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Review Article

# The association between depressive symptom severity and metabolic disturbances in major depressive and bipolar disorders: A systematic review and meta-analysis

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ABSTRACT

*Background:* Persons with depression are differentially affected by metabolic alterations, notably, insulin resistance and dyslipidemia. Metabolic alterations affect acute pharmacotherapy response and predispose risk for cardiovascular diseases. We aimed to extend knowledge pertaining to the depression-metabolic alteration association by evaluating whether depressive symptom severity moderates the association.

*Methods:* We conducted a systematic search of PubMed, Ovid and Scopus from inception to May 2025. Two reviewers (S.W. and G.H.L.) independently screened the identified studies. Studies were included if they enrolled adults with depression and reported on at least one metabolic parameter (i.e., fasting glucose, insulin, lipid panels). Standardized mean differences of metabolic parameters were pooled across studies.

*Results:* We identified 28 studies for inclusion. Persons with depression exhibited higher fasting glucose (SMD = 0.30, 95 % CI [0.12, 0.48]) and dyslipidemia [i.e., trends of increased low-density lipoprotein (SMD = 0.21, 95 % CI [−0.03, 0.44]) and lower high-density lipoprotein (SMD = −0.72, 95 % CI [−1.41, −0.03])]. Measures of insulin resistance were positively associated with anhedonia severity, sleep disturbances, and suicidal ideation.

*Limitations:* Between-study methodological differences, including study design and sociodemographics, affects the synthesis of overall trends.

*Conclusion:* Herein, we identify an association between depressive symptom severity and dysglycemia, dyslipidemia and insulin resistance. The results augment the conceptual framework implicating metabolic disturbances in depression pathophysiology and indirectly support testing that therapeutics currently in development in the treatment of depression (e.g., GLP-1 receptor agonists) may exhibit differential efficacy as a function of illness severity.

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## 1. Introduction

Mood disorders, including major depressive disorder (MDD) and bipolar depression (BD), are among the most common mental health disorders, affecting approximately 5 % and 1 % of the global population with rates increasing annually (McIntyre et al., 2023; Merikangas et al., 2011; Oliva et al., 2024; Santomauro et al., 2021; World Health Organization, 2022). Chronic and debilitating symptoms including, but not limited to anhedonia, sleep disturbances, and cognitive impairments, are characteristic of MDD and BD as well as directly contribute to deficits in health-related quality of life and functional impairments in affected individuals (Gillissie et al., 2023; Le et al., 2025, 2024; Nutt et al., 2008; Wong et al., 2024). Furthermore, persons with MDD and BD are at an increased risk of suicidality (i.e., suicidal ideation and behaviour, and suicide attempts) (Baldessarini et al., 2019; Cai et al., 2021; Holma et al., 2014). In addition to conventional monoamine-based antidepressants being ineffective for a substantial portion of persons diagnosed with MDD and BD, there still remains an incomplete understanding of the pathophysiology of depressive disorders (McIntyre et al., 2023).

Persons with depressive disorders commonly display alterations in metabolic functions, including appetite and feeding behaviour (Simmons et al., 2020; Wong et al., 2025a). Extant literature indicates that persons with depressive disorders are also at an increased risk of comorbid metabolic disorders (i.e., metabolic syndrome, type 2 diabetes mellitus) (Chourpiliadis et al., 2024; Jawad et al., 2023; Liu et al., 2022; Mansur et al., 2020; McIntyre et al., 2007). A prevailing working hypothesis with regard to the pathophysiology of depression implicates alterations in metabolic as well as inflammatory effectors (Penninx et al., 2025). Specifically, chronic stress and the activation of pro-inflammatory cytokines are posited to promote hypothalamic inflammation, as well as increase the permeability of the blood-brain barrier (Dantzer et al., 2021; Penninx et al., 2025). Moreover, chronic inflammation may further exacerbate metabolic disruptions, including insulin resistance, dyslipidemia, mitochondrial dysfunction, and disruptions in energy homeostasis (Xiao et al., 2025).

Evidence from population-based cohort studies indicate that characteristic metabolic profiles [i.e., elevated glucose and triglycerides, and lower high-density lipoprotein (HDL)] are associated with a greater risk of incident depressive, anxiety and stress-related disorders (Chourpiliadis et al., 2024). Considering that insulin resistance and hyperlipidemia are also implicated in disruptions in cognitive and reward-related processes, converging lines of evidence indicate that disruptions in metabolic processes and differences in metabolic parameters may differentially contribute to depression psychopathology (Gill et al., 2025; Rashidian et al., 2021; Miola et al., 2023; Maksyutynska et al., 2024).

Individuals diagnosed with depressive disorders are differentially affected by metabolic alterations, notably insulin resistance and dyslipidemia, which may contribute to poor antidepressant response and increased cardiovascular risk (Fanelli et al., 2025; Krupa et al., 2024; McIntyre, 2021; Rashidian et al., 2023). Emerging evidence suggests that these metabolic disturbances are not uniformly distributed across all individuals with mood disorders (Grigolon et al., 2021; Xiao et al., 2021). Herein, we aimed to extend knowledge pertaining to the depressive disorder-metabolic alteration association by evaluating whether depressive symptom severity moderates the association. Moreover, to ensure a comprehensive analysis was conducted, we aimed to evaluate multiple metabolic parameters, which may be differentially associated with disparate depression symptom severity.

## 2. Methodology

### 2.1. Database search and eligibility criteria

Herein, this systematic review and meta-analysis was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The completed PRISMA checklist is included in the Supplementary Material. The protocol for this systematic review and meta-analysis was not pre-registered. A comprehensive search of PubMed, Ovid (MEDLINE, Embase, AMED, PsychINFO, JBI EBP Databases), and Scopus databases were conducted from inception to May 22, 2025. An updated search was also conducted on September 15, 2025. The following search string was used across all of the aforementioned databases: (Glucose OR Insulin OR Glucose-Insulin Homeostasis OR Insulin Signaling OR Glucose Metabolism OR Insulin Sensitivity OR Insulin Resistance OR Insulin Response OR Glucose Tolerability OR Lipid Abnormalities OR Dyslipidemia OR Hyperlipidemia) AND (Depressive symptoms OR Depression Prognosis OR Depressive Symptom Severity) AND (Depressive Disorder* OR Major Depressive Disorder OR MDD OR Bipolar Disorder OR BD OR BD-I OR BD-II). An additional manual search of Google Scholar and reference searching was conducted to ensure all relevant articles were retrieved.

Articles were deemed eligible for inclusion if they met the following inclusion criteria: 1) must be primary research (i.e. cohort studies, case control studies, cross-sectional studies), 2) must include participants with a diagnosis of major depressive disorder or bipolar disorder according to DSM or ICD criteria, 3) must have participants between 18 and 64 years of age, inclusive, 4) must use a validated blood measure of metabolic parameter(s).

Articles were ineligible for inclusion if they met at least one of the following exclusion criteria: 1) non-primary research (e.g., reviews, meta-analyses, editorials, letters to the editors, commentaries, dissertations, conference abstracts, protocols), 2) preclinical in vitro or in vivo studies, 3) case reports or case series, 4) intervention studies that are testing the safety and/or efficacy of an investigational agent for the treatment of depressive symptoms or metabolic disorders, 4) evaluates the efficacy of a treatment on metabolic parameters and/or depressive symptoms, 5) no confirmed diagnosis of a depressive disorder, 6) participants with a psychiatric comorbidity or mixed diagnoses, 7) studies evaluating metabolic parameters as predictors of antidepressant response, 8) not published or translated to English, 9) no full-text availability.

### 2.2. Study screening process

Screenings of the identified studies were conducted independently on Covidence by two reviewers (S.W. and G.H.L.). Following the automatic removal of duplicates by Covidence, studies were screened by title and abstract. Studies that were determined to be relevant by at least one of the two reviewers were subsequently screened against the full text based on the eligibility criteria. Studies included in this review had to receive a unanimous decision for inclusion. Any discrepancies at both stages of the screening process were resolved through discussion.

### 2.3. Data extraction

The data extraction process was conducted by two reviewers (S.W. and G.H.L.) using a standard data extraction template. All data that was extracted was established a priori and included the following categories: 1) authors and date of publication, 2) study design, 3) sample population and size, 4) sample age distribution, 5) sex distribution of sample, 6) aim (s)/objective(s), 7) metabolic parameter(s) investigated, 8) association of metabolic disruptions and clinical symptom severity. The metabolic parameters to be extracted were established a priori and included fasting glucose, insulin, HDL, LDL, triglycerides, total cholesterol and any validated clinical marker of insulin resistance [i.e., Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Homeostatic Model Assessment of Beta-cell Function (HOMA-B), HbA1c]. When reported, the group mean and standard deviation of metabolic parameters, as well as correlation coefficients between clinical symptom severity and

metabolic parameters, were collected for both baseline and endpoints. Within intervention studies, only baseline measures of metabolic parameters were extracted to remove treatment effects (e.g., diabetes treatments, antidepressant pharmacotherapies).

### 2.4. Statistical analysis

All statistical analyses and plot generation were conducted using R Studio version 2025.05.0 + 496 "Mariposa Orchid" Release. Analysis and forest plot generation utilized the "meta" package (Balduzzi et al., 2019). To evaluate differences in metabolic parameters between persons with depressive disorders and healthy controls, the mean and standard deviations of metabolic parameters for mood disorder participants and healthy controls were used to calculate standardized mean differences (SMD). Effect size measures were weighted using a generic inverse-variance method and then pooled using a random-effects model. Confidence intervals for the pooled effect sizes were calculated using the Hartung-Knapp-Sidik-Jonkman method. Between-study heterogeneity was calculated using the Higgins & Thompson $I^2$ value.

### 2.5. Risk of bias assessment process

All included studies were evaluated for potential risk of bias independently by two reviewers (S.W. and G.H.L). Studies were evaluated based on the study design employed. Two risk of bias tools were utilized, including the National Institute of Health (NIH) Quality Assessment Tool

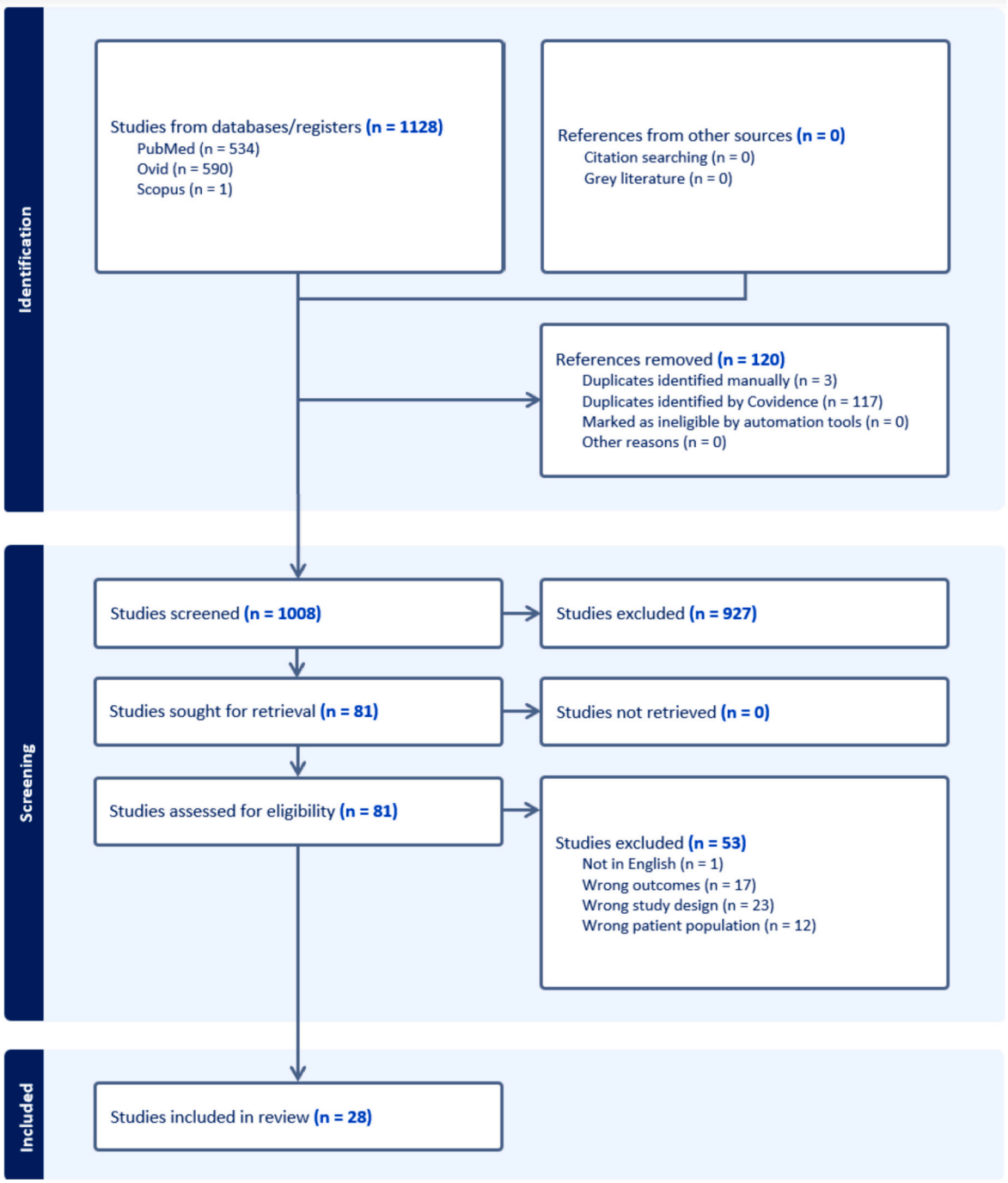


**Fig. 1.** PRISMA diagram of study screening and inclusion/exclusion process.

for Observational Cohort and Cross-Sectional Studies and the NIH Quality Assessment of Case-Control Studies. Any discrepancies in the evaluation were resolved through discussion.

## 3. Results

### 3.1. Study screening results and characteristics of included studies

The systematic search resulted in the identification of 1125 studies. Following the removal of 120 duplicate studies, 1005 studies underwent title and abstract screening. Subsequently, 78 studies underwent full-text screening. Studies were excluded due to irrelevant outcomes ($n$ = 17) (i.e., did not relate metabolic outcomes to depressive symptoms), incorrect study design ($n$ = 23), not published/translated in English (n = 1), incorrect study population ($n$ = 12) (Fig. 1). Of the 78 screened studies, a total of 25 studies were deemed eligible for inclusion. The updated search resulted in the identification of three additional studies, resulting in a total of 28 studies in this review.

From the 28 included studies, a total of 22,897 participants were included in this review, with sample sizes ranging between 59 and 4168 participants. Mean sample ages ranged between 19.4 and 62.4 years of age. Moreover, the included studies comprised 12 cohort studies, including 9 case-control studies, and 8 cross-sectional studies. Notably, 3 of the included studies enrolled both MDD and BD participants (Margari et al., 2013; Moreira et al., 2017; Silarova et al., 2015) while 24 studies only evaluated MDD patients. Only 1 included study evaluated BD patients (Cuellar-Barboza et al., 2021). Further details on the included studies are described in Tables 1 and 2.

### 3.2. Results from risk of bias assessment

Across the included bias, the main potential sources of bias included inadequate descriptions regarding sample size justifications, as well as whether the investigators were blinded throughout the study. As the component studies did not consistently report sample size justifications, it is difficult to determine whether the evaluated metabolic parameters have clinically meaningful effects on depressive symptom severity. Therefore, our results reported herein can only be considered as exploratory. In terms of the blinding integrity of the investigators, reported associations should be interpreted with caution, as a lack of blinding towards study participants may introduce bias in the rating of depressive symptom severity.

### 3.3. Comparison of glucose-insulin homeostasis between persons with depressive disorders and healthy controls

From the 28 included studies, we included 14 studies that reported on differences in glucose-insulin homeostasis between persons with depressive disorders and healthy controls (Bajaj et al., 2012; Cizza et al., 2012; Cuellar-Barboza et al., 2021; Lee et al., 2018; Margari et al., 2013; Moreira et al., 2017; Nyboe et al., 2016; Peng et al., 2017; Silarova et al., 2015; Singhal et al., 2018; Weber et al., 2000; Chang et al., 2013; Stanković et al., 2011; Vaghef-Mehrabani et al., 2021). Notably, measures of fasting glucose were the most commonly reported metabolic parameter across the included studies. In addition, results of the meta-analysis indicate that fasting glucose was significantly elevated in persons with depressive disorders compared to healthy controls (SMD = 0.30, 95 % CI = [0.12, 0.48]) (Fig. 2A). Moreover, of the five studies that reported nonsignificant differences in fasting glucose, Chang et al. (2013), Cuellar-Barboza et al. (2021) and Stanković et al. (2011) observed trends of elevated fasting glucose. The aforementioned trend was replicated in a study conducted by Nyboe et al. (2016), wherein young adults aged 18 to 45 with depressive disorders had significantly higher fasting glucose levels compared to healthy controls (median = 5.5 mmol/L; min, max = 4.2–5.9 mmol/L). Furthermore, while Weber et al. (2000) did not observe significant differences in basal glucose levels between persons with MDD and healthy controls (both 5.4 ± 1 mmol/L), persons with MDD were observed to have greater glucose intolerance as evidenced by greater increases in stimulated glucose levels following a test meal (5.4 ± 0.6 mmol/L vs 5.1 ± 0.7 mmol/L, respectively, F = 6.30, $p < 0.05$) (Weber et al., 2000).

Notwithstanding the foregoing results, fasting insulin levels (SMD = 0.20, 95 % CI = [−0.81, 1.22]) were nonsignificantly different between persons with depressive disorders and healthy controls (Fig. 2B). When evaluating the component studies individually, Cizza et al. (2012) and Margari et al. (2013) reported significantly elevated fasting insulin levels, which contrasts with the findings of Chang et al. (2013), who observed persons with depressive disorders to have significantly lower fasting insulin levels compared to healthy controls (Fig. 2B). A study conducted by Weber et al. (2000) did not observe significant differences in fasting insulin in persons with depressive disorders compared to healthy controls (SMD = −0.05, 95 % CI = [−0.56, 0.47]).

Analysis of studies reporting differences in HOMA-IR values further supports the trend of elevated insulin resistance in individuals with depressive disorders (Chang et al., 2013; Lee et al., 2018; Cizza et al., 2012) (Fig. 2C). Specifically, trends indicate that HOMA-IR values were elevated, albeit nonsignificantly (SMD = 0.16, 95 % CI = [−0.52, 0.84]). While Chang et al. (2013) did not observe significant differences in HOMA-IR and HOMA-B, values were significantly lower in persons with MDD compared to healthy controls (74.8 % ± 52.0 % vs 114.2 % ± 72.3 %, respectively, $p = 0.005$). Taken together, results indicate that persons with depressive disorders are at an elevated risk of insulin resistance.

### 3.4. Comparison of lipid measures between persons with depressive disorders and healthy controls

Our systematic search resulted in the inclusion of ten studies that reported on differences in total cholesterol, HDL, LDL, and/or triglyceride levels in persons with depressive disorders compared to healthy controls (Cuellar-Barboza et al., 2021; Vaghef-Mehrabani et al., 2021; Margari et al., 2013; Peng et al., 2017; Moreira et al., 2017; Singhal et al., 2018; Cizza et al., 2012; Silarova et al., 2015; Stanković et al., 2011; Lee et al., 2018). With respect to total cholesterol levels, an increase in total cholesterol trended in persons with depressive disorders (SMD = 0.19, 95 % CI = [−0.14, 0.53]) (Fig. 3A). Notably, while studies conducted by Moreira et al. (2017), Singhal et al. (2018) and Cizza et al. (2012) observed significantly elevated levels of total cholesterol, Peng et al. (2017), Cuellar-Barboza et al. (2021) and Vaghef-Mehrabani et al. (2021) did not observe significant differences, along with Margari et al. (2013) reporting significantly lower total cholesterol in persons with depressive disorders. Therefore, persons diagnosed with depression may be at an elevated risk of hyperlipidemia.

In terms of HDL and LDL specifically, HDL levels were significantly lower in people with depressive disorders compared to healthy controls (SMD = −0.72, 95 % CI = [−1.41, −0.03]) (Fig. 3B). Specifically, five of the eight studies included in the meta-analysis reporting on HDL reported significantly lower HDL levels (Silarova et al., 2015; Stanković et al., 2011; Margari et al., 2013; Singhal et al., 2018; Moreira et al., 2017). It should be noted, however, that Werremeyer et al. (2016) did not observe significant differences in HDL levels when comparing severe MDD patients to non-severe MDD patients (mean = 45.05 mg/dL, 95 % CI = [42.20, 47.91] vs mean = 45.83 mg/dL, 95 % CI = [44.42, 47.42], respectively, $p = 0.651$). Across the studies that reported on differences in LDL levels, there are currently mixed results; however, persons with depression displayed trends towards elevated LDL levels (SMD = 0.21, 95 % CI = [−0.03, 0.44]) (Fig. 3C). Notably, even in the studies that did not observe significant differences in LDL levels, these studies reported trends towards an elevation in LDL levels (Lee et al., 2018; Margari et al., 2013; Peng et al., 2017). In addition, LDL levels may be associated with greater depressive symptom severity as evidenced by persons with severe MDD having significantly higher LDL compared to non-severe MDD patients (mean = 109.12 mg/dL, 95 % CI = [99.23, 119.00] vs mean =

**Table 1**
Prevalence of disrupted glucose-insulin homeostasis in persons with depressive disorders.

| Study | Study design | Sample size | Sample age | Sex distribution | Aim(s) | Outcome measure tools | Main results |
|---|---|---|---|---|---|---|---|
| Bajaj et al. (2012) | Case-control study | 120 total participants<br>60 participants with MDD<br>60 HC | MDD: 47.67<br>HC: 46.85 | MDD: 21 (35 %) | Association of depression with diabetes in newly diagnosed T2DM patients | Laboratory markers: Fasting glucose, HbA1c | Fasting glucose was significantly higher in the MDD sample (177.80 ± 47.15 mg/dL) compared to HC (149.5 ± 26.85 mg/dL, $p = 0.0048$).<br>HbA1c was not significantly different in MDD (8.56 ± 1.66 %) compared to HC (8.04 ± 1.88 %) ($p = 0.26$). |
| Chang et al. (2013) | Case-control study | 154 total participants<br>50 MDD participants<br>104 HC | MDD: 38.6 (11.2)<br>HC: 34.1 (11.7) | MDD: 36 (72.0 %)<br>HC: 61 (58.7 %) | Effects of antidepressants on glucose-insulin homeostasis in MDD patients compared to healthy controls | Laboratory markers: HbA1c, AC glucose, insulin, HOMA-IR, HOMA-B<br>Psychometrics: HDRS | Fasting insulin and HOMA-B were significantly lower in MDD patients compared to healthy controls prior to antidepressant treatment (7.7 ± 4.8 uIU/mL vs 5.1 ± 4.2 uIU/mL, $p = 0.006$; 114.2 ± 72.3 % vs 74.8 ± 52.0 %, $p = 0.005$, respectively).<br>There were no significant differences in HbA1c, AC glucose, or HOMA-IR. |
| Cizza et al. (2012) | Cross-sectional study | 133 total participants<br>89 participants with MDD<br>44 HC | Undifferentiated MDD: 38.2 (5.4)<br>Atypical MDD: 34.3 (7.8)<br>Melancholic: 34.3 (7.0)<br>HC: 34.7 (6.8) | All female | Characterize metabolic features, bone mineral density and endocrine circadian profiles in clinical subtypes of MDD | Laboratory markers: HOMA-IR, protein and lipid profile | MDD participants had significantly greater HOMA-IR (2.37 ± 2.16 vs 1.46 ± 1.13), fasting glucose (94.1 ± 11.8 vs 87.6 ± 9.5 mg/dL), and insulin (9.72 ± 8.16 vs 6.06 ± 4.28 mcU/mL) along with greater LDL, log triglycerides, and total cholesterol. |
| Cuellar-Barboza et al. (2021) | Case-control study | 1367 total participants<br>661 participants with BD<br>706 HC | BD: 52.82 (11.38)<br>HC: 52.12 (11.73) | BD: 355 (53.7 %)<br>HC: 392 (55.5 %) | Investigate cardiometabolic markers in BD compared to non-psychiatric controls | Laboratory markers: Total cholesterol, triglycerides, LDL, HDL, fasting glucose, HbA1c | **Total cholesterol, mean (sd):**<br>BD = 188.4 mg/dL 43.1<br>HC = 190.3 mg/dL (35.7)<br>**Triglycerides, mean (sd):**<br>BD = 149.4 mg/dL (97.5)<br>HC = 121.3 mg/dL (61.9)<br>**LDL, mean (sd):**<br>BD = 106.3 mg/dL (35.4)<br>HC = 109.6 mg/dL (30.9)<br>**HDL, mean (sd):**<br>BD = 55.1 mg/dL (20.3)<br>HC = 56.2 mg/dL (17.6)<br>**Fasting glucose, mean (sd):**<br>BD = 101.7 mg/dL (25.8)<br>HC = 99.6 mg/dL (21.6)<br>**HbA1c, mean (sd):**<br>BD = 5.8 % (1.2)<br>HC = 5.9 % (1.0)<br>Only triglycerides were significantly different in persons with BD compared to HC. |

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**Table 1** (*continued*)

| Study | Study design | Sample size | Sample age | Sex distribution | Aim(s) | Outcome measure tools | Main results |
|---|---|---|---|---|---|---|---|
| Lee et al. (2018) | Case-control study | 184 total participants<br>121 participants with MDD<br>63 HC | MDD: 41.80 (10.46)<br>HC: 40.82 (10.33) | MDD: 86 (71.1 %)<br>HC: 44 (69.8 %) | Examine metabolic parameters in medicated MDD patients and compare with those of HC. | Laboratory markers: HOMA-IR, HOMA-B, LDL | The MDD participants did not have any significant differences in HOMA-IR (2.13 ± 5.25, 1.71 ± 1.82, respectively, $p = 0.59$), HOMA-B (93.65 ± 80.22, 94.19 ± 54.30, respectively, $p = 0.90$), LDL (122.02 ± 39.21, 118.54 ± 30.23, respectively, $p = 0.74$). |
| Margari et al. (2013) | Case-control study | 160 total participants<br>83 psychiatric inpatients (24 schizophrenia, 27 bipolar disorder, 14 MDD, 19 other)<br>77 participants with metabolic syndrome | MDD: 44.00<br>Bipolar disorder: 50.00 | Not reported | Differences of metabolic syndrome among psychiatric inpatients and internal medicine patients | Laboratory markers: HOMA, HDL, fasting insulin, TG/HDL ratio | Comparing all the psychiatric inpatients with the controls, there were significant differences in HDL (36.8 ± 7 vs 48 ± 11.3 mg/dL, p = 0.00), insulinemia (26 ± 12.5 vs 16.4 ± 8.8 uU/mL, p = 0.00), hyperglycemia (40.4 % vs 64.7 %, $p = 0.02$) and low HDL (76.6 % vs 51 %, $p = 0.01$).<br>Within the psychiatric inpatient sample, there were no significant differences in glycemia (F = 0.92, $p = 0.437$; BD = 108.44 mg/dL; MDD = 94.00 mg/dL), insulinemia (F = 0.59, $p = 0.622$; BD = 22.83 uU/mL; MDD = 17.92 uU/mL), glycosylated hemoglobin (F = 1.40, $p = 0.251$; BD = 5.74 %; MDD = 6.58 %), HOMA (F = 0.77, $p = 0.513$; BD = 6.07; MDD = 3.96), and TG/HDL (F = 1.11, $p = 0.349$; BD = 3.38; MDD = 4.93). |
| Moreira et al. (2017) | Cross-sectional study | 972 total participants<br>77 participants with MDD<br>32 participants with BD<br>863 HC | MDD: 26.09 (2.22)<br>BD: 25.59 (2.24)<br>HC: 25.81 (2.17) | MDD: 64 (11.2 %)<br>BD: 26 (4.6 %)<br>HC: 480 (84.2 %) | Assess differences in prevalence of metabolic syndrome in persons with BD compared to MDD in a current depressive episode and general population | Laboratory markers: Glucose, total cholesterol, LDL, HDL | There were significant between group differences in glucose (BD: 104.40 ± 34.00, MDD: 101.36 ± 45.53, HC: 85.89 ± 16.11 mg/dL, $p < 0.001$), total cholesterol (BD: 233.44 ± 66.15, MDD: 214.24 ± 56.91, HC: 196.68 ± 51.82 mg/dL, $p < 0.001$), and HDL (BD: 38.59 ± 10.03, MDD: 35.88 ± 10.63, HC: 45.65 ± 15.98 mg/dL, p < 0.001). |
| Nyboe et al. (2016) | Prospective cohort study | 102 total participants<br>52 participants with MDD<br>50 HC | MDD, median (min-max): 25.6 (18.7–45.5)<br>HC: 23.1 (18.3, 42.8) | MDD: 26 (52 %)<br>HC: 21 (42 %) | Evaluating the prevalence and progression of metabolic syndrome in young patients with MDD | Laboratory markers: triglycerides, HDL, fasting glucose | When comparing the MDD sample to the HC, there were significant differences in triglycerides (median = 1.1, min = 0.5, max = 2.7; median = 0.8, min = 0.4, max = 2.6 mmol/L), fasting glucose (median = 5.5, min = 4.2, max = 5.9; median = 5.0, min = 4.1, max = 5.8 mmol/L).<br>There were no significant differences in HDL (median = 1.25, min = 0.75, max = 2.7; median = 1.4, min = 0.85, max = 2.6 mmol/L). |
| Peng et al. (2017) | Retrospective cohort study | 617 total participants<br>305 participants with MDD<br>312 HC | MDD: 39.9 (8.47)<br>HC: 33.8 (9.86) | MDD: 239 (45.6 %)<br>HC: 140 (44.9 %) | Association of serum fructosamine and fasting blood glucose with MDD | Laboratory markers: Total cholesterol, HDL, fasting blood glucose, triglycerides, serum fructosamine | When comparing MDD and HC, there were significant differences in HDL (1.3 ± 0.34 vs 1.2 ± 0.33 mmol/L, $p = 0.002$), fasting blood glucose (4.7 ± 0.45 vs 4.5 ± 0.45 mmol/L, p < 0.001), and serum fructosamine (2.3 ± 0.26 vs 2.1 ± 0.27, $p = 0.018$).<br>Both serum glucose (OR = 2.251, 95 % CI = [1.037–1.082], p < 0.001) and fructosamine (OR = 6.313, 95 % CI = [2.953–13.393], p < 0.001) were significantly associated with MDD in multivariate regression analysis. |
| Silarova et al. (2015) | Cohort study | 2431 total participants<br>1648 participants with MDD<br>241 participants with BD<br>542 HC | MDD: 44.34 (12.54)<br>BD: 46.45 (11.60)<br>HC: 43.37 (14.61) | MDD: 1136 (68.9 %)<br>BD: 143 (59.3 %)<br>HC: 329 (60.7 %) | Investigate the prevalence of metabolic syndrome in BD compared to MDD and HC. Also to elucidate which metabolic syndrome components is most strongly associated with BD | Laboratory markers: triglycerides, HDL, glucose | No significant differences between BD and MDD participants in terms of triglycerides (1.46 ± 0.03 vs 1.37 (0.01), $p = 0.22$), but was significant for HDL (1.47 ± 0.03 vs 1.55 (0.01), p = 0.02) and glucose level (5.31 ± 0.11 vs 5.36 ± 0.03, p = 0.02).<br>Similarly, when comparing BD to HC, there were |

(*continued on next page*)

**Table 1** (*continued*)

| Study | Study design | Sample size | Sample age | Sex distribution | Aim(s) | Outcome measure tools | Main results |
|---|---|---|---|---|---|---|---|
| | | | | | | | no significant differences in triglycerides (1.46 ± 0.03 vs 1.30 ± 0.02, $p = 0.06$), but was significant for HDL (1.47 ± 0.03 vs 1.54 ± 0.02, $p = 0.04$) and glucose (5.31 ± 0.11 vs 5.31 ± 0.05, $p = 0.009$). |
| Singhal et al. (2018) | Cross-sectional study | 144 total participants<br>94 participants with MDD<br>50 HC | MDD: 39.24 (11.63)<br>HC: 38.17 (10.92) | MDD: 34 (37.8 %)<br>HC: Not explicitly reported but are age and sex matched | Evaluating metabolic syndrome and cardiovascular disease risk in MDD | Laboratory markers: total cholesterol, triglycerides, HDL, LDL, fasting glucose | Between MDD and HC, there were significant differences in fasting glucose (99.43 ± 53.47 vs 82.54 ± 20.34 mg/dL, $p = 0.007$), total cholesterol (198.96 ± 39.67 vs 171.99 ± 52.82 mg/dL, $p = 0.002$), HDL (38.24 ± 2.86 vs 40.40 ± 1.45, $p < 0.001$), and LDL (128.12 ± 40.02 vs 102.69 ± 29.68, $p < 0.001$). |
| Weber et al. (2000) | Case-control study | 59 total participants<br>26 participants with MDD<br>33 HC | MDD: 47 (16)<br>HC: 51 (19) | Not reported | Circadian pattern of insulin secretion and glucose concentration in MDD participants under basal conditions and after a standardized meal compared to HC | Laboratory markers: insulin, glucose | Under basal conditions between MDD and HC, there were no significant differences in insulin (154.3 ± 189.4 vs 164.3 ± 226 pmol/L, F = 0.15, $p > 0.05$) and glucose (5.4 ± 1 vs 5.4+/1 mmol/L, F = 0.14, $p > 0.05$).<br>Following a test meal, depression had a significant effect on stimulated glucose compared to HC (5.4 ± 0.6 mmol/L vs 5.1 ± 0.7 mmol/L, F = 6.30, $p < 0.05$) and stimulated insulin (338 ± 372 pmol/L vs 215 ± 225 pmol/L, F = 5.45, $p < 0.05$). |

94.22 mg/dL, 95 % CI = [90.89, 97.55], respectively, $p = 0.006$) (Werremeyer et al., 2016). With respect to LDL, two studies reported numerically lower LDL levels in persons with depressive disorders compared to healthy controls; however, these differences were not significant (Cuellar-Barboza et al., 2021; Vaghef-Mehrabani et al., 2021). Taken together, the results of HDL and LDL indicate that persons with depression exhibit an atherogenic lipid profile, characterized by elevated LDL and, to a lesser extent, trends of reduced HDL levels, which may contribute to poorer clinical outcomes over time.

In addition, the foregoing trends are further supported by observed differences in triglyceride levels in persons with depression. Across nine studies, trends towards elevated triglycerides were observed in persons with depressive disorders compared to healthy controls (SMD = 0.85, 95 % CI = [−0.58, 2.27]) (Fig. 3D). While overall trends indicate that there were no statistically significant differences in triglycerides, four studies reported significantly higher triglyceride levels, with the remaining five studies reporting elevated, albeit nonsignificant, triglyceride levels compared to healthy controls (Silarova et al., 2015; Stanković et al., 2011; Margari et al., 2013; Singhal et al., 2018; Moreira et al., 2017; Peng et al., 2017; Cizza et al., 2012; Cuellar-Barboza et al., 2021; Vaghef-Mehrabani et al., 2021). Overall, our results indicate that triglyceride levels are not differentially affected in depression populations.

### 3.5. *Associations between metabolic disturbances and clinical symptom severity*

We included 18 studies that reported on the association between metabolic disturbances and depressive symptom severity in persons with MDD or BD. Across the included studies, there are mixed results regarding the association between glucose control and disparate depressive symptom severity. For example, HbA1c levels were significantly associated with total scores on the Patient Health Questionnaire-9 (PHQ-9), but not the Beck Depression Inventory (BDI) or the Center for Epidemiological Studies Depression (CESD) scale (Bächle et al., 2015; Fisher et al., 2007; Stanković et al., 2011). Preliminary evidence also indicates that fasting blood glucose is significantly and positively associated with total scores on the Hamilton Depression Rating Scale (HAMD) ($r = 0.229$–$0.238$, $p < 0.001$) and BDI scores ($r = -0.158$, $p = 0.017$) (Chen et al., 2024; Peng et al., 2023; Vaghef-Mehrabani et al., 2021).

Notably, glucose disturbances and/or insulin resistance may be differentially associated with depressive symptom domains (i.e., appetite, sleep disturbances, psychomotor disturbances, suicidal ideation). For example, Bächle et al. (2015) reported that higher HbA1c levels were significantly associated with changes in appetite (standardized β = 0.33, SE = 0.29, p < 0.001), lethargy (standardized β = 0.24, SE = 0.31, p - 0.001) and psychomotor disturbances (standardized β = 0.19, SE = 0.90, $p = 0.010$). Similar trends have been replicated when evaluating the association between insulin and HOMA-IR with other validated measures of depressive symptoms, including sleep disturbances, changes in appetite, anhedonia, and suicidal ideation wherein greater levels of fasting glucose, insulin and/or insulin resistance may confer greater depressive symptom severity (Chae et al., 2023; Krupa et al., 2024; Peng et al., 2023; Steiner et al., 2019; Timonen et al., 2005). Steiner et al. (2019) conducted a case-control study and did not observe significant associations between HOMA-IR and HAM-D scores. However, the investigators did not disaggregate their sample by diagnosis, which may have affected the interpretation of their results. Notwithstanding, the foregoing trends underscore the role of insulin signaling in depression psychopathology, such that glucose intolerance and insulin resistance may directly and/or indirectly contribute to deficits in reward-related processes as well as regulation of energy homeostatic processes.

Separately, preliminary evidence indicates that measures of lipid metabolism are also associated with the severity of disparate symptoms of depressive disorders. A cross-sectional study conducted by Liu et al.

**Table 2**
Association of glucose-insulin homeostasis and depressive symptoms in persons with major depressive disorder.

| Study | Study design | Sample size | Sample age | Sex distribution; female | Aim(s) | Outcome measure tools | Main results |
|---|---|---|---|---|---|---|---|
| Bächle et al. (2015) | Cohort study | 211 total participants | 19.4 (0.9) | 121 (53.5 %) | Analyze associations between metabolic control and each of the nine DSM-5 symptoms of depression | Laboratory markers: HbA1c<br>Psychometrics: PHQ-9 | For the simple regression models, HbA1c was significantly associated with PHQ-9 total score (beta = 0.10, standardized beta = 0.26, SE = 0.03, $p = 0.001$) and changes in appetite (beta = 1.38, standardized beta = 0.33, SE = 0.29, $p < 0.001$), lethargy (beta = 1.00, standardized beta = 0.24, SE = 0.31, p = 0.001) and psychomotor disturbances (beta = 2.35, standardized beta = 0.19, SE = 0.90, $p = 0.010$). |
| Chae et al. (2023) | Population-based cohort study | 266 total participants | 41.47 [95 % CI = 39.2, 43.7] | 72.0 % | Evaluate the association between immunometabolic markers and depressive symptoms in MDD | Laboratory markers: Protein and lipid panel, HbA1c, glucose, insulin<br>Psychometrics: CIDI | For univariable associations, fasting glucose was not significantly associated with individual depressive symptoms; however, non-fasting glucose was associated with hypersomnia (beta = 0.17, SE = 0.08, $p = 0.034$) and suicidal ideation (beta = 0.08, SE = 0.04, p = 0.04). Similarly, fasting insulin was not significantly associated with individual depressive symptoms; however, non-fasting insulin was associated with decreased appetite (beta = −0.34, SE = 0.15, $p = 0.029$), hypersomnia (beta = 0.79, SE = 0.21, p = 0.002), fatigue/energy loss (beta = 0.39, SE = 0.13, p = 0.004), and suicidal ideation (beta = 0.32, SE = 0.14, $p = 0.020$). Following adjustment for sociodemographic and behavioural variables, medication use, and depression severity, glucose was associated with suicidal ideation (beta = 0.1, $p = 0.025$) while insulin was associated with increased appetite (beta = 0.2, $p = 0.024$), insomnia (beta = 0.2, $p = 0.042$), hypersomnia (beta = 0.3, $p = 0.023$), and suicidal ideation (beta = 0.2, $p = 0.003$). |
| Chen et al. (2024) | Cross-sectional study | 1718 total participants | 34.87 (12.43) | 1130 (65.8 %) | Investigate the incidence and clinical profile of comorbid glucose disturbances in first-episode drug-naive MDD patients and identify related factors correlated with glucose disturbances in the population | Laboratory markers: Plasma glucose<br>Psychometrics: PANSS, HAMD, HAMA | Between MDD participants with and without glucose disturbances, there were significant differences in HAMD scores (31.37 ± 2.87 vs 30.13 ± 2.94, F = 36.913, p < 0.001), HAMA scores (21.99 ± 3.64 vs 20.61 ± 3.41, F = 32.369, p < 0.001), and suicide attempts (35.5 % vs 17.7 %, chi-square = 39.585, p < 0.001).<br>HAMD ~ FBG = 0.238, df 1718, p < 0.001<br>HAMA ~ FBG = 0.132, df = 1718, p < 0.001<br>Duration of disease ~ FBG = 0.066, df 1718, p = 0.007 |

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**Table 2** (*continued*)

| Study | Study design | Sample size | Sample age | Sex distribution; female | Aim(s) | Outcome measure tools | Main results |
|---|---|---|---|---|---|---|---|
| | | | | | | | Suicide attempts ~ FBG = 0.115, df = 1718, p < 0.001<br>Multiple linear regression indicated significant associations between FBG and HAMD ($t = 7.610$, $p < 0.001$), HAMA ($t = 2.635$, $p < 0.05$), suicide attempts ($t = 3.389$, $p < 0.05$), which remained significant following Bonferroni correction.<br>Binary logistic regression indicated glucose disturbances were associated with increased HAMD (OR = 1.087, 95 % CI 1.021–1.157, p = 0.009) and a history of suicide attempt (OR = 1.871, 95 % CI 1.333–2.628, p < 0.001). |
| Fisher et al. (2007) | Cohort study | 506 total participants | 57.83 (9.86) | 288 (57 %) | To determine differences between diagnoses and symptoms of depression in patients with diabetes | Laboratory markers: A1C, non-HDL cholesterol<br>Psychometrics: Center for Epidemiological Studies Depression (CESD) scale | Used cutoffs of greater than or equal to 16 and 22 as "likely depression" along with CIDI diagnoses. Scores of 16 or greater on CESD were significantly and independently associated with higher A1C (F = 10.93, p < 0.001). However, when controlling for CESD scores, having a CIDI diagnosis of MDD resulted in nonsignificant associations. |
| Krupa et al. (2024) | Cross-sectional study | 97 total participants<br>67 MDD participants<br>30 HC | MDD: 42.97 (13.52)<br>HC: 44.50 (12.37) | MDD: 53<br>HC: 27 | Assessing insulin resistance in MDD and associations with clinical presentation and treatment response | Laboratory markers: HOMA-IR, insulin<br>Psychometrics: QIDS, HADS-D, SHAPS, DARS, SHAPS, STAI, PSQI | All of the following were significant associations:<br><br>Associations with insulin:<br>STAI-Trait ~ Insulin = 0.29<br>STAI-State ~ Insulin = 0.31<br>SHAPS ~ Insulin = 0.23<br>QIDS ~ Insulin = 0.36<br>PSQI ~ Insulin = 0.24<br>HADS-D ~ Insulin = 0.4<br>DARS ~ Insulin = −0.22<br>Associations with IR:<br>STAI-Trait ~ IR = 0.31<br>STAI-State ~ IR = 0.29<br>SHAPS ~ IR = 0.23<br>QIDS ~ IR = 0.37<br>PSQI ~ IR = 0.27<br>HADS-D ~ IR = 0.41<br>DARS ~ IR = −0.22 |
| Liu et al. (2022) | Cross-sectional study | 1279 total participants | MDD with suicide attempt (s): 36.12 (12.35)<br>MDD without suicide attempt (s): 34.55 (12.43) | MDD with suicide attempt(s): 75 (65.2 %)<br>MDD without suicide attempt(s): 764 (65.6 %) | Association of fasting glucose and thyroid stimulating hormones with suicidal tendency and severity of MDD | Laboratory markers: Fasting blood glucose, total cholesterol, HDL-C<br>Psychometric: Suicide attempt history, HAM-A | Fasting glucose levels were significantly different in patients with or without suicide attempt history ($t = -6.16$, $p < 0.001$) and greater anxiety severity ($t = -5.79$, $p < 0.001$).<br>Similar results were observed for total cholesterol for suicide attempt history ($t = -10.19$, $p < 0.001$), and anxiety severity ($t = -7.15$, $p < 0.001$).<br>Similar results were also seen for HDL-C wherein persons with suicide attempt history ($t = 6.05$, $p < 0.001$), and higher anxiety ($t = 4.47$, $p < 0.001$) had lower HDL-C.<br>Significant results were also observed for triglycerides and LDL-C. |

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**Table 2** (*continued*)

| Study | Study design | Sample size | Sample age | Sex distribution; female | Aim(s) | Outcome measure tools | Main results |
|---|---|---|---|---|---|---|---|
| Luppino et al. (2014) | Prospective cohort study | 827 total participants<br>302 primary care outpatients<br>445 secondary care outpatients<br>80 inpatients | Primary care outpatients: 45.9 (11.7)<br>Secondary care outpatients: 39.0 (11.3)<br>Inpatients: 44.8 (11.3) | Primary care outpatients: 68.5 %<br>Secondary care outpatients: 64.0 %<br>Inpatients: 50 % | Compare MDD patients and metabolic syndrome prevalences and metabolic variables with their role to clinical characteristics | Laboratory markers: Protein and lipid panel, glucose<br>Psychometrics: CIDI | Depressive symptom severity was significantly associated with lower HDL-C (beta = −0.11, p = 0.005) and higher glucose (beta = 0.07, p = 0.04). Other factors such as waist circumference, triglycerides, blood pressure, BMI, total cholesterol, LDL were not associated with depressive symptom severity. Glucose was not associated with comorbid anxiety, number of affected months or psychotropic drug use in outpatients. |
| Ma et al. (2019) | Cross-sectional study | 288 total participants | 41(24) | 188 (65.28 %) | Investigating prevalence of suicide attempts in MDD inpatients and association with clinical and biological factors | Laboratory markers: Plasma glucose, serum total cholesterol, triglycerides, HDL-C, LDL-C<br>Psychometrics: Self-rating depression scale (SDS), self-rating anxiety scale (SAS), suicide attempt history | Between persons with suicide attempt history and no history, there were no significant differences in glucose ($z = -0.12$, $p = 0.91$), triglycerides ($z = -0.91$, $p = 0.37$), HDL-C ($z = -0.97$, $p = 0.33$), LDL-C ($z = -1.97$, $p = 0.05$). There were significant differences in total cholesterol ($z = -2.17$, $p = 0.03$).<br>Suicide attempts were significantly associated with LDL-C ($r = 0.17$, $p = 0.05$) and total cholesterol ($r = -0.13$, $p = 0.03$). |
| Peng et al. (2023) | Cohort study | 1718 total participants | Median = 34 (IQR = 23, 45) | 1130 (66 %) | Association between thyroid dysfunction, metabolic disturbances, and clinical symptoms in first-episode, untreated MDD patients using Bayesian network analyses | Laboratory markers: triglycerides, fasting glucose, total cholesterol, HDL-C, LDL-C<br>Psychometrics: HAMD, HAMA, PANSS | Partial correlations between metabolic parameters and clinical symptoms:<br><br>HAMD ~ Glucose = 0.229, p < 0.001<br>HAMA ~ Glucose = 0.124, p < 0.001<br>PANSS ~ Glucose = 0.16, p < 0.001 |
| Stanković et al. (2011) | Case-control study | 90 total participants<br>46 participants with T2DM and MDD<br>44 participants with T2DM only | T2DM + MDD: 54.39 (6.55)<br>T2DM: 57.18 (5.78) | T2DM + MDD: 35 (76.1 %)<br>T2DM: 24 (54.6 %) | Investigate differences between patients with T2DM and depression compared to those with just T2DM | Laboratory markers: Fasting glucose, triglycerides, HbA1c, HDL | Persons with depression and T2DM had trends of higher fasting glucose (11.35 ± 4.12) compared to just T2DM patients (10.60 ± 2.92) albeit nonsignificant.<br>This was similarly observed with triglycerides (2.95 ± 2.15 vs 2.87 ± 1.80, p > 0.05), HbA1c (8.69 ± 1.92 vs 9.11 ± 1.65, p > 0.05), HDL (1.05 ± 0.27 vs 1.14 ± 0.29, p > 0.05).<br>Notably there was a significant correlation between BDI som. Subscores and HbA1c ($r = 0.343$, $p = 0.020$) in the depression group, but not with BDI total score. |
| Steiner et al. (2019) | Case-control study | 85 total participants<br>18 MDD<br>24 Schizophrenia<br>43 HC | MDD: 46.0 (33.50, 52.75)<br>HC: 35.0 (26.0, 45.0) | MDD: 7 (38.9)<br>HC: 17 (39.5 %) | Glucose homeostasis in MDD and Schizophrenia in drug-naive first-episode patients | Laboratory markers: HOMA-IR<br>Psychometric: HAMD-21 sum | When controlling for BMI, there were significant differences in HOMA-IR between diagnostic groups ($F = 5.360$, $p = 0.006$) wherein persons with MDD had the lowest HOMA-IR (median = 0.45, quartile 1 and 3 = [0.33, 0.62]) compared to HC (median = 0.56, quartile 1 and 3 = [0.36, 0.85]). HOMA-IR was not significantly |

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**Table 2** (*continued*)

| Study | Study design | Sample size | Sample age | Sex distribution; female | Aim(s) | Outcome measure tools | Main results |
|---|---|---|---|---|---|---|---|
| | | | | | | | associated with HAMD-21 sum ($r = -0.253$, $p = 0.326$); however, this was not separated by diagnosis. |
| Timonen et al. (2005) | Cross-sectional study | 491 total participants<br>367 participants with normal glucose tolerance<br>92 participants with impaired glucose tolerance<br>32 participants with T2DM | Not reported | Not reported | Investigating pathophysiological changes in depression and association with glucoregulatory functions | Laboratory markers: Qualitative insulin sensitivity check<br>Psychometric: BDI-21 | In the total sample, insulin resistance was significantly correlated with BDI-21 scores ($r = -0.13$, $p = 0.004$). In the impaired glucose tolerance group, this was also significant ($r = -0.24$, $p = 0.029$); however, this was not consistent in the normal glucose tolerance group ($r = -0.037$, $p = 0.492$). |
| Vaghef-Mehrabani et al. (2021) | Case-control study | 225 total participants<br>75 MDD<br>150 HC | MDD: 39.64 (7.70)<br>HC: 39.97 (7.58) | All female | Compare oxidative stress and metabolic syndrome features between depressed and non-depressed obese women | Laboratory markers: Fasting glucose, HDL, LDL, total cholesterol, triglycerides<br>Psychometrics: BDI-II | **Fasting glucose, mean (sd):**<br>MDD = 86.49 mg/dL (14.60)<br>HC = 82.67 mg/dL (11.01)<br>**Triglycerides, mean (sd):**<br>MDD = 162.99 mg/dL (82.03)<br>HC = 155.49 mg/dL (59.68)<br>**Total cholesterol, mean (sd):**<br>MDD = 205.89 mg/dL (37.63)<br>HC = 204.79 mg/dL (33.44)<br>**HDL, mean (sd):**<br>MDD = 49.52 mg/dL (10.19)<br>HC = 48.77 mg/dL (9.79)<br>**LDL, mean (sd):**<br>MDD = 123.78 mg/dL (36.04)<br>HC = 124.92 mg/dL (31.11)<br>No significant differences in any metabolic parameters between MDD and HC. There was a significant association between fasting glucose and BDI-II scores ($r = 0.158$, $p = 0.017$), but not triglycerides ($r = 0.007$, $p = 0.912$) or HDL ($r = -0.017$, $p = 0.802$). |
| Virtanen et al. (2017) | Prospective cohort study | 1172 total participants | 62.4 (6.6) | 449 (38.3 %) | Association of metabolic syndrome with symptom resolution in MDD patients | Laboratory markers: HDL, triglycerides, fasting glucose<br>Psychometrics: CES-D | Impaired glucose signaling/ diabetes, abdominal obesity and hypertension were not associated with symptom resolution. Even when prediabetes and diabetes were analyzed separately, there was no association with symptom resolution. Low HDL (RR = 0.82, 95 % CI = 0.68, 1.00; $p = 0.045$) and high triglycerides (RR = 0.81, 95 % CI = [0.70, 0.95], p = 0.007) were associated with decreased likelihood of symptom resolution. |

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**Table 2** (*continued*)

| Study | Study design | Sample size | Sample age | Sex distribution; female | Aim(s) | Outcome measure tools | Main results |
|---|---|---|---|---|---|---|---|
| Werremeyer et al. (2016) | Cross-sectional study | 517 total participants<br>97 participants with severe MDD<br>420 participants with non-severe MDD | Severe MDD: 55.08 (52.38–57.78)<br>Non-severe MDD: 59.65 (58.40–60.91) | Severe MDD: 61 (62.89 %)<br>Non-severe MDD: 284 (67.65 %) | Disease characteristics of patients with T2DM and moderate-severe depression | Laboratory markers: HbA1c, LDL, HDL<br>Psychometrics: PHQ-9 | Comparing severe to non-severe participants, there were significant differences in HbA1c (mean = 7.56 %, 95 % CI = [7.18, 7.94] vs 7.09 % 95 % CI = [6.94, 7.24], p = 0.023) and LDL (mean = 109.12 mg/dL, 95 % CI = [99.23, 119.00] vs 94.22, 95 % CI = [90.89, 97.55], p = 0.006). HDL did not significantly differ between groups (mean = 45.05 mg/dL, 95 % CI = [42.20, 47.91] vs 45.83, 95 % CI = [44.42, 47.42], $p$ = 0.651). |
| Yu et al. (2020) | Prospective cohort study | 2796 total participants<br>110 MDD participants<br>2686 HC | MDD: 54.56 (10.48)<br>HC: 52.10 (10.25) | MDD: 44 (40 %)<br>HC: 1499 (55.8 %) | Estimating whether baseline metabolic disorders increase the incidence of MDD in a prospective analysis. Also investigating whether metabolic disorders are associated with MDD | Laboratory markers: fasting plasma glucose, lipid profiles<br>Psychometrics: PHQ-9 | The female participants had significantly higher prevalence rates of MDD in persons with metabolic syndrome (9.3 % vs 7.1 %, p = 0.001), which was not observed in males.<br>In a cross-sectional analysis there was no significant relationship between metabolic syndrome, metabolic disorders and MDD.<br>Within the females, the presence of metabolic syndrome, hypertriglyceridemia and elevated blood pressure were associated with an increased incidence of MDD, but not other lipid parameters or hyperglycemia. |

(2022) reported that people living with depression also reported greater severity of anxiety and were observed to have significantly higher levels of LDL and triglycerides as well as lower HDL. Similarly, lower HDL levels have been reported to be associated with decreased overall depressive symptom severity ($\beta = -0.11$, $p = 0.005$) (Luppino et al., 2014). Moreover with respect to the study conducted by Vaghef-Mehrabani et al. (2021), while a significant association between depressive symptom severity with HDL was not observed, trends of lower HDL ($r = -0.018$, $p = 0.802$) were reported. While Werremeyer et al. (2016) did not observe significant differences in HDL between participants with severe vs non-severe MDD, persons with severe MDD had significantly higher LDL (mean = 109.12 mg/dL, 95 % CI = [99.23, 119.00]) compared to non-severe (mean = 94.22 mg/dL, 95 % CI = [90.89, 97.55]). When considering the association between lipid metabolism and suicide attempt history, there are currently mixed results regarding whether persons with a history of suicide attempt have differential lipid profiles (Liu et al., 2022; Ma et al., 2019).

The mechanistic interaction between lipid measures and depressive symptom severity is further supported by replicated observations that hypertriglyceridemia was associated with increased incidence rates of MDD (Yu et al., 2020). Moreover, a decreased likelihood of depressive symptom resolution was associated with lower HDL (Risk Ratio; RR = 0.82, 95 % CI = [0.68, 1.00], $p = 0.045$) and higher triglycerides (RR = 0.81, 95 % CI = [0.70, 0.95], $p = 0.007$) (Virtanen et al., 2017). In contrast, overall depressive symptom severity was not found to be associated with triglyceride levels ($r = 0.007$, $p = 0.912$) (Vaghef-Mehrabani et al., 2021). Overall, replicated evidence indicates that measures of lipid metabolism may also differentially contribute to the severity and prognosis of symptoms in persons with depressive disorders.

## 4. Discussion

The results of our systematic review and meta-analysis accord with other research findings that persons with depressive and bipolar disorders are differentially affected by metabolic alterations and related comorbidity. Our results inform the available evidence base by identifying an association between the severity of depressive and related symptoms (e.g., anxiety and sleep) and the occurrence of metabolic disorders. The consistent association observed between metabolic alterations and depression, particularly among individuals with greater illness severity, raises the possibility that, for a subpopulation of persons with lived experiences, the pathophysiology of their illness involves metabolic pathways. Although the observational and cross-sectional nature of the included studies precludes definitive conclusions about causality, these findings are consistent with the hypothesis that metabolic pathways could play a contributory or modulatory role in the clinical expression or progression of mood disorders in certain subpopulations (Fernandes et al., 2022; Miola et al., 2023; Calkin et al., 2015).

Multiple factors mediate and moderate the observed differential association between mood disorders and metabolic alterations (McIntyre, 2021). For example, available literature indicates that psychotropic agents commonly used in the treatment of depressive/bipolar disorders (e.g., mirtazapine, olanzapine) include weight gain, insulin resistance and dyslipidemia (McIntyre et al., 2024; Yoon et al., 2013; Zhang et al., 2017). Our results also accord with prior studies indicating that

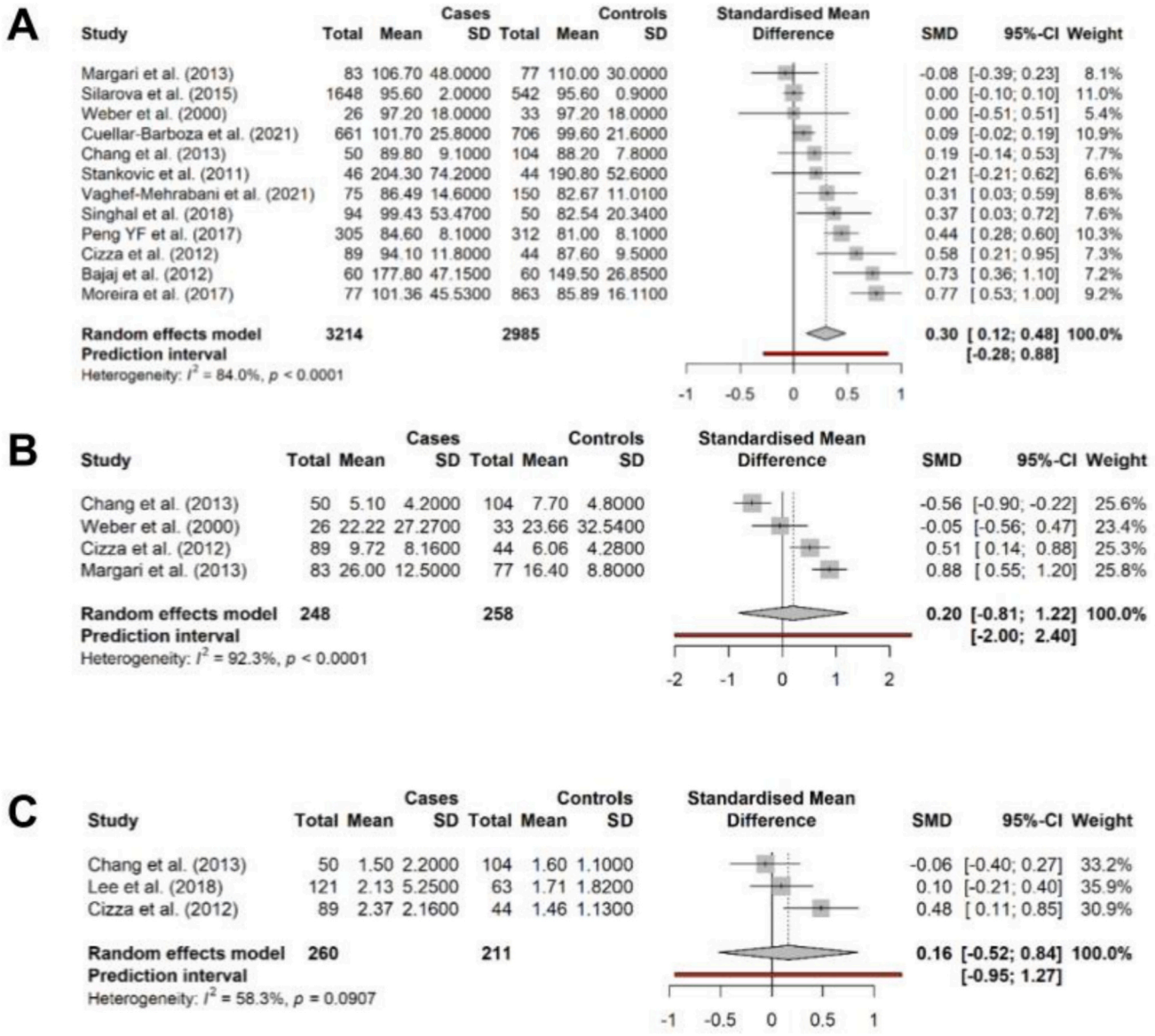


**Fig. 2.** Standardized mean differences in measures of insulin resistance between persons with mood disorders and controls. A. Fasting glucose. B. Fasting insulin. C. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).

metabolic disturbances are not only associated with elevated depression risk but are also associated with attenuated antidepressant response (Imaizumi et al., 2022; Rashidian et al., 2023; Vogelzangs et al., 2014; Possidente et al., 2023; Miola et al., 2023). More than half of persons with depressive disorders fail to achieve remission after two sequential monoamine-based antidepressants, suggesting that a percentage of persons with difficult-to-treat depression may have attenuated antidepressant responses partially due to the existence of metabolic alterations (Mansur et al., 2020; McIntyre et al., 2023, 2007).

Current research of glucagon-like peptide-1 (GLP-1) receptor agonists for the treatment of various psychiatric disorders (e.g., substance use disorders, neurodegenerative disorders) has shown preliminary evidence to support the role of metabolism and insulin signaling in disorders of the brain (Au et al., 2025a, 2025b; Cooper et al., 2023; Kabahizi et al., 2022; Lee et al., 2024; McIntyre et al., 2025). In addition, ketamine and esketamine have demonstrated replicable rapid-acting antidepressant effects in persons with difficult-to-treat depression (Abbar et al., 2022; Anand et al., 2023; Bennett et al., 2022; McIntyre et al., 2021). Preliminary preclinical, pharmacologic and translational evidence supports direct and/or indirect insulin modulating effects of ketamine and esketamine through functional connectivity between *N*-methyl-D-aspartate and insulin receptors. While clinical efficacy estimates for ketamine and esketamine are mixed, NMDA and insulin receptor interactions may represent a plausible mechanism for metabolic modulation and their antidepressant effects; however, the clinical significance of this interaction has yet to be evaluated in adequately-powered longitudinal studies (Ansari et al., 2025; Cyranka et al., 2022; Freeman et al., 2020; Noguera Hurtado et al., 2023; Petersen et al., 2024; Wong et al., 2025b). Overall, evaluating metabolic targets may serve as a novel therapeutic target in drug discovery and development for mood disorders.

These findings support the integration of metabolic screening management into routine psychiatric care, particularly for individuals with severe or treatment-resistant mood disorders. Monitoring metabolic parameters should be integrated into personalized treatment planning for patients with mood disorders, especially MDD and BD.

Guidelines for MDD and BD should incorporate recommendations for routine metabolic assessment, especially in patients with poor antidepressant response, severe symptomatology, or atypical features. This could facilitate early identification of high-risk individuals and optimize

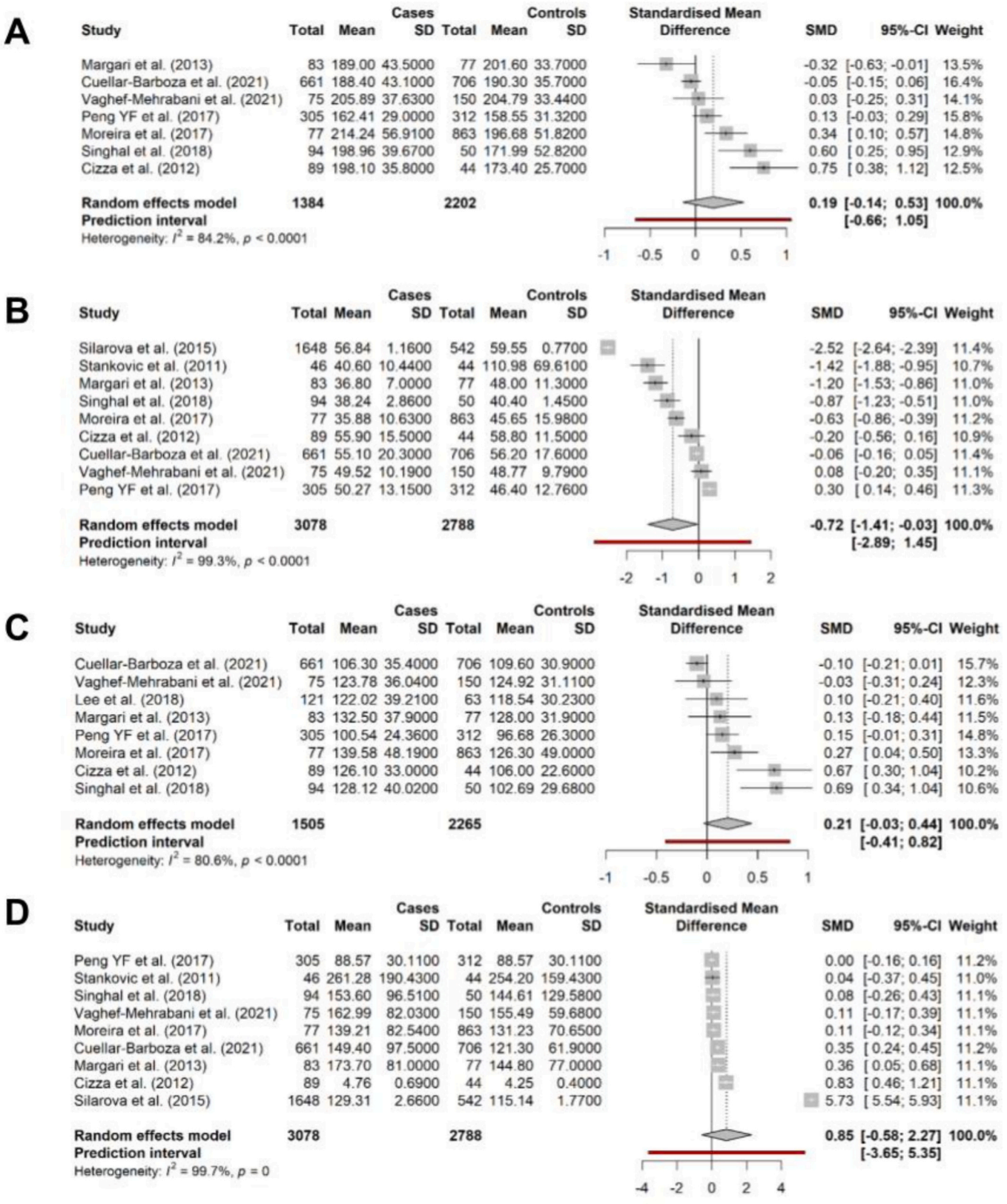


**Fig. 3.** Standardized mean differences in lipid panel measures between persons with depression and controls. A. Total cholesterol. B. High-density lipoprotein. C. Low-density lipoprotein. D. Triglycerides.

therapeutic strategies, including the potential use of metabolically targeted interventions. Specifically, metabolic disturbances, including insulin resistance and dyslipidemia, may serve as biological signatures to identify patient subgroups with distinct pathophysiological profiles. Such biological signatures may improve predictive modeling of treatment response to psychotropic agents. Early identification of metabolic dysfunction would also aid the selection of metabolically-neutral psychotropic agents in high-risk individuals or prescription of novel treatments that directly modulate both metabolic and neuroaffective pathways. Taken together, the incorporation of routine metabolic assessment into clinical psychiatric practice may reduce heterogeneity in treatment outcomes, improve long-term treatment adherence and efficacy as well as aid in the discovery and development of mechanistically-informed treatments for persons with mood disorders.

Our systematic review and meta-analysis are not without methodological limitations. Primarily, due to substantial inter-study methodological heterogeneity, the synthesis of overall trends between the association of the investigated metabolic parameters and depressive symptom severity should be considered with caution. Specifically, the scales utilized to assess depressive symptoms significantly differed, which may address different depressive symptoms and have varying clinical thresholds for detecting clinically meaningful differences. In addition, differences in metabolic parameters may be affected by various factors that could not be controlled for in our analyses and interpretation of the results, including, but not limited to, illness duration, medical comorbidities (e.g., cardiovascular disease, diabetes mellitus) and concomitant antidepressant treatments during the trial duration. Most included studies did not adequately account for underlying somatic comorbidities or concurrent medications, which may have introduced bias and limits the generalizability of our findings. Furthermore, we were unable to evaluate whether there are significant metabolic differences between persons with MDD compared to BD, which may be differentially associated with depressive symptom presentation and severity. Finally, as the current body of evidence is correlational in nature, we are unable to evaluate bidirectionality. Therefore, we are unable to determine whether metabolic disturbances exacerbate depressive symptom severity, whether depression symptomatology contributes to metabolic disturbances, or whether both are driven by shared pathophysiological mechanisms.

Future research should prioritize prospective, longitudinal designs to clarify causal links between metabolic dysfunction and symptom severity in mood disorders. Trials should incorporate metabolic biomarkers as moderators to identify subgroups responsive to emerging treatments. Additionally, studies must account for psychotropic exposure, illness duration, and metabolic comorbidities, while distinguishing between unipolar and bipolar depression. Developing integrated clinical staging models that combine psychiatric and metabolic burden may ultimately improve personalized care strategies.

Notwithstanding, to our knowledge, this is the first systematic review and meta-analysis to quantitatively evaluate differences in clinical metabolic parameters between persons with depressive/bipolar disorders and healthy controls, as well as evaluate their association with depressive symptom severity. Our results purport the likely scenario that not all persons living with depressive and bipolar disorders are at an increased risk of metabolic alterations and relatedly, it is unlikely that metabolic disturbances are pertinent to their mood disorder. Instead, there is likely a sub-population of persons with lived experience wherein their illness occurrence, clinical presentation, longitudinal course in response to antidepressants, is related to the occurrence of metabolic alteration.

A derivative of this likelihood is a testable hypothesis that populations living with depressive and bipolar disorders are more likely to benefit from repurposed or de novo therapeutics that primarily target the metabolic system if they also exhibit metabolic alterations (Calkin et al., 2022). Incretin receptor agonists have moved into late-phase development in the treatment and prevention of depressive and bipolar disorders. Although these agents affect metabolic systems, they also have direct effects on molecular and cellular pathways implicated in the pathophysiology of depression, independent of their effects on metabolic systems (Cooper et al., 2023; McIntyre et al., 2025). It will be interesting to explore whether outcomes with these agents in the treatment and prevention of depression or bipolar disorder are moderated by pre-existing metabolic alterations.

## CRediT authorship contribution statement

**Sabrina Wong:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Gia Han Le:** Writing – review & editing, Investigation, Data curation. **Hernan F. Guillen-Burgos:** Writing – review & editing. **Roger Ho:** Writing – review & editing. **Bing Cao:** Writing – review & editing. **Heidi K.Y. Lo:** Writing – review & editing. **Kayla M. Teopiz:** Writing – review & editing. **Roger S. McInyre:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

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## Appendix A. Supplementary data

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