. Furthermore, sensitivity analyses, which excluded one study at a time, consistently supported these results. Finally, subgroup analyses indicated that the correlation between the TyG index and the prevalence of depression in the adult population was not significantly affected by age, sex of the participants, cutoff

values of the TyG index, or methods for the diagnosis of depression. In summary, the results of this meta-analysis collectively suggest that a high TyG index may be associated with a higher prevalence of depression in the adult population.

Based on our current understanding, this study represents the first systematic review and meta-analysis that comprehensively

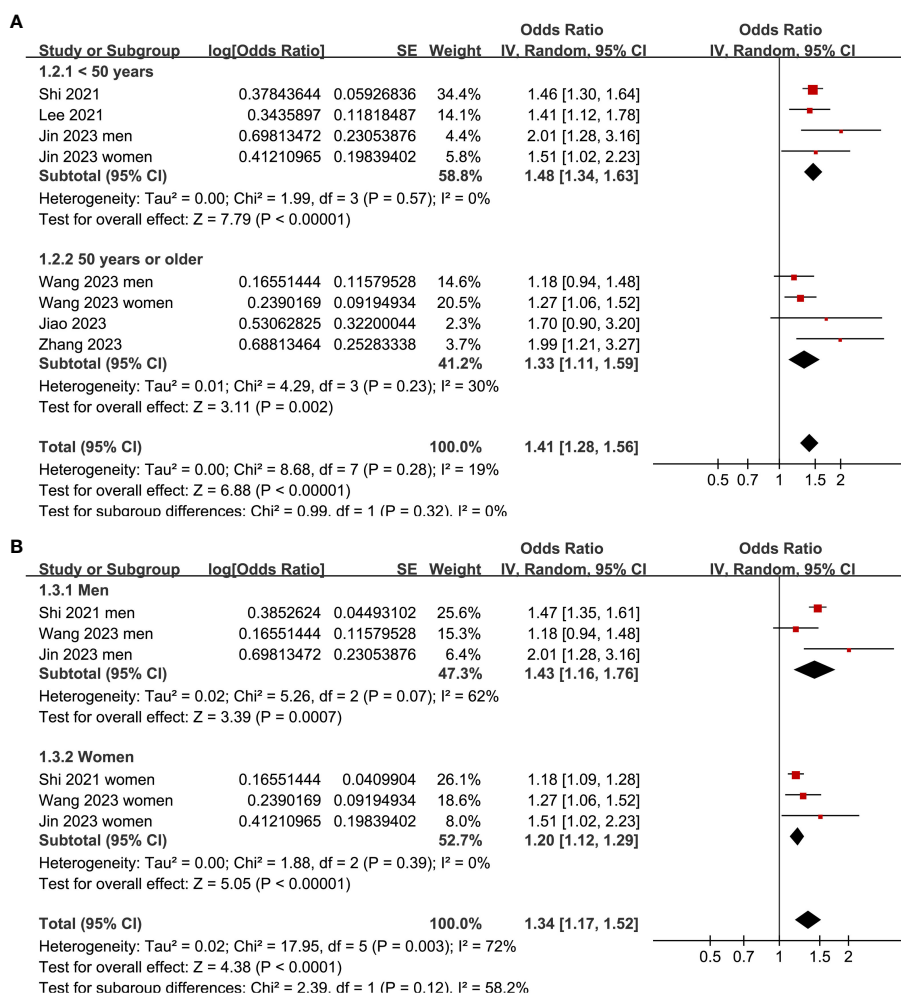


FIGURE 3 Forest plots for the subgroup analyses of the association between the TyG index and depression in the adult population. (A) Subgroup analysis according to the age of the participants. (B) Subgroup analysis according to the sex of the participants.

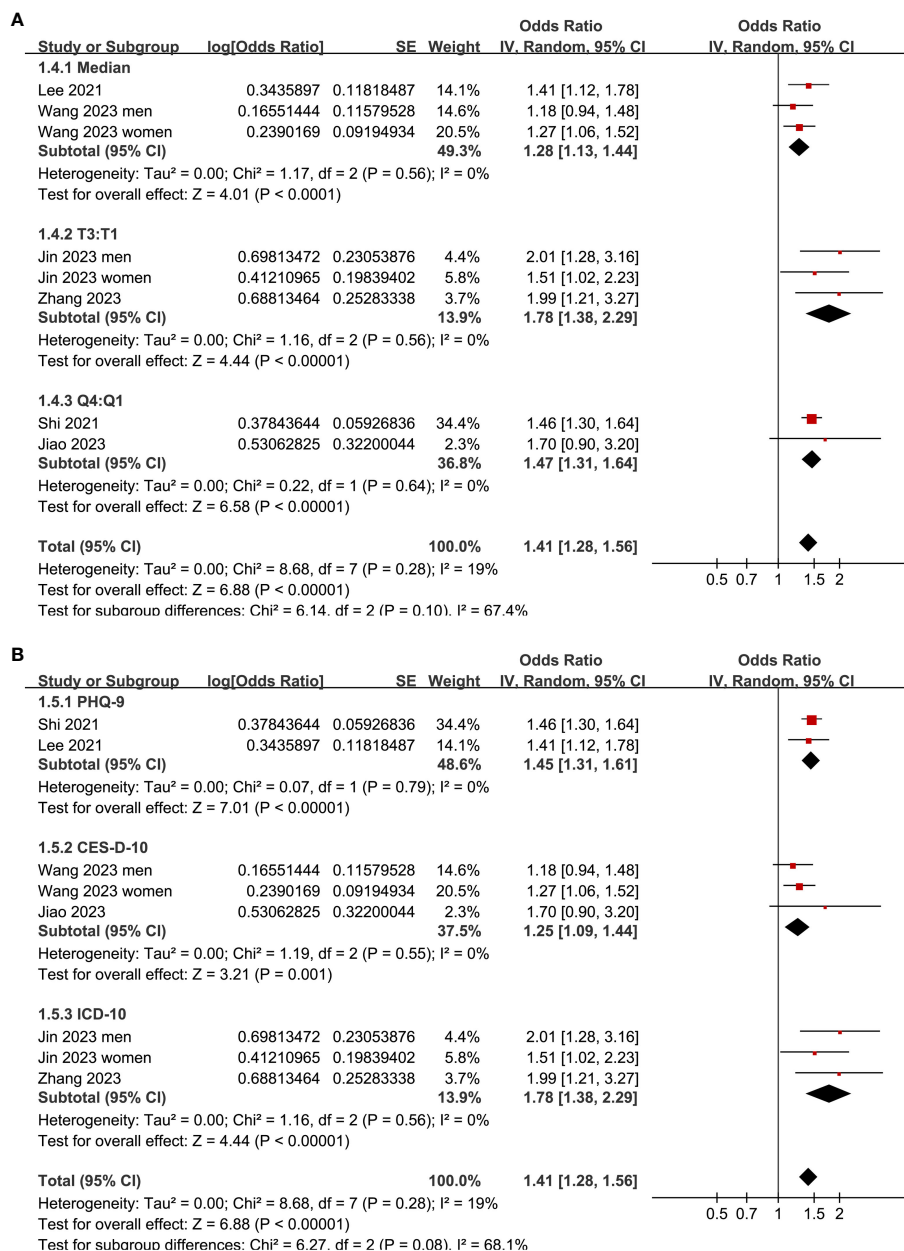


FIGURE 4 Forest plots for the subgroup analyses of the association between the TyG index and depression in the adult population. (A) Subgroup analysis according to the cutoffs of the TyG index. (B) Subgroup analysis according to the methods for the diagnosis of depression.

examines the potential relationship between the TyG index and depression in the adult population. Compared to the gold standard of hyperinsulinemic euglycemic clamp data or the commonly used HOMA-IR, the TyG index can be easily obtained via fasting TG and FPG measurements (34). Determining the TyG index is quick, cheap, and easy to implement in real-world clinical settings, which makes it a reliable and convenient indicator of IR (34). The results of our meta-analysis were consistent with previous findings, showing that both the TG and FPG levels are associated with depression. A previous meta-analysis including 11 case-control studies showed that an elevated TG level may be associated with first-episode major depressive disorder (35). Similarly, a recent

study from the 2009–2018 National Health and Nutrition Examination Survey (NHANES) suggested that an elevated TG level may mediate the association between reduced physical activity and sedentary behavior in the development of depression (36). In addition, in a previous study of an urbanizing rural population in Bangladesh, it was shown that depression was significantly associated with a high FPG level (37). Similarly, in a subsequent study using the 2013–2014 NHANES data, it was demonstrated that a higher FPG level was associated with greater depressive symptoms among females, although the association was not significant in males (38). Collectively, the results of the current meta-analysis further confirmed the association between IR and depression.

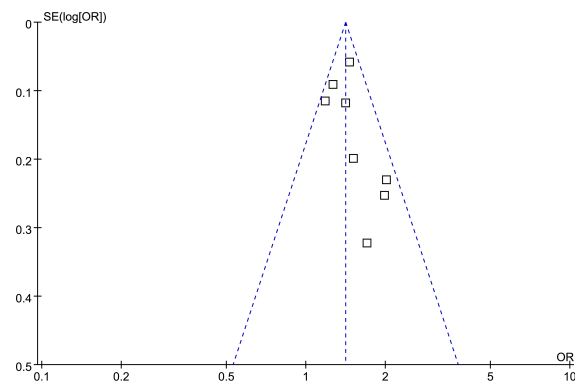


FIGURE 5

Funnel plots for the evaluation of the publication bias of the meta-analysis of the association between the TyG index and depression in the adult population.

Even though several mechanisms underlying the association between IR and depression have been elucidated, such as low-grade inflammation (39), changes of brain dopamine signaling (40), and cortisol dysregulation (41), the exact molecular pathways underlying this association remain to be clarified. For example, IR as indicated by a high TyG index, is linked to chronic inflammation and oxidative stress (39). Chronic low-grade inflammation, a hallmark of IR, can influence brain function by altering neurotransmitter metabolism, reducing neurogenesis, and impairing neuroplasticity, all of which have been implicated in the development of depressive symptoms (42). Additionally, IR is associated with increased levels of pro-inflammatory cytokines such as interleukin 6 and tumor necrosis factor  $\alpha$  (43), which have been shown to affect mood and behavior by crossing the blood-brain barrier and impacting brain function. Furthermore, IR often correlates with disruptions in the hypothalamic-pituitary-adrenal (HPA) axis. These disruptions can lead to altered cortisol secretion patterns, which have been consistently linked to depression (44). Dysregulation of the HPA axis can exacerbate the body's stress response, potentially contributing to depressive symptoms (45). Oxidative stress, another consequence of IR, can also lead to neuronal damage and affect brain regions implicated in mood regulation, such as the hippocampus and prefrontal cortex (46). The core signaling pathways underlying these proposed mechanisms remain to be determined.

Clinically, the findings of the meta-analysis underscore the significance of incorporating metabolic health evaluations into the management of depression. Screening for IR and related metabolic markers, including the TyG index, in individuals at risk for or experiencing depression could facilitate early intervention. Addressing IR through lifestyle interventions such as dietary changes and physical activity, or through pharmacological means when necessary, may improve both metabolic and mental health outcomes. This approach could lead to a more holistic treatment paradigm that considers both metabolic and psychological factors. Future research should aim to conduct longitudinal studies to better understand the temporal relationship between TyG index fluctuations and depressive symptoms. Investigating the detailed biological pathways, including the

roles of inflammation, oxidative stress, and HPA axis dysregulation, could further elucidate the mechanisms driving the observed association. Additionally, exploring the impact of interventions targeting IR on depressive symptoms could provide valuable insights into potential therapeutic strategies. Such research could contribute to the development of more effective, multi-faceted treatment approaches for depression that address both metabolic and mental health components.

It is important to acknowledge the methodological rigor of this meta-analysis. Notably, a thorough search of five widely utilized electronic databases was conducted, resulting in the identification of six up-to-date cross-sectional studies that align with the objectives of this meta-analysis. All of the studies included in this analysis were published within the past three years, thus offering up-to-date insights into the role of the TyG index as a marker of depression in the general population. Furthermore, multivariate analyses were used for all of the included studies when the association between the TyG index and depression was estimated, therefore indicating that the association was independent of potential confounding factors, such as age, sex, or socioeconomic status of the participants. Finally, the robustness of the findings was further confirmed through various sensitivity and subgroup analyses. Taken together, these findings support the association between the TyG index and depression in the general population.

This study also has some limitations that must be addressed. One important issue is that the cutoff for the TyG index varied among the included studies. However, to the best of our knowledge, a universal cutoff for the TyG index for predicting IR remains to be established. Furthermore, all of the included studies were cross-sectional studies, and prospective studies should be performed to determine if a high TyG index is a risk factor for depression in the adult population. Moreover, we were unable to determine the potential influences of comorbidities and concurrent medications of the participants on the association between TyG index and depression because stratified data according to these characteristics of the participants were not reported among the included studies. However, participants with these conditions were rare among these studies because community population or general population were included. Additionally, our study solely encompassed observational studies, thus precluding the



establishment of a causal relationship between IR and the development of depression. In fact, it is important to determine if there is a bidirectional relationship between a high TyG index and the prevalence of depression. In this regard, a recent study showed that major depressive disorder in adolescents appears to be a risk factor for development of dyslipidemia (47). Finally, although multivariate analyses were used, there might still be unadjusted factors that may confound the association between the TyG index and depression.

## Conclusion

In conclusion, the findings from this meta-analysis suggest that compared to those with a low TyG index, the adult population with a high TyG index may have a higher prevalence of depression. Although large-scale prospective studies are needed to validate the results, the findings of this meta-analysis support the potential association between a high TyG index and the prevalence of depression in general population.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

## Author contributions

WW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing –

original draft, Writing – review & editing. YY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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