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Neurocognitive correlates of metabolic dysregulation in individuals with mood disorders: a systematic review and meta-analysis

Kateryna Maksyutynska[1,2], Nicolette Stogios[1,2], Femin Prasad[1,2], Jashan Gill[1,3], Zaineb Hamza[1,4], Riddhita De[1,2], Emily Smith[1,2], Angelina Horta[1,4], Benjamin I. Goldstein[1,5,6,7], Daphne Korczak[1,5,8], Ariel Graff-Guerrero[1,5,9], Margaret K. Hahn[1,2,5] and Sri Mahavir Agarwal[1,2,5]

[1]Institute of Medical Science, University of Toronto, Toronto, ON, Canada; [2]Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, ON, Canada; [3]Faculty of Science, McMaster University, Hamilton, ON, Canada; [4]Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada; [5]Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [6]Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada; [7]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada; [8]Department of Psychiatry, Hospital for Sick Children, Toronto, ON, Canada and [9]Research Imaging Centre, Centre for Addiction and Mental Health, Toronto, ON, Canada

Review Article

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Corresponding author:
Sri Mahavir Agarwal;
Email: Mahavir.Agarwal@camh.ca

Abstract

Individuals with mood disorders are predisposed to metabolic dysfunction, while those with metabolic dysregulation such as diabetes and obesity experience more severe depressive symptoms. Both metabolic dysfunction and mood disorders are independently associated with cognitive deficits. Therefore, given their close association, this study aimed to explore the association between metabolic dysfunction in individuals with mood disorders in relation to cognitive outcomes. A comprehensive search comprised of these three domains was carried out; a random-effects meta-analysis pooling mean cognitive outcomes was conducted (PROSPERO ID: CRD42022295765). Sixty-three studies were included in this review; 26 were synthesized in a quantitative meta-analysis. Comorbid metabolic dysregulation was associated with significantly lower global cognition among individuals with mood disorders. These trends were significant within each mood disorder subgroup, including major depressive disorder, bipolar disorder, and self-report depression/depressive symptoms. Type 2 diabetes was associated with the lowest cognitive performance in individuals with mood disorders, followed by peripheral insulin resistance, body mass index $\geqslant 25\ kg/m^2$, and metabolic syndrome. Significant reduction in scores was also observed among individual cognitive domains (in descending order) of working memory, attention, executive function, processing speed, verbal memory, and visual memory. These findings demonstrate the detrimental effects of comorbid metabolic dysfunction in individuals with mood disorders. Further research is required to understand the underlying mechanisms connecting mood disorders, metabolism, and cognition.

Introduction

Mood disorders, encompassing depressive and bipolar disorder (BD), are prime contributors to the global burden of disease and are associated with a significant reduction in the quality of life of patients (Cramer, Torgersen, & Kringlen, 2010; Frey et al., 2020). This may, in part, be attributed to the cardiometabolic comorbidities to which individuals with mood disorders are predisposed, including type 2 diabetes (T2D), obesity, and metabolic syndrome (MetS) and its components (Qiu et al., 2021). These metabolic features are independently associated with insulin resistance, which on its own has been associated with more severe depressive symptoms (Singh et al., 2019). This is further reflected in the observation that the prevalence of depression in individuals with diabetes is two to three times greater than in a metabolically healthy population (Roy & Lloyd, 2012). This evidence suggests a bidirectional relationship between metabolic dysfunction and mood disorders, such that it has been referred to as a 'metabolic-mood syndrome' (Mansur, Brietzke, & McIntyre, 2015).

Metabolic dysfunction and mood disorders have also, independently, been linked to cognitive impairment. Interestingly, these relationships are dynamic, whereby increases in symptom severity distinct to mood and metabolic disorders are associated with greater cognitive decline (Karlsson, Gatz, Arpawong, Dahl Aslan, & Reynolds, 2021; Marvel & Paradiso, 2004). Understanding these interactions is of great importance due to the impact of cognitive

function on symptom severity and functioning in individuals with mood disorders (Burdick, Goldberg, & Harrow, 2010; Siegel-Ramsay et al., 2022). A recent meta-analysis examined the association between depression and cognition in persons with diabetes mellitus and reported significant impairment in overall cognition, executive function, language, and memory among individuals with comorbid diabetes and depression in comparison to those with only diabetes (Chow, Verdonschot, McEvoy, & Peeters, 2022). Another meta-analysis found obese/overweight BD patients to have more severe cognitive deficits *v.* normal-weight patients, especially in global cognition, executive function, and processing speed domains (Bora, McIntyre, & Ozerdem, 2019). However, there has been no synthesis of the association between metabolic dysfunction and cognitive outcomes in individuals across the mood disorder spectrum including major depressive disorder (MDD).

Therefore, this review sought to broadly explore the association between metabolic dysregulation and global cognition and individual cognitive domains in individuals with mood disorders. It was hypothesized that due to the bidirectional relationship observed between mood and metabolic disorders, and supporting evidence outlining its impact on cognition, that individuals with a mood and metabolic disorder comorbidity would exhibit poorer cognitive performance compared to those with only a mood disorder. Furthermore, exploratory analysis investigated the association between the severity of metabolic dysregulation and cognition.

Methods

This systematic review and meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with ID: CRD42022295765.

Inclusion criteria

Inclusion criteria were structured with the PICOS framework, as outlined.

(a) **Population**: Individuals with a diagnosed mood disorder (including depressive disorders and bipolar and related disorders) or those experiencing depressive symptoms as measured through validated scales and/or self-reported depression. Studies of participants with type 1 diabetes and those that were pregnant and/or breastfeeding were excluded to address potential confounding hormonal and genetic interactions with cognitive function. Similarly, studies of populations with predefined cognitive impairment and/or neurocognitive disorders at baseline were excluded.

(b) **Intervention/exposure**: Comorbid metabolic dysregulation, including MetS and/or at least one of its components such as abdominal obesity, high blood pressure, impaired fasting glucose, high triglycerides, reduced HDL cholesterol levels; T2D; insulin resistance; elevated body mass index (BMI) (overweight/obesity).

(c) **Comparator**: Individuals with the same mood disorder, but metabolically healthy in relation to the exposure/metabolic variable being studied.

(d) **Outcome**: Global cognition was explored as a single outcome when reported as an overall or composite score for assessments measuring various cognitive domains or as an average of the individual cognitive domains assessed in the study. The individual cognitive domains included verbal memory, attention, executive function, processing speed, visual memory, and working memory. The method of averaging scores and classifying assessments under distinct cognitive domains was adapted from Bora, Akdede and Alptekin (2017) and Bora et al. 2019) reviews (Table S1). Measures of cognitive deficits/failures were not included in the meta-analysis (e.g. scales or self-report of perceived memory deficits) but summarized qualitatively. IQ and measures of crystallized or fluid intelligence were not assessed as cognitive outcomes (Dennis et al., 2009).

(e) **Study design**: Randomized control trials, cross-sectional studies, observational studies, longitudinal studies. Longitudinal and intervention studies were excluded if the population and comparator groups were matched for cognitive function at baseline and not representative of the trends being explored.

Search strategy

A comprehensive search, encompassing mood disorder, metabolic dysregulation, and cognitive domains, was carried out in December 2021, and updated in January and September 2023. Six databases were used to conduct this search of published and grey literature: Ovid MEDLINE, APA PsycINFO, Embase, Scopus, Web of Science, and CINAHL. Limits were applied to English language and human studies in Ovid databases, but not to publication date or study design (Table S2). The reference lists of relevant reviews identified through the search were screened for additional articles. The grey literature search was supplemented by searching Google Scholar and contacting corresponding authors of included studies for unpublished data to synthesize in this review.

Study selection

The study selection process was managed using the Covidence software. Any combination of two reviewers involved in each step of the study selection process independently screened titles and abstracts (K. M., N. S., R. D., E. S., F. P., Z. H.), followed by full-text screening (K. M., N. S., J. G., A. H., F. P., Z. H., R. D., E. S.). Any disagreements in the study selection process were resolved through referencing studies and discussion between authors.

Data extraction

Data extraction was completed independently, and in duplicate, to verify the accuracy of information by any combination of two authors involved in data extraction (K. M., N. S., F. P., J. G., A. H., Z. H.). A standardized extraction form was utilized to collect information on study identifiers, population descriptors, and outcomes of interest. Discrepancies in data collection were resolved by referencing the original text and through discussion between authors. If applicable, data were extracted from figures using an online software, WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/). Corresponding authors were contacted for any additional information that was not reported or could not be extracted from the included studies.

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Risk of bias assessment

An adapted version of the Newcastle-Ottawa Scale (NOS) for cross-sectional data was utilized to perform a quality assessment of the studies to assess for risk of bias (Modesti et al., 2016). Two authors (K. M. and Z. H.) completed these assessments and any differences in ratings were addressed through discussion. A high risk of bias was defined as a rating of equal to or less than four. Furthermore, funnel plots with 10 or greater studies were analyzed for reporting bias and supplemented with the Egger's test performed using Stata 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX, USA: StataCorp LLC.).

Data synthesis

Summaries of included studies were tabulated. A random-effects meta-analysis was conducted using Review Manager (RevMan) Version 5.4 by calculating the standardized mean difference (SMD) of continuous data reporting cognitive outcomes. A minimum of two studies were required for a meta-analysis. The effect sizes of individual cognitive domains/assessments used in studies were pooled to calculate global/total cognition when it was not reported as a single score (Bora et al., 2017, 2019). Only objective measures of cognitive function were included in these analyses. For studies with overlapping populations, only one with the largest population size experiencing the greatest metabolic burden was included in the meta-analysis. Mean effect sizes were multiplied by −1 if higher scores were associated with worse cognitive performance to ensure consistency in reporting the direction of exposure effects. All outcomes of all effect sizes were reported to ensure no reporting bias and completeness of data. Heterogeneity was assessed with the I^2 statistic. A Firepower plot was created to assist in the visualization of the power of effect sizes of cognitive outcomes in RStudio (R Foundation for Statistical Computing, Vienna, Austria, v 4.3.2) using the *metameta* package (Quintana, 2023).

Sub-analyses

A sensitivity analysis was conducted by removing studies of populations with a reported history of stroke, heart attack, and other comorbid conditions that have an independent association with cognition; outliers in funnel plots with a large effect size; and studies with a high risk of bias. A meta-regression was performed using Stata 16 (StataCorp. 2019. Stata Statistical Software: Release 16. StataCorp LLC.) to assess the association between age, BMI, and percentage of males in the comorbid study population; difference in BMI between the comorbid and control group; and SMD in depression severity between the comorbid and control group with global cognition. If separate characteristics were not provided for the male/female subgroups, the cognitive data for these subgroups was averaged and included in meta-regressions. Furthermore, if the average population BMI was not provided, the average height and weight were used to calculate BMI (kg/m^2).

Certainty assessment

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework was used to identify the quality of evidence surrounding the association between metabolic dysregulation and cognition in individuals with mood disorders. Given the observational nature of this data, all evidence was rated starting from a very low level of certainty.

Results

Study selection

A summary of the study selection process is outlined in Fig. 1. A total of 26 708 articles were identified from the search. Following title and abstract screening, 1 970 articles were assessed at the full-text level for eligibility. Sixty-three studies met the pre-specified inclusion criteria and were included in the review.

Study characteristics

The characteristics of included studies are summarized in Table 1. Twenty-seven studies explored the impact of metabolic dysregulation on cognitive outcomes in individuals with BD (Bai et al., 2016; Beunders et al., 2021; Bond et al., 2017; Chang et al., 2022; Dalkner et al., 2021a, 2021b; Depp et al., 2014; Hubenak, Tuma, & Bazant, 2015; Hui et al., 2019; Kadriu et al., 2023; La Montagna et al., 2017; Lackner et al., 2016; Li et al., 2015; Liebing et al., 2023; Mehra, Jagota, Sahoo, & Grover, 2022; Mora et al., 2017; Naiberg, Newton, Collins, Bowie, & Goldstein, 2016a; Naiberg et al., 2016b; Qiu et al., 2022; Reininghaus et al., 2022; Ringin et al., 2023a, 2023b; Salvi et al., 2020; Silveira et al., 2014; Tsai, Lee, Chen, & Huang, 2007; Van Rheenen, McIntyre, Balanzá-Martínez, Berk, & Rossell, 2021; Yim et al., 2012), 15 in MDD (Cao et al., 2023; Fourrier et al., 2020; Geraets et al., 2022; Guan et al., 2021; Hidese et al., 2018; Kloiber et al., 2007; Kopchak & Pulyk, 2017; Kraus et al., 2023; Lan et al., 2022; Marijnissen et al., 2017; Péterfalvi et al., 2019; Shao et al., 2017; Smith et al., 2018; Wroolie, Kenna, Singh, & Rasgon, 2015; Zhang, Wang, Shi, & Li, 2021), 17 in participants with measures of depressive symptoms/self-rated depression (Borda et al., 2019; Borhaninejad & Saber, 2022; Chang, Lung, & Yen, 2015; Chen et al., 2014; Choi et al., 2019; Demakakos, Muniz-Terrera, & Nouwen, 2017; Downer, Vickers, Al Snih, Raji, & Markides, 2016; Ferri, Deschênes, Power, & Schmitz, 2021; Janocha et al., 2010; Jia et al., 2020; Johar, Schaefer, & Su, 2023; Kontari & Smith, 2019; Lin et al., 2022; Liu et al., 2023; Ng, Niti, Zaw, & Kua, 2009; Scuteri et al., 2011; Wei et al., 2019), and four in a mixed population of MDD and BD, of which some analyzed data independently for each mood disorder diagnosis (Chen et al., 2021; Mansur et al., 2020; McIntyre et al., 2015; Zhuo et al., 2022). Specifically, BMI, MetS/comorbid metabolic risk factors, and T2D were studied most frequently in these populations.

In addition to the variety of mood and metabolic disorder subgroups, study populations ranged from an average of 17.21 (Naiberg et al., 2016a, 2016b) to ⩾80 years old (Wei et al., 2019). A range in the duration of illness was captured, including first-episode patients and those with a more chronic course of illness of up to 34.2 years (Beunders et al., 2021).

The use of psychotropic medication was reported in nearly all studies. This review included medication-free/naïve populations in the BD (Qiu et al., 2022), MDD (Smith et al., 2018), and mixed BD/MDD (Zhuo et al., 2022) subgroups. Medication history was not reported for the depressive symptom/self-reported depression group likely because these were community-based samples.

No studies included in the meta-analysis met the criteria for high risk of bias as per evaluation of the quality of their sample selection, comparability of outcomes, and outcome assessment; however, most did not justify their sample size or outline non-respondents. Two studies identified through the grey literature

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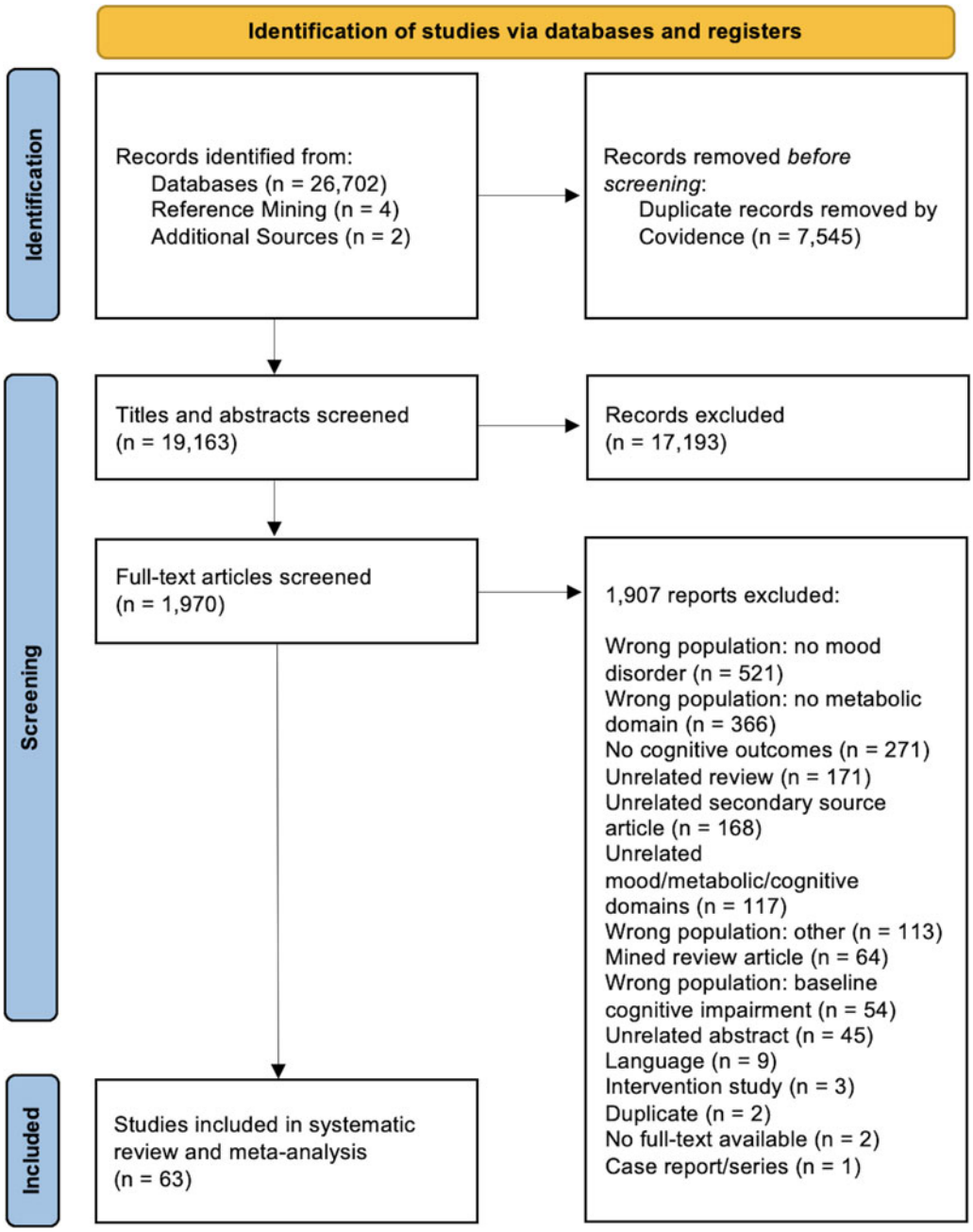

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of studies included in the systematic review and meta-analysis.

search were summarized qualitatively and received a high risk of bias assessment as they were abstracts reporting limited information (La Montagna et al., 2017; Mehra et al., 2022). A full summary of the study risk of bias is provided in Table S3.

Association between metabolic dysregulation and cognition within different mood disorders (meta-analysis)

Comorbid metabolic dysregulation was associated with significantly lower global cognition in individuals with mood disorders, compared to metabolically healthy individuals with mood disorders (−0.37 SMD, 95% confidence interval [CI] [−0.46 to −0.27], $p < 0.00001$, $I^2 = 80\%$, $n = 6593$, $k = 26$) (Fig. 2). These associations were significant within each mood disorder group, with no significant differences in effect sizes between subgroups ($p = 0.86$, $I^2 = 0\%$).

Association between individual metabolic parameters and cognition across all mood disorder populations

Analysis of the relationship between individual metabolic parameters with cognition (Fig. 3) identified T2D to be associated with the greatest difference in cognitive performance among individuals with mood disorders (−0.56 SMD, 95% CI [−0.84 to −0.27], $p = 0.0001$, $I^2 = 84\%$, $n = 2478$, $k = 7$). This medium effect size was followed by peripheral insulin resistance (−0.46 SMD, 95% CI [−0.62 to −0.30], $p < 0.00001$, $I^2 = 0\%$, $n = 157$, $k = 2$), BMI ⩾25 (−0.35 SMD, 95% CI [−0.48 to −0.21], $p < 0.00001$, $I^2 = 76\%$, $n = 1268$, k

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Table 1. Summary of studies included in the systematic review

Study		Sample	Mean age ± s.d.	Male (%)	Race/ethnicity/ cultural identifiers	Socioeconomic status (mean ± s.d./%)	Mood disorder diagnosis	Metabolic parameter	Duration of illness ± s.d.	Psychotropic medication use	Cognitive measures	Outcome
Bipolar disorder (BD)												
Bai et al. (2016)*		42 BD + MetS 101 BD no MetS	BD + MetS: 47.5 ± 11.2 BD no MetS: 43.7 ± 12.2	BD + MetS: 32.1 BD no MetS: 30.2	Participants recruited in Taiwan	Education (more than 12 years) BD + MetS: 33.3% BD no MetS: 33.7% Occupation (regular work) BD + MetS: 28.6% BD no MetS: 33.7%	DSM-IV	MetS: 2005 International Diabetes Federation Asia criteria	Age of onset, years BD + MetS: 31.5 ± 12.7 BD no MetS: 28.4 ± 11.7	BD + MetS: mood stabilizers only (9.5%), atypical APs only (21.4%), combination (69%) BD no MetS: mood stabilizers only (33.7%), atypical APs only (15.8%), combination (50.5%)	WCST	BD patients with MetS performed significantly worse on the WCST compared to those without MetS
Beunders et al. (2021)		172 BD	65.5 ± 7.5	45.9	Participant data derived from study in Dutch population	Level of education (scale 1–5): 3.4 ± 1.2	DSM-IV	Hypertension, obesity (BMI>30), WC, diabetes mellitus, dyslipidemia, MetS	34.2 ± 14.4 years	Lithium (62.1%), APs (41.4%), anticonvulsants (26.9%), antidepressants (26.3%), benzodiazepines (37.0%)	TMT-A/B, Digit Span Forward and Backwards, 10 Word Test, Delayed Recall, Recognition, COWAT letter D-A-TT, Animal Naming and Occupation Naming, Stroop Color Word Test, Mazes, Rule Shift Cards	Presence of MetS and dyslipidemia was negatively associated with the composite cognitive score. Other metabolic parameters were not significantly associated with cognition
Systematic Treatment Optimization Program for Early Mania (STOP-EM)	Bond et al. (2017)	80 BD 46 HC	BD: 22.8 ± 4.3 HC: 23.7 ± 5.3	BD: 48.8 HC: 50.0	BD: Caucasian (76.2%), Asian (20.0%), other (3.8%) HC: Caucasian (58.7%), Asian (34.8%), other (6.5%)	Years of education BD: 14.3 ± 2.3 HC: 15.2 ± 2.5	Comprehensive interview with research psychiatrist and confirmed with MINI	BMI	2.7 ± 3.9 years	Mood stabilizer (87.5%), second generation APs (72.5%), mood stabilizer + APs (67.5%), no medication (7.5%)	TMT-A/B, Stroop Color and Word Test, Letter Fluency, CANTAB battery, CVLT-II, Wechsler Memory Scale	In the combined BD and HC sample, neither baseline nor change in BMI were associated with changes in global cognition or cognitive domains. No diagnosis × BMI interaction effects were discovered
	Silveira et al. (2014)*	25 BD overweight/ obese 40 BD normal weight	BD overweight/ obese: 23.80 ± 4.54 BD normal weight: 22.12 ± 4.10	BD overweight/ obese: 44 BD normal weight: 47.5	BD overweight/ obese: Caucasian (68%), Asian (8%) BD normal weight: Caucasian (77.5%), Asian (17.5%)	Years of education BD overweight/ obese: 14.00 ± 1.87 BD normal weight: 13.45 ± 2.42	DSM-IV	Overweight/ obese BMI ⩾25, normal weight 18.5⩽BMI⩽24.99	First episode of mania	BD overweight/ obese: lithium (44%), valproate (56%), atypical APs (76%), mood stabilizer + atypical APs (76%), antidepressants (8%) BD normal weight: lithium (45%), valproate (40%), atypical APs (80%), mood stabilizer + atypical APs	TMT-A/B, Stroop Color and Word Test, Letter Fluency, CANTAB battery, CVLT-II, Wechsler Memory Scale	BMI was inversely associated with the non-verbal memory score among BD patients. No effect of weight on cognitive outcomes was found in the patient population

(*Continued*)

Table 1. (*Continued.*)

Study		Sample	Mean age ± s.d.	Male (%)	Race/ethnicity/ cultural identifiers	Socioeconomic status (mean ± s.d./%)	Mood disorder diagnosis	Metabolic parameter	Duration of illness ± s.d.	Psychotropic medication use	Cognitive measures	Outcome
										(70%), antidepressants (7.5%)		
Chang et al. (2022)*		33 BD + IR 29 BD no IR	BD + IR: 36.58 ± 11.36 BD no IR: 35.07 ± 14.18	Total BD population: 38.7	Participants recruited in Taiwan	Educational year BD + IR: 15.00 ± 2.10 BD no IR: 14.85 ± 2.18	DSM-5	HOMA-IR≥2.6	NR	Total BD population: Valproic acid (33.9%), valproic acid + APs (30.6%), lithium + APs (19.4%), APs (16.1%)	WCST, CPT	BD patients with IR had more preservative errors in the WCST compared to those with BD alone. No significant effects were found for WCST completed categories or CPT scores
The Bipolar Disorder in the Longitudinal Course Study (BIPFAT/ BIPLONG)	Liebing et al. (2023)	17 BD + MetS 35 BD no MetS	BD + MetS and BD no MetS groups did not differ in age	More male patients in the BD + MetS group compared to BD no MetS group	Participants recruited in Austria	Significant difference in the distribution of MetS in the average number of years of education	DSM-IV	MetS: International Diabetes Federation 2006 criteria	NR	NR	TMT-A/B, DSST, CVLT, Verbal Learning and Memory Test	Processing speed/ attention scores were significantly lower in the BD + MetS population at baseline and 1-year follow-up compared to the BD only group. There was no association between MetS and global cognition, verbal learning and memory, executive function, and processing speed/ attention over time
	Reininghaus et al. (2022)	56 BD	39.78 ± 11.29	51.8	Participants recruited in Austria	NR	DSM-IV	WHtR	NR	NR	CVLT, TMT-A/ B, Stroop Color and Word Interference Test, d2 Test of Attention	In multiple hierarchical regression, WHtR was associated with performance on the CVLT, TMT-A, Stroop interference, and d2 Test of Attention. No significant association was found for TMT-B
	Dalkner et al. (2021b) (BMI)	19 BD overweight/ obese 19 BD normal weight	BD overweight/ obese: 41.14 ± 10.66 BD normal weight: 39.70 ± 13.36	BD overweight/ obese: 57.9 BD normal weight: 21.1	Participants recruited in Austria	High-school education or higher BD overweigh/ obesity: 31.6% BD normal weight: 52.6%	DSM-IV	BD overweight/ obese BMI≥25; BD normal weight BMI≤24.9	BD overweight/ obese: 17.0 ± 11.3 years BD normal weight: 15.7 ± 9.3 years	BD overweight/ obese: lithium (53.3%), atypical APs (53.3%), anticonvulsants (20%) BD normal weight: lithium (20%), atypical APs (50%), anticonvulsants (50%)	CVLT, TMT-A/ B, d2 Test of Attention, DST, Digit Span Backwards	Higher BMI at baseline was associated with lower Digit-Span backwards scores at 12 months. In contrast, there was a negative association between BMI and TMT-A, indicating improved performance with higher BMI. No significant associations were found for d2 Test of Attention, DST, or TMT-B performance.

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											No difference in cognitive performance between normal weight and overweight patients at baseline was noted
	Dalkner et al. (2021a) (MetS)*	45 BD + MetS 103 BD no MetS	BD + MetS: 44.16 ± 12.59 BD no MetS: 41.65 ± 12.48	BD + MetS: 41.5 BD no MetS: 58.5	Participants recruited in Austria	NR	DSM-IV	MetS: International Diabetes Federation criteria	BD + MetS: 18.50 ± 13.37 years BD: 19.04 ± 11.25 years	BD + MetS: lithium (33.3%), atypical APs (40%), antileptics (17.8%), mood stabilizer combination (20%) BD: lithium (29.1%), atypical APs (53.4%), antileptics (22.3%), mood stabilizer combination (27.2%)	TMT-A/B, d2 Test of Attention, Stroop Color and Word Interference Test, CVLT	Comorbid MetS and BD was associated with lower executive function performance compared to patients with just BD. Similar results were not observed for attention/processing speed or verbal learning/memory outcomes
	Lackner et al. (2016)	71 BD overweight/ obese 29 BD normal weight	Total BD population: 43.9 ± 13.0	Total BD population: 48	BD overweight/ obese: Caucasian (100%) BD normal weight: Caucasian (100%)	No significant difference in school educational level between BD and healthy controls, as well as normal weight and overweight groups	DSM-IV	Overweight/ obese BMI⩾25; normal weight BMI⩽24.9	NR	Total BD population: lithium (26%), atypical APs (63%), anticonvulsants (24%), combination therapy (94%)	TMT-A/B, Stroop Color and Word Interreference Test, d2 Test of Attention, CVLT	Overweight/obese patients performed worse in some attention and verbal learning and memory cognitive tasks compared to normal weight BD patients. Abdominal obesity was associated with worse cognitive outcomes in the BD population
Depp et al. (2014)*		109 BD obese 116 BD overweight 116 BD normal weight	Total BD population: 48.3 ± 12.9	Total BD population: 48.1	Mixed or full Ashkenazi descent 100%	Education, years Total BD population: 15.0 ± 2.5	DSM-IV	Obese BMI⩾30, overweight BMI 25.0–29.9, normal weight BMI 18.5–24.9	NR	Total BD population: Atypical APs (41.3%), typical APs (3.2%), antidepressant (37.5%), mood stabilizer (66.9%), anticholinergic (2.4%), benzodiazepine (32.7%)	RAVLT, TMT-A/B, Digit Symbol, Letter Number Sequencing, Animal Fluency, WCST, CPT	BMI (categorical and continuous stratification) was negatively associated with global cognition in BD patients. Performance on individual cognitive subtests varied between BMI groups
Hubenak et al. (2015)*		15 BD + MetS 25 BD no MetS	BD + MetS: 59.2 ± 13.1 BD no MetS: 53.1 ± 14.8	BD + MetS: 40.0 BD no MetS: 36.0	Participants recruited in Czech Republic	Education, years BD + MetS: 14.9 ± 3.6 BD no MetS: 15.2 ± 3.0	ICD-10	MetS: National Cholesterol Education Program Adult Treatment Panel III	BD + MetS: 28.0 ± 11.9 years BD no MetS: 21.2 ± 12.6 years	BD + MetS: Lithium (53.3%), valproic acid (40.0%), carbamazepine (6.7%) BD no MetS: Lithium (48.0%), valproic acid (40.0%), carbamazepine (12.0%)	RAVLT, Spatial Span and Digit Span from Wechsler Memory Scale-III, CPT-II, Tower of London, WCST	Abdominal obesity, hypertension, and MetS were associated with lower cognitive scores in BD patients
Hui et al. (2019)		37 BD	29.78 ± 10.05	40.5	Han Chinese descent 100%	Education, years 10.14 ± 2.98	DSM-IV	HDL cholesterol	107.62 ± 101.94 months	Valproate (81.10%), lithium (8.10%), not	RBANS	Serum HDL levels were positively correlated with the

(*Continued*)

Table 1. (*Continued.*)

Study	Sample	Mean age ± s.d.	Male (%)	Race/ethnicity/ cultural identifiers	Socioeconomic status (mean ± s.d./%)	Mood disorder diagnosis	Metabolic parameter	Duration of illness ± s.d.	Psychotropic medication use	Cognitive measures	Outcome
									taking mood stabilizers (10.80%)		language and immediate memory subdomains, along with the RBANS total score
Kadriu et al. (2023)	178 BD + BMI ⩾40 242 BD + BMI 35–39.9 526 BD + BMI 30–34.9 861 BD + BMI 25–29.9 834 BD + BMI 20–24.9 98 BD + BMI 18.5–19.9 51 BD + BMI <18.5	Total BD population: 39.6	45.6	White or Caucasian: 89.9% Black or African American: 5.6% Native American or American Indian: 0.9% Asian or Pacific Islander: 2.0% No primary race: 0.6% Other: 1.0%	Full-time employment: 58.3% College degree: 25.4%	DSM-IV	BMI ranging from <18.5 to >40	Bipolarity Index Total Score – Age of Onset Total BD population: 15.9 ± 3.0 (minimum) to 16.8 ± 3.1 (maximum)	Mood stabilizer (2.5%), stimulant (4.0%), APs (2.7%), anticonvulsant (0.9%), antidepressant (3.4%), anxiolytic (10.1%), complex pharmacotherapy (⩾2 psychotropic medications; 3.3%)	MADRS concentration sub-item	A bimodal distribution was observed for concentration difficulties, with greatest severity observed at both extremes of the BMI spectrum
La Montagna et al. (2017)	26 BD overweight/ obese 20 BD normal weight	43.17	39.1	Participants recruited in Italy	NR	NR	Overweight/ obese BMI⩾25	NR	NR	MATRICS	Processing speed and reasoning/ problem solving were impaired in the overweight/obese BD patients
Li et al. (2015)	27 BD	39.7 ± 9.8	55.6	NR	Education ⩽12 years: 48.1% 12–16 years: 40.7% >16 years: 11.1%	DSM-IV	Insulin	13.4 ± 9.3 years	Valproic acid (74%), carbamazepine (3.7%), lithium (18.5%)	MoCA	Higher fasting insulin levels were significantly correlated with higher cognitive scores in BD patients
Mora et al. (2017)*	37 BD overweight 15 BD normal weight	BD overweight: 48.19 ± 11.2 BD normal weight: 35.20 ± 10.4	BD overweight: 48.6 BD normal weight: 53.3	Participants recruited in Spain	Education, years BD overweight: 10.11 ± 2.7 BD normal weight: 12.20 ± 2.7 Current work status BD overweight: active (32.4%), inactive (13.5%), retired/ disabled (54.0%) BD normal weight: active (66.7%), inactive (33.3%), retired/disabled (0%)	DSM-IV	Overweight BMI⩾25; normal weight BMI 18.5–24.9	BD overweight: 22.65 ± 12.5 years BD normal weight: 12.47 ± 9.1 years	BD overweight: Lithium monotherapy (24.3%), lithium + combination (70.2%), other mood stabilizers (5.4%), antidepressants (37.8%), APs (43.2%), benzodiazepines (8.1%) BD normal weight: lithium monotherapy (53.3%), lithium + combination (40.0%), other mood stabilizers (6.7%), antidepressants (26.7%), APs (33.3%), benzodiazepines (0%)	WCST, Stroop Color and Word Test, FAS Verbal Fluency, TMT-A/B, CPT-II, CVLT, RCFT	Overweight/obesity was significantly associated with worse cognitive performance in BD patients in short- and long-term outcomes
Mehra et al. (2022)	70 BD	43.9 ± 13.1	NR	NR	NR	NR	MetS: International Diabetes Federation	16.1 ± 10.1 years	NR	MoCA (mild cognitive impairment score <26)	Lower cognitive scores were associated with higher diastolic BP, WC, and hip circumference. There was no association between MetS and cognitive impairment

Naiberg et al. (2016a) (BP and WC) Naiberg et al. (2016b) (TG)		34 BD	17.21 ± 0.76	41.2	White 85.3%	NR	DSM-IV	BP, TG, WC	NR	Second generation APs (76.5%), typical APs (5.9%), SSRI (14.7%), non-SSRI antidepressant (2.9%), stimulants (8.8%)	CANTAB (IED), Cambridge Gambling Test	TG and diastolic BP were inversely correlated with executive function. High BP and WC were associated with impulsivity
Qiu et al. (2022)		132 BD	21 (range 18–23)	31.1	Participants recruited in China	Education, years 15	DSM-5	TG, total cholesterol, LDL cholesterol, HDL cholesterol, fasting blood glucose	2 years (range 1–3)	Drug-naïve	RBANS, Stroop Color and Word Test	TG levels were associated with a lower RBANS total score, and attention and delayed memory subscale scores. Fasting blood glucose levels and BMI were negatively associated with language subscale and Stroop test performance, respectively. HDL levels were positively correlated with the total Stroop score. No associations were found for total or LDL cholesterol
UK Biobank	Ringin et al. (2023a)*	85 BD + T2D 1426 BD no T2D	BD + T2D: 57.7 ± 7.7 BD no T2D: 54.2 ± 8.01	BD + T2D: 72.9 BD no T2D: 49.6	Participants recruited in the United Kingdom	Townsend deprivation index (higher scores indicate lower socioeconomic status) BD + T2D: 0.5 ± 3.5 BD no T2D:−0.003 ± 3.3 Education level (percent attended university) BD + T2D: 28.2 BD no T2D: 40.0	'Probable BD' as per DSM-IV criteria	'Probable T2D' as identified by algorithm using medical history	NR	BD T2D: mood stabilizers (14.1%), antidepressants (49.1%) first generation APs (2.4%), second generation APs (7.1%), sedatives/ hypnotics (7.1%) BD no T2D: mood stabilizers (12.0%), antidepressants (26.0%) first generation APs (1.7%), second generation APs (5.7%), sedatives/ hypnotics (3.6%)	UK Biobank battery (pairs matching, reaction time, prospective memory)	T2D was negatively associated with visuospatial memory and processing speed in individuals with BD. Additional analyses identified an interaction of T2D × age for processing speed and visuospatial memory outcomes. No significant interaction effects were observed for prospective memory
	Ringin et al. (2023b)	996 BD	54.29 ± 8.01	54.3	Participants recruited in the United Kingdom	Townsend deprivation index (higher scores indicate lower socioeconomic status): −0.12 ± 3.20 Education level (percent attended university): 39.3	'Probable BD' as per DSM-IV criteria	Systolic and diastolic BP, WC, fat mass index, HDL cholesterol, LDL cholesterol, TG	NR	NR	UK Biobank battery (pairs matching, reaction time, prospective memory)	Global cognitive performance was negatively associated with WC and systolic BP, and positively associated with diastolic BP. No significant association was found with fat mass index, HDL and LDL cholesterol, or TG
Salvi et al. (2020)*		24 BD + IR 71 BD no IR	BD + IR: 49.2 ± 9.3 BD no IR: 43.7 ± 14.3	BD + IR: 58.3 BD no IR: 47.9	Participants recruited in Italy and Czech Republic	Education, years BD + IR: 12.9 ± 3.3 BD no IR: 14.9 ± 2.7	Diagnosis verified with SCID-I	IR: HOMA-IR ⩾3.5 (75th percentile of the population)	BD + IR: 19.9 ± 14.4 years BD no IR: 19.3 ± 13.4 years	BD + IR: APs (75%), mood stabilizers (100%), antidepressants (29.2%) BD no IR: APs (57.4%),	CVLT, Digit Span Forward and Backwards	BD patients with IR had worse composite verbal memory scores, but not working memory

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Table 1. (*Continued.*)

Study	Sample	Mean age ± s.d.	Male (%)	Race/ethnicity/ cultural identifiers	Socioeconomic status (mean ± s.d./%)	Mood disorder diagnosis	Metabolic parameter	Duration of illness ± s.d.	Psychotropic medication use	Cognitive measures	Outcome
									mood stabilizers (82.4%), antidepressants (13.2%)		scores, compared to patients with only BD
Tsai et al. (2007)*	16 BD + diabetes 36 BD no diabetes	Total BD population: 66.0 ± 6.5	Total BD population: 25.0	Participants recruited in Taiwan	Education, years Total BD population: 7.0 ± 5.7	DSM-IV	Diabetes diagnosis from chart review	Age of onset, years Total BD population: 27.1 ± 6.1	Lithium (88.5%), carbamazepine (57.7%), APs (90.4%), valproate (50%)	MMSE, Cognitive Abilities Screening Instrument	Comorbid diabetes mellitus in BD patients was associated with lower Cognitive Abilities Screening Instrument, but not MMSE scores
Van Rheenen et al. (2021)	23 BD	40.04 ± 10.59	34.8	Participants recruited in Australia	NR	DSM-IV	TG, BMI, WC	Age of onset, years 22.38 ± 12.03	Second generation APs (34.8%), mood stabilizers (69.6%), antidepressants (43.5%)	Stroop Color-Word Test, TMT-B	High TG levels were correlated with worse TMT-B performance, but not BMI or WC. No correlations were identified for the Stroop Color-Word Test.
Yim et al. (2012)*	48 BD + overweight/ obese 19 BD normal weight	BD + overweight/ obese: 41.48 ± 9.90 BD normal weight: 36.68 ± 10.36	BD + overweight/ obese: 62.5 BD normal weight: 26.3	BD + overweight/ obese: White (93.8%), Black (0%), Asian (6.2%), other (0%) BD normal weight: White (89.5%), Black (5.3%), Asian (0%), other (5.3%)	Education, years BD + overweight/ obese: 15.73 ± 3.00 BD normal weight: 16.78 ± 2.61	DSM-IV	Overweight/ obese BMI≥25.0, normal weight BMI 18.5–24.9	Age of onset (first depressive episode), years BD + overweight/ obese: 19.50 ± 9.78 BD normal weight: 17.22 ± 5.91 Age of onset (first manic episode), years BD + overweight/ obese: 19.50 ± 9.78 BD normal weight: 17.22 ± 5.91	BD + overweight/ obese: antidepressants (41.7%), sleep medication (22.9%), anxiolytic (27.1%), anticonvulsants (79.2%), APs (62.5%), hormonal (16.7%) BD normal weight: antidepressants (57.9%), sleep medication (26.3%), anxiolytic (26.3%), anticonvulsants (78.9%), APs (57.9%), hormonal (26.3%)	CVLT-II, TMT-A/B, DSST, Verbal Fluency, Recollection and Habit Memory, Cognitive Failures Questionnaire	Overweight/obese BD patients performed significantly worse on the verbal fluency test compared to normal weight patients. BMI was negatively correlated with DSST scores. There were no significant differences in reports of subjective cognitive failures or memory deficits between groups
Major depressive disorder (MDD)											
Cao et al. (2023)	16 MDD + T2D 23 MDD no T2D	Median (P25, P75) MDD + T2D: 59.00 (41.00, 65.00) MDD no T2D: 45.50 (38.25, 55.25)	MDD + T2D: 62.5 MDD no T2D: 34.8	Participants recruited in China	NR	DSM-5	T2D	Median (P25, P75) MDD + T2D: 4.50 (2.00, 8.00) years MDD no T2D: 0.75 (0.33, 3.00) years	NR	RBANS	No significant difference in cognitive outcomes between the comorbid MDD + T2D and MDD only group
Fourrier et al. (2020)*	26 MDD severe obesity 27 MDD moderate obesity	MDD severe obesity: 46.46 ± 12.96 MDD moderate obesity: 48.00 ± 13.46	MDD severe obesity: 22.08 MDD moderate obesity: 37.04	Participant data derived from study in Australian population	Education, years MDD severe obesity: 13.56 ± 2.41 MDD moderate	Diagnosis verified with MINI	Severe obesity BMI>35, moderate obesity BMI 30–34.9,	NR	Some participants reported taking antidepressants	THINC-it	MDD patients with a BMI>25 performed worse on various attention and

	32 MDD overweight 34 MDD normal weight	MDD overweight: 48.69 ± 14.04 MDD normal weight: 37.15 ± 14.39	MDD overweight: 53.12 MDD normal weight: 50.00		obesity: 15.94 ± 3.15 MDD overweight: 14.44 ± 2.66 MDD normal weight: 14.25 ± 2.45		overweight BMI 25–29.9, normal BMI<25				executive function subscales compared to normal weight patients
Geraets et al. (2022)*	145 MDD + cardiometabolic symptoms 103 MDD no cardiometabolic symptoms	Total MDD population: 58.8 ± 8.5	Total MDD population: 48.8	Participants recruited in the Netherlands	Total MDD population: education level low (51.6%), medium (29.0%), high (17.7%)	DSM-IV	Cardiometabolic risk factors defined by the National Cholesterol Education Program Adult Treatment Panel III	NR	Antidepressants (29.4%)	Battery of tests assessing memory, information processing speed, executive functioning and attention	MDD patients with cardiometabolic comorbidities performed worse on tasks assessing memory, information processing speed, and executive functioning and attention compared to patients with MDD only
Guan et al. (2021)*	88 MDD + high TG 95 MDD normal TG	MDD high TG: 45.64 ± 12.65 MDD normal TG: 43.68 ± 12.96	MDD high TG: 47.7 MDD normal TG: 40.0	Han Chinese 100%	Education, years MDD high TG: 9.08 ± 3.42 MDD normal TG: 9.59 ± 3.16	DSM-IV	High TG: ⩾1.7 mmol/L Normal TG: <1.7 mmol/L	MDD high TG: 6.34 ± 6.97 years MDD normal TG: 5.91 ± 6.74 years	MDD high TG: SSRIs (19.1%), SNRIs (9.3%), drug combination (10.9%), other (8.7%) MDD normal TG: SSRIs (19.7%), SNRIs (13.1%), drug combination (7.7%), other (11.5%)	RBANS	The attention and language scores were lower in the high TG, compared to normal TG group. Female MDD patients with high TG levels had lower immediate memory, language, attention, delayed memory, and total scores, but not a visuospatial score, compared to patients with normal TG levels. No differences were observed in males
Hidese et al. (2018)*	17 MDD obese 65 MDD overweight 185 MDD normal weight	Total MDD population: 41.2 ± 11.3	Total MDD population: 46.3	Japanese 100%	Education, years Total MDD population: 14.9 ± 2.2	DSM-IV	Obese BMI ⩾30, overweight 25⩽BMI<30, normal 18.5⩽BMI<25	Total MDD population: 7.0 ± 6.9 years	Total MDD population: any psychotropic medication (56.4%), typical APs (5.2%), atypical APs (10.4%), APs (14.7%), antidepressants (31.3%), minor tranquilizer (44.3%)	BACS	Working memory, motor speed, executive function, and BACS composite scores were significantly lower in obese, compared to normal weight, MDD patients
Kloiber et al. (2007)*	147 MDD overweight/obese 173 MDD normal weight	MDD overweight/obese: 50.01 ± 13.57 MDD normal weight: 45.45 ± 15.05	MDD overweight/obese: 55.10 MDD normal weight: 35.80	Participants recruited in Germany	Socioeconomic status (0–3) MDD overweight/obese: 1.55 ± 0.09 MDD normal weight: 1.56 ± 0.08	DSM-IV	Overweight/obese BMI >25, normal weight BMI ⩽25	Age of onset, years MDD overweight/obese: 36.55 ± 14.38 MDD normal weight: 35.92 ± 16.05	Patients were treated with antidepressants as per physicians' orders	ZVT (similar to TMT), d2 Test of Attention, TAP (visual and auditory stimuli)	MDD patients with a BMI⩾25 had lower selective attention scores, compared to normal weight patients, at discharge. There was no significant difference in attention test performance at baseline
Kopchak and Pulyk (2017)	60 Depressive disorder + MetS	Total depressive disorder population: 62.1 ± 11.1	Two groups are comparable for sex	NR	Two groups are comparable for education	DSM-IV	MetS: International	NR	NR	MMSE	Patients with depressive disorder and MetS had a

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Table 1. (*Continued.*)

Study	Sample	Mean age ± s.d.	Male (%)	Race/ethnicity/ cultural identifiers	Socioeconomic status (mean ± s.d./%)	Mood disorder diagnosis	Metabolic parameter	Duration of illness ± s.d.	Psychotropic medication use	Cognitive measures	Outcome
	48 Depressive disorder no MetS						Diabetes Federation				higher incidence of severe cognitive impairment, compared to patients with only a depressive disorder
Kraus et al. (2023)	17 MDD + BMI ⩾40 29 MDD + BMI 35–39.9 106 MDD + BMI 30–34.9 278 MDD + BMI 25–29.9 377 MDD + BMI 20–24.9 58 MDD + BMI 18.5–19.9 27 MDD + BMI <18.5	Total MDD population: 50.5 ± 13.6	Total MDD population: 35.0	Caucasian 96%	NR	Diagnosis verified with MINI	Obese BMI >30, overweight BMI 25–29.9, normal/ underweight BMI <25	Overweight and obese individuals with MDD had an earlier age of onset	Treated with at least one antidepressant agent at sufficient duration and dose during their current major depressive episode	MADRS concentration sub-item	Higher BMI was associated with greater impairment of concentration
Lan et al. (2022)*	72 MDD overweight/ obese 149 MDD normal weight	MDD overweight/ obese: 36.6 ± 11.8 MDD normal weight: 32.2 ± 11.3	MDD overweight/ obese: 61.1 MDD normal weight: 46.3	Participants recruited in China	Employed MDD overweight/ obese: 58.3% MDD normal weight: 65.8% Education, years MDD overweight/ obese: 11.9 ± 3.5 MDD normal weight: 12.3 ± 3.2	DSM-5	Overweight/ obese BMI⩾24.0, normal weight 18.5⩽BMI<24.0	MDD overweight/ obese: 36.0 ± 74.0 months MDD normal weight: 25.1 ± 45.2 months	MDD overweight/ obese: APs (27.8%), mood stabilizers (4.7%), benzodiazepines (12.1%) MDD normal weight: APs (16.1%), mood stabilizers (12.5%), benzodiazepines (22.2%)	MATRICS	Obese/overweight patients performed worse on processing speed and working memory tasks compared to normal weight patients. BMI was negatively associated with processing speed and working memory performance. No association was found for verbal or visual learning outcomes
Marijnissen et al. (2017)*	119 depression* + MetS 166 depression* no MetS *MDD (n = 359), dysthymia (n = 100), minor depression in the last month (n = 20); some patients have overlapping diagnoses	Depression + MetS: 70.2 ± 7.1 Depression no MetS: 70.9 ± 7.8	Depression + MetS: 32.8 Depression no MetS: 35.5	Participants recruited in the Netherlands	Education, years Depression + MetS: 10.2 ± 3.4 Depression no MetS: 10.9 ± 3.5	DSM-IV	MetS: National Cholesterol Education Program Adult Treatment Panel III	NR	Depression + MetS: SSRI (22.9%), TCA (20.2%), other antidepressants (31.1%), APs (12.6%) Depression: SSRI (30.1%), TCA (20.0%), other antidepressants (25.9%), APs (10.8%)	MMSE	Cognitive functioning did not significantly differ between individuals with comorbid depression + MetS and depression alone
Péterfalvi et al. (2019)	42 MDD	35.4 ± 9.73	21.4	Participants recruited in Hungary	Education, years 12.00	DSM-5	Total cholesterol, LDL cholesterol, HDL cholesterol, TG	Age of onset, years 25.5	Antidepressants (97.6%), low dose APs (50%), mood stabilizers (11.9%)	WCST, CPT-II	Among MDD patients, a higher LDL/HDL cholesterol ratio and total/HDL cholesterol ratio were associated with worse performance on certain WCST domains. Higher HDL cholesterol was associated with less WCST errors. No associations for TG,

											total, or LDL cholesterol were found. No metabolic effects on other cognitive tests we reported
Shao et al. (2017)	115 MDD	37.76 ± 12.48	39.1	Han Chinese 100%	Education, years 9.77 ± 3.46	DSM-IV	TG	NR	SSRIs (40.9%), SNRIs (10.4%), NaSSAs (18.3%), TCAs (3.5%), drug-naïve (27.0%)	RBANS	TG levels were negatively associated with the RBANS total, visuospatial/ constructional, attention and delayed memory score
Smith et al. (2018)	202 MDD	51.7 ± 7.6	24.3	Black (25.7%), Caucasian (67.8%), Other (6.4%)	NR	DSM-IV	HDL, LDL	NR	Patients taking psychotropic medication were excluded	TMT-A/B, Stroop, Verbal Paired Associates, COWAT, Digit Span, Verbal Fluency, Ruff 2&7 Test, DSST	HDL and LDL cholesterol were not significantly associated with working memory, executive function, or verbal memory in hierarchical regressions
Wroolie et al. (2015)	39 MDD	48.41 ± 13.38	15.4	Participants recruited in the United States	Education, years 16.56 ± 2.35	DSM-IV	IR as measure with steady-state plasma glucose level, BMI	Age of onset, years 26.71	Stable dose of psychotropic medication for at least 6 months prior to study start. Use of psychotropic medication with metabolic confounds was exclusionary	BVRT, Digit Span, Symbol Coding, Delis-Kaplan Executive Functioning System (Color-Word Interference Test and TMT Condition 4), Purdue Pegboard	In all MDD patients, steady-state plasma glucose levels were not associated with performance on cognitive tests. Higher BMI was only associated with worse dominant hand fine motor ability. In the <45-year subgroup, IR was associated with worse executive function, but not attention and processing speed. No significant associations were found in the ≥45-year group
Zhang et al. (2021)*	49 MDD + T2D 54 MDD no T2D	MDD + T2D: 53.84 ± 8.23 MDD no T2D: 50.61 ± 9.05	MDD + T2D: 57.1 MDD no T2D: 53.7	Participants recruited in China	Education, years MDD + T2D: 11.27 ± 4.09 MDD no T2D: 12.61 ± 3.47	ICD-10	T2D	NR	NR	RBANS	Patients with MDD + T2D had significantly lower immediate memory, attention, and delayed memory scores compared to those with MDD alone
Depressive symptoms/self-rated depression											
Borhaninejad and Saber (2022)*	36 depressive symptoms + diabetes 28 depressive symptoms no diabetes	Total diabetes population: 66.07 ± 5.80 Total non-diabetes population: 65.02 ± 6.02	Total diabetes population: 49.0 Total non-diabetes population: 48.0	Participants recruited in Iran	Employment Total diabetes population: unemployed (82.0%), employed (18.0%) Total non-diabetes population: unemployed (85.0%), employed (15.0%) Education level	GDS (15-item; cut-off not defined)	Self-report T2D	NR	NR	MMSE, Informant Questionnaire for Cognitive Decline in the Elderly (self-report)	Individuals with depressive symptoms and T2D scored higher on the self-report questionnaire, indicating greater cognitive decline, compared to those with only depressive

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Table 1. (*Continued.*)

Study	Sample	Mean age ± s.d.	Male (%)	Race/ethnicity/ cultural identifiers	Socioeconomic status (mean ± s.d./%)	Mood disorder diagnosis	Metabolic parameter	Duration of illness ± s.d.	Psychotropic medication use	Cognitive measures	Outcome
					Total diabetes population: primary (38.0%), under diploma (32.0%), diploma (30.0%) Total non-diabetes population: primary (40.0%), under diploma (31.0%), diploma (29.0%)						symptoms. There was no significant difference in the MMSE score between the two groups
Borda et al. (2019)	240 depressive symptoms + high BP 193 depressive symptoms normal BP	Depressive symptoms + high BP: 68.59 ± 6.31 Depressive symptoms normal BP: 69.09 ± 6.66	Depressive symptoms + high BP: 44.56 Depressive symptoms normal BP: 27.08	Community-dwelling Mexican adults	Education, years Depressive symptoms + high BP: 5.12 ± 4.38 Depressive symptoms normal BP: 5.11 ± 4.73	Mexican Health and Aging Study questionnaire (9-item) ⩾5	'Have you ever been told by a doctor or medical provider that you have high BP?'	NR	NR	Cross-Cultural Cognitive Examination test (cognitive impairment cut-off at −1.5 s.d.)	Incidence of cognitive impairment was greater for individuals with high BP and depressive symptoms compared to depressive symptoms only
Chang et al. (2015)	19 cognitive impairment 281 no cognitive impairment	Cognitive impairment: 67.9 ± 2.1 No cognitive impairment: 69.3 ± 2.7	Cognitive impairment: 42.1 No cognitive impairment: 59.8	Community-dwelling Southern Taiwanese adults	Education level Cognitive impairment: illiterate (52.6%), literate (47.4%) No cognitive impairment: illiterate (44.8%), literate (55.2%)	Taiwanese Depression Questionnaire (18-item) ⩾19	MetS: National Cholesterol Education Program Adult Treatment Panel III	NR	NR	Short Portable Mental Status Questionnaire (cognitive impairment cut-off takes education level into account)	Higher depression severity scores and MetS were independently associated with cognitive impairment. The association with depression was attenuated (but still significant) when both variables were added to the same model, suggesting confounding associations
Chen et al. (2014)	3164 self-report depression	NR	NR	United States adults	NR	'Have you ever been told by a physician or nurse that you have depression?'	'Have you ever been told by a physician or nurse that you have diabetes?'	NR	NR	Subjective memory complaints: 'Do you have any problems with your memory?'	Diabetes was associated with more subjective memory impairment in younger (age 18–39) individuals with depression that exercise more. Significant interactions were identified between diabetes and depression

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Choi et al. (2019)	292 high depressive-symptom trajectory + hypertension 650 high depressive-symptom trajectory no hypertension 690 moderate depressive-symptom trajectory + hypertension 1723 moderate depressive-symptom trajectory no hypertension	Total high depressive-symptom trajectory population: 45–54 (27.0%), 55–64 (33.2%), 65–74 (29.7%), ⩾75 (10.1%) Total moderate depressive-symptom trajectory population: 45–54 (32.1%), 55–64 (35.0%), 65–74 (27.7%), ⩾75 (6.1%)	Total high depressive-symptom trajectory population: 45.5 Total moderate depressive-symptom trajectory population: 43.3	South Korean population	Household assets quartile Total high depressive-symptom trajectory population: 1st quartile (27.7%), 2nd quartile (20.6%), 3rd quartile (24.3%), 4th quartile (27.4%) Total moderate depressive-symptom trajectory population: 1st quartile (19.9%), 2nd quartile (24.8%), 3rd quartile (28.8%), 4th quartile (26.6%) Employment status Total high depressive-symptom trajectory population: employed (46.2%), unemployed (53.8%) Total moderate depressive-symptom trajectory population: employed (50.1%), unemployed (49.9%) Education level Total high depressive-symptom trajectory population: elementary school or under (41.2%), middle school (19.0%), high school (29.7%), university or above (10.1%) Total moderate depressive-symptom trajectory population: elementary school or under (39.3%), middle school (18.7%), high school	CES-D (10-item) Total high depressive-symptom trajectory population: 5.5 ± 2.4 Total moderate depressive-symptom trajectory population: 3.3 ± 2.5	Hypertension previously diagnosed by a doctor	NR	NR	MMSE	Participants with hypertension in the high depressive-symptom trajectory had lower cognitive performance compared to those without hypertension

(*Continued*)

Table 1. (*Continued.*)

Study	Sample	Mean age ± s.d.	Male (%)	Race/ethnicity/ cultural identifiers	Socioeconomic status (mean ± s.d./%)	Mood disorder diagnosis	Metabolic parameter	Duration of illness ± s.d.	Psychotropic medication use	Cognitive measures	Outcome
					(33.4%), university or above (8.5%)						
Demakakos et al. (2017)	169 depressive symptoms + diabetes 1526 depressive symptoms no diabetes	Depressive symptoms + diabetes: 67.4 ± 9.3 Depressive symptoms no diabetes: 65.9 ± 10.8	Depressive symptoms + diabetes: 42.0 Depressive symptoms no diabetes: 34.5	Community-dwelling English adults	Occupational class Depressive symptoms + diabetes: managerial and professional occupations (15.4%), intermediate occupations (11.8%), semi-routine and routine occupations (72.8%) Depressive symptoms no diabetes: managerial and professional occupations (19.9%), intermediate occupations (21.6%), semi-routine and routine occupations (58.5%) Education level Depressive symptoms + diabetes: A-level or higher (14.8%), secondary or equivalent (20.1%), no qualifications (65.1%) Depressive symptoms no diabetes: A-level or higher (18.4%), secondary or equivalent (24.7%), no qualifications (56.9%)	CES-D (8-item) ⩾4	Self-report of a doctor's diagnosis of diabetes	NR	NR	Immediate and Delayed Recall, Semantic Verbal Fluency Test	Individuals with comorbid depressive symptoms and diabetes experienced significant acceleration in memory and executive function decline which was not observed in those with depressive symptoms alone
Downer et al. (2016)*	198 depression + diabetes 458 depression no diabetes	Depression + diabetes: 72.6 ± 6.3 Depression no diabetes: 73.5 ± 6.7	Depression + diabetes: 30.8 Depression no diabetes: 29.9	Community-dwelling Mexican Americans	Education, years Depression + diabetes: 0 (18.2%), 1–4 (38.9%), 5–8 (31.8%), ⩾9 (11.1%) Depression no diabetes: 0 (15.5%), 1–4 (42.8%), 5–8 (29.9%), ⩾9 (11.8%)	CES-D (20-item) ⩾16 high depressive symptoms	Self-report: 'Have you ever been told by a doctor that you have diabetes mellitus, sugar in your urine or high blood sugar?'; use of insulin, oral hypoglycemic medication, or both	NR	NR	MMSE	Individuals with comorbid depression and diabetes had significantly greater cognitive decline over time comparted to those with neither condition, while those with depression only did not. After adjusting for covariates and excluding participants with cognitive impairment at baseline, those with comorbid depression and diabetes experienced a greater decrease in MMSE scores over time compared to those with depression only, but the difference was not statistically significant

Ferri et al. (2021)*	336 depressive symptoms + metabolic dysregulation 498 depressive symptoms no metabolic dysregulation	Depressive symptoms + metabolic dysregulation: 54.3 ± 6.9 Depressive symptoms no metabolic dysregulation: 51.6 ± 6.7	Depressive symptoms + metabolic dysregulation: 43.5 Depressive symptoms no metabolic dysregulation: 36.3	White 93.5% (total sample; including healthy controls)	Education level Depressive symptoms + metabolic dysregulation: less than high school (3.9%), high school (30.1%), college/ graduate studies/ university (66.0%) Depressive symptoms no metabolic dysregulation: less than high school (1.0%), high school (22.2%), college/ graduate studies/ university (76.8%)	PHQ (9-item) ⩾6	Metabolic dysregulation: 2005 International Diabetes Federation definition for MetS, excluding individuals with diabetes	NR	NR	Reaction time, Paired Associates Learning Test	There is a trending decrease in cognitive performance from the reference group (no depressive symptoms or metabolic dysregulation) to the comorbid group with both depressive symptoms and metabolic dysregulation. The comorbid group with both depressive symptoms and metabolic dysregulation had the lowest cognitive scores
Janocha et al. (2010)*	10 recurrent depressive episodes (including MDD) ± >10 years diabetes 13 moderate depressive episodes ± >5–10 years diabetes 14 recurrent depressive episodes (including MDD) 16 moderate depressive episodes	Recurrent depressive episodes (including MDD) ± >10 years diabetes: 50.2 ± 1.54 Moderate depressive episodes ± >5–10 years diabetes: 45.69 ± 2.21 Recurrent depressive episodes (including MDD): 44.21 ± 2.95 Moderate depressive episodes: 43.99 ± 3.71	Total population with diabetes: 38.6 Total population with depression but without diabetes: 36.7	Participants recruited in Poland	NR	Beck Depression Inventory (21-item) >12	Self-report T2D confirmed with clinical and laboratory assessment	NR	NR	MSS-2001E system developed by GPE Psychotronics and EIEWIN	Individuals with comorbid depression and T2D performed significantly worse on the coordination/ motor skills assessment compared to those with depression alone
Jia et al. (2020)	59 depressive symptoms	31.98 ± 11.04	22.0	Participants recruited in China	Education, years 12.17 ± 3.85	Self-Rating Depression Scale (20-item) >50	Total cholesterol, HDL cholesterol, LDL cholesterol, TG	NR	NR	RBANS	TG was negatively associated with attention in participants with depressive symptoms. TC, HDL, and LDL were not significantly associated with cognitive outcomes in this group
Johar et al. (2023)	379 depressive symptoms + diabetes 50 depressive symptoms no diabetes	Total depressive symptom population: 63.8 ± 6.5	Total depressive symptom population: 46.3	Total depressive symptom population: Malay (64.9%), Chinese (10.8%), Indian (23.9%), Other (7.7%)	Total depressive symptom population: Low income (<MYR1000): 47.6% Lower levels of education: 76.5%	Depression, Anxiety and Stress Scale (21-item) ⩾10	Self-report: 'Have you ever been told by a doctor/ medical assistant that you have raised blood sugar or diabetes?'	NR	NR	Subjective cognitive complaints: 'Overall in the last 30 days, how much difficulty did you have learning a new task' and 'Overall in the last 30 days, how much difficulty did you have with concentrating or remembering things?'	A significant positive association between depressive symptoms and subjective cognitive complaints was reported. No significant association between diabetes × depressive symptoms interaction on cognitive outcomes was found
Kontari and Smith (2019)*	342 depressive symptoms + cardiometabolic abnormality	Depressive symptoms + cardiometabolic abnormality: 67.39 ± 9.37	Depressive symptoms + cardiometabolic abnormality: 36.3	The sample was recruited from a 98% Caucasian prospective cohort study	Net wealth (1 lowest – 5 highest) Depressive symptoms + cardiometabolic	CES-D (8-item) ⩾4	Cardiometabolic risk factors: C-reactive protein, central obesity, high TG,	NR	NR	Word List Learning Task, Prospective Memory, Animal	Comorbid depression and cardiometabolic risk factors was significantly associated with

(*Continued*)

Table 1. (*Continued.*)

Study	Sample	Mean age ± s.d.	Male (%)	Race/ethnicity/ cultural identifiers	Socioeconomic status (mean ± s.d./%)	Mood disorder diagnosis	Metabolic parameter	Duration of illness ± s.d.	Psychotropic medication use	Cognitive measures	Outcome
	309 depressive symptoms	Depressive symptoms: 66.50 ± 11.13	Depressive symptoms: 27.5		abnormality: 5 (7.9%), 4 (17.0%), 3 (19.9%), 2 (24.0%), 1 (31.3%) Depressive symptoms: 5 (18.7%), 4 (14.1%), 3 (22.0%), 2 (22.3%), 1 (23.0%) Education Depressive symptoms + cardiometabolic abnormality: higher education (15.3%), high school or college (32.6%), no qualification (52.1%) Depressive symptoms: higher education (23.0%), high school or college (37.9%), no qualification (39.2%)		low HDL cholesterol, hypertension, hyperglycemia/ diabetes			Fluency, Letter Cancellation Task	lower cognitive performance compared to depression alone
Lin et al. (2022)	492 depressive symptoms	11–18 years old	NR	Participants recruited in China	NR	Depression Anxiety and Stress Scale (21-item) ⩾14	WHtR ⩾0.46 overweight	NR	NR	Behavior Rating Inventory of Executive Function: Metacognitive Index	Abdominal overweight was associated with greater working memory impairment only in adolescents with depression
Liu et al. (2023)	454 persistent depression 789 worsening depression 3565 mild depression	Persistent depression: 69.65 ± 12.73 Worsening depression: 65.12 ± 13.13 Mild depression: 65.04 ± 12.71	Persistent depression: 32.4 Worsening depression: 36.2 Mild depression: 48.3	Participants with European ancestry	Non-housing financial wealth Persistent depression: 1st quintile; least wealthy (24.9%), 5th quintile; most wealthy (22.2%) Worsening depression: 1st quintile (34.5%), 5th quintile (12.2%) Mild depression: 1st quintile (20.8%), 5th quintile (22.7%) >12 education years Persistent depression: 51.4% Worsening depression: 50.3% Mild depression: 63.5%	CES-D (8-item) ⩾4	BMI (underweight, normal weight, overweight, obesity)	NR	NR	Immediate and Delayed Recall, Serial 7s, Backward Counting	No significant interaction between depressive symptom trajectories and BMI on cognitive performance was identified
Ng et al. (2009)*	Male: 32 depression + hypertension 26 depression no hypertension Female: 50 depression + hypertension 50 depression no hypertension	Total population with depression: 65.0 ± 7.1	Total population with depression: 36.7	Chinese 100%	Total population with depression: ⩽6 years of education 48.7%	GDS (15-item) ⩾5	Hypertension (self-reported, use of antihypertensive medications, or measured sitting systolic BP ⩾140 mmHg or diastolic BP ⩾90 mmHg)	NR	NR	MMSE	Cognitive scores were significantly lower for males with comorbid hypertension and depression compared to males with only depression. This trend was not significant in females

Scuteri et al. (2011)	505 depressive symptoms + hypertension 1345 depressive symptoms no hypertension	79.8 ± 5.8	34.7	Participants recruited in Italy	NR	GDS (15-item) >6	Hypertension as defined by hospital discharge records	NR	NR	MMSE <21	Hypertension was associated with an increased risk for cognitive impairment only in the presence of depression, when compared to normotensive, non-depressed individuals
Wei et al. (2019)	778 depressive symptoms	15.8% ⩾80 years	37	Non-Hispanic White (41.4%), Non-Hispanic Black (25.6%), Hispanic (26.0%), Non-Hispanic Asian (5.7%), other (1.4%)	High school graduate 64.5%	PHQ (9-item) ⩾5	Self-report hypertension, diabetes; BMI (weight and height) measured by trained staff	NR	NR	Delayed Word Recall Test, Animal Fluency Test, DSST	Comorbid depression and diabetes was associated with lower memory, language, executive function/processing speed, and overall cognition scores. The magnitude of the negative associations was greater for the comorbid group compared to individuals with depression alone (a synergistic relationship was identified between depression and diabetes on cognitive performance)
Combined populations: major depressive disorder (MDD) + bipolar disorder (BD)											
Chen et al. (2021)	59 BD 51 MDD* *110 patients total (combined population used for analysis)	BD: 37.24 ± 9.56 MDD: 37.16 ± 12.04	BD: 38.98 MDD: 25.49	Participants recruited in Taiwan	Education BD: <6 years (3.39%), 6–12 years (49.15%), ⩾13 years (47.46%) MDD: <6 years (0.00%), 6–12 years (35.29%), ⩾13 years (64.71%)	DSM-IV or DSM-5	Overweight/ obese BMI ⩾25	BD: 13.49 ± 8.68 years MDD: 6.92 ± 7.41 years	BD: antidepressants (8.47%), mood stabilizers (62.71%), atypical APs (76.27%) MDD: antidepressants (82.35%), mood stabilizers (0.00%), atypical APs (21.57%)	WCST, Go-no-go task	In the combined patient population, BMI and overweight/ obesity were not significantly associated with cognitive function
McIntyre et al. (2015), included in secondary analysis by Mansur et al. (2020)	25 BD 43 MDD	42.63 ± 12.26	51.5	Participant data derived from a predominantly Caucasian population	Participant data derived from a sample with a majority of individuals with a post-secondary diploma/degree and varied employment status	DSM-IV	BMI, IR, glucotoxicity	Participant data derived from individuals with a median illness duration of 14 to 21 years	NR	DSST	The secondary analysis noted that the glucotoxic-clustered individuals had lower cognitive performance when compared to metabolically healthy or IR-clustered subjects. BMI was associated with better cognitive performance in IR and glucotoxic-clustered individuals, but worse performance in metabolically healthy mood disorder patients

(*Continued*)

Table 1. (*Continued.*)

Study	Sample	Mean age ± s.d.	Male (%)	Race/ethnicity/ cultural identifiers	Socioeconomic status (mean ± s.d./%)	Mood disorder diagnosis	Metabolic parameter	Duration of illness ± s.d.	Psychotropic medication use	Cognitive measures	Outcome
Zhuo et al. (2022)	787 BD 899 MDD* *Analyses conducted separately for both groups	BD: 27.8 ± 3.9 MDD: 27.0 ± 2.6	BD: 0 MDD: 0	Participants recruited in China	Education BD: ⩽12 years (31.26%), >12 years (68.74%) MDD: ⩽12 years (40.04%), >12 years (59.96%)	DSM-IV	HbA1c, fasting blood glucose, 2-h post-prandial blood glucose, HDL cholesterol, TG	BD: 42.5 ± 10.2 months MDD: 41.9 ± 6.9 months	Medication free (pre-treatment)	MATRICS	In both the BD and MDD cohort, all metabolic parameters increased the risk for cognitive impairment. Ordered from greatest to lowest risk: HbA1c, fasting blood glucose, 2-h post-prandial blood glucose, TG, HDL cholesterol

APs, antipsychotics; BACS, Brief Assessment of Cognition in Schizophrenia; BD, bipolar disorder; BMI, body mass index (kg/m^2); BP, blood pressure; CANTAB, Cambridge Neuropsychological Test Automated Battery; CES-D, Center for Epidemiologic Studies-Depression; COWAT, Controlled Oral Word Association Test; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSST, Digit Symbol Substitution Test; GDS, Geriatric Depression Scale; HDL, High-Density Lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; ICD, International Classification of Diseases; IR, insulin resistance; LDL, low-density lipoprotein; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MetS, metabolic syndrome; MINI, Mini-International Neuropsychiatric Interview; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NaSSAs, Noradrenergic and Specific Serotonergic Antidepressants; NR, not reported; PHQ, Patient Health Questionnaire; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCFT, Rey Complex Figure Test; SD, standard deviation; SNRI, serotonin/norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; T2D, type 2 diabetes; TCA, tricyclic antidepressants; TG, triglycerides; TMT-A/B, Trail-Making-Test-A/B; WC, waist circumference; WCST, Wisconsin Card Sorting Test; WHtR, waist-to-height ratio; ZVT, Zahlenverbindungstest.
*Included in meta-analysis.

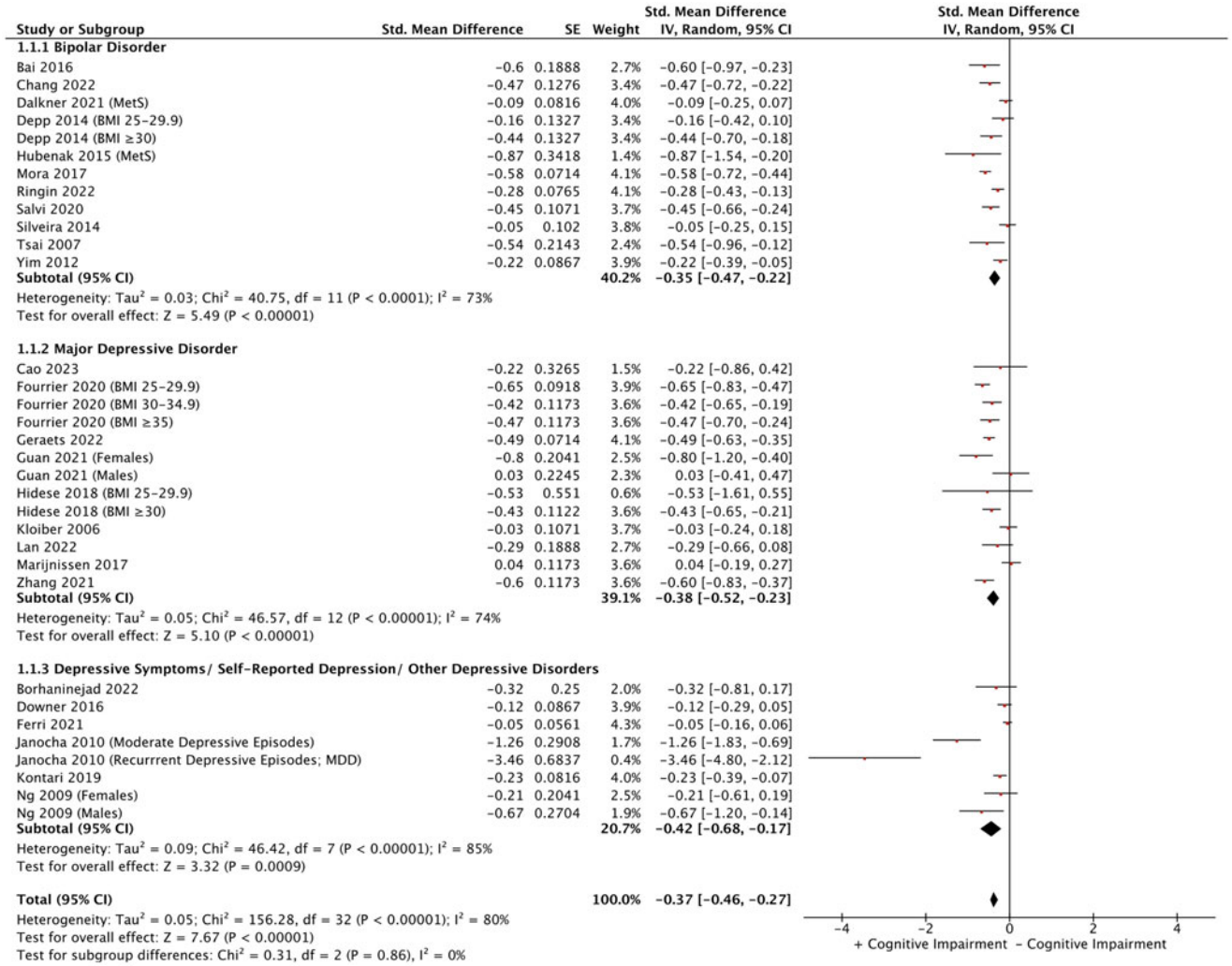

Figure 2. Forest plot of the association between metabolic dysregulation with global cognition in individuals with mood disorders.

= 8) and MetS/multiple cardiometabolic risk factors (−0.25 SMD, 95% CI [−0.44 to −0.07], $p = 0.006$, $I^2 = 84\%$, $n = 2349$, $k = 7$). The overall effect of triglycerides and hypertension could not be summarized across studies as these parameters were reported in only one study each. However, separating these populations by sex showed significant effects of high triglyceride levels in females, and hypertension in males (Guan et al., 2021; Ng et al., 2009).

Association between metabolic dysregulation and individual cognitive domains across all mood disorder populations

Analyzing these effects further within individual cognitive subdomains demonstrated similar trends (Fig. 4; Fig. S1a–g). Comorbid metabolic dysregulation was associated with worse performance on attention tasks in the pooled mood disorder population (−0.42 SMD, 95% CI [−0.68 to −0.16], $p = 0.002$, $I^2 = 81\%$, $n = 1537$, $k = 8$); however, not among all diagnosis subgroups. Executive function scores were significantly reduced in the pooled comorbid metabolic dysregulation group (−0.40 SMD, 95% CI [−0.53 to −0.27], $p < 0.00001$, $I^2 = 44\%$, $n = 1393$, $k = 11$), and also in the BD and MDD subgroups in which this association was assessed. Similarly, small effect sizes were observed when analyzing processing speed (−0.40 SMD, 95% CI [−0.54 to −0.26], $p < 0.00001$, $I^2 = 50\%$, $n = 2834$, $k = 10$) and verbal memory (−0.29 SMD, 95% CI [−0.43 to −0.14], $p = 0.0001$, $I^2 = 70\%$, $n = 1488$, $k = 11$) performance in both the BD and MDD populations. Visual memory (−0.24 SMD, 95% CI [−0.43 to −0.05], $p = 0.01$, $I^2 = 77\%$, $n = 2735$, $k = 8$) and working memory (−0.47 SMD, 95% CI [−0.63 to −0.30], $p < 0.00001$, $I^2 = 55\%$, $n = 1144$, $k = 9$) scores were also lower in the pooled comorbid population, but not in all diagnosis subgroups. Furthermore, cognitive outcomes that were reported using mixed methods, such as by response time or performance score, showed similar small effect sizes highlighting worse performance in attention, executive function, and processing speed domains independent of the reporting method (Fig. S2a–f). The power of these associations is visually represented in Fig. S3.

Examining the association between other clinical variables and cognition using meta-regression

No significant association was discovered between the average age ($\beta = 0.002$; $p = 0.704$), percentage of males ($\beta = 0.001$; $p = 0.816$), or BMI ($\beta = -0.004$; $p = 0.806$) of the comorbid metabolic dysregulation group and global cognition. Due to significant heterogeneity between the clinical scales used to measure depression severity, the SMD was calculated to assess any differences between

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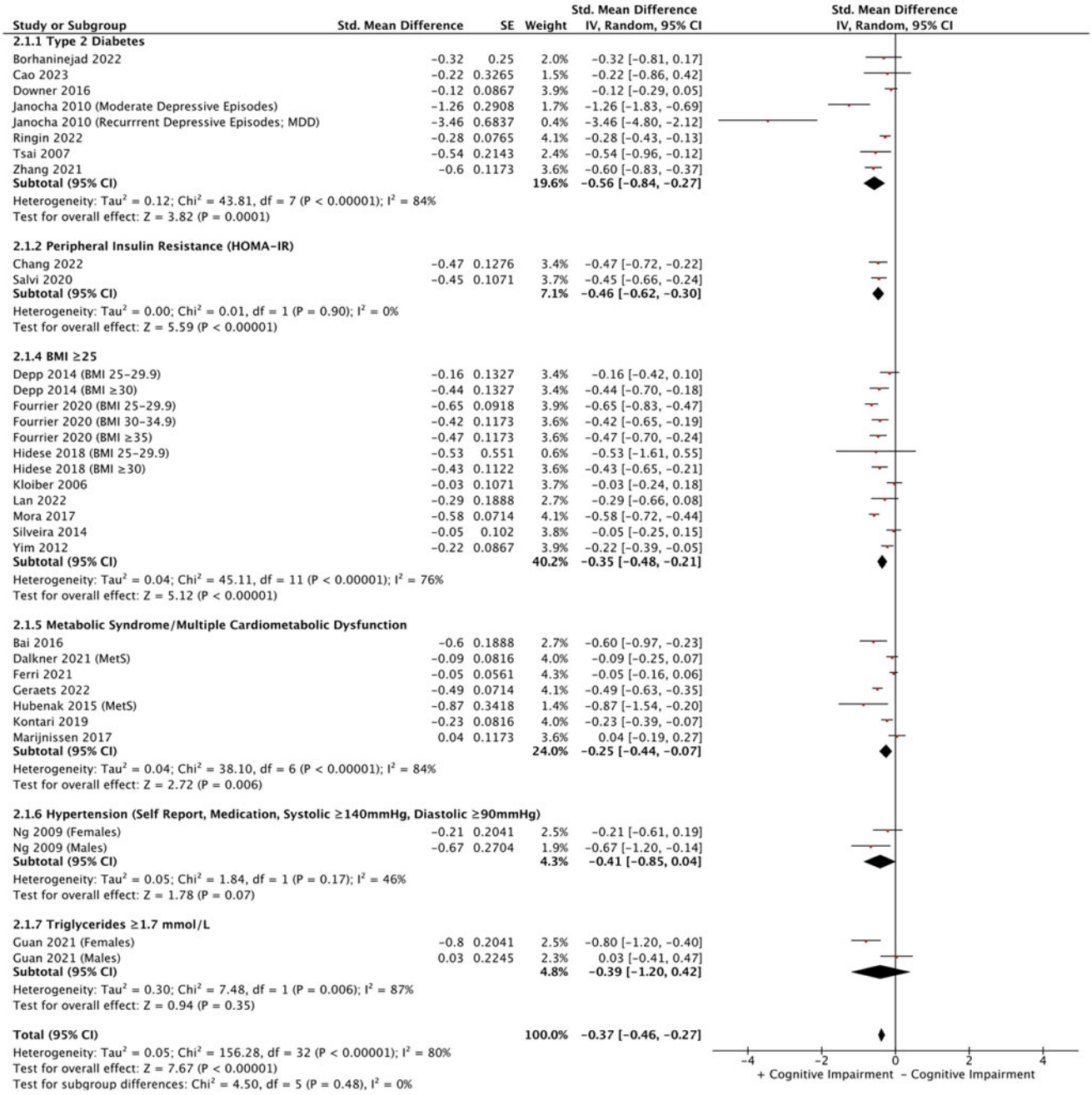

Figure 3. Forest plot of the association between individual metabolic parameters with global cognition in individuals with mood disorders.

the comorbid and mood disorder only group, and no significant difference was found (0.08 SMD, 95% CI [−0.02 to 0.18], $p = 0.12$, $I^2 = 14\%$, $n = 2387$, $k = 13$). Consequently, there were no significant trends between depression severity and cognitive outcomes ($\beta = -0.062$; $p = 0.847$). Similarly, the difference in BMI between the comorbid and mood disorder only group was not associated with the effect size of metabolic dysfunction on cognitive outcomes ($\beta = -0.001$; $p = 0.951$). Additional information on the meta-regressions can be found in Fig. S4a–e.

Publication bias

A visual funnel plot analysis of comparisons between 10 or more studies for all outcomes did not outline publication bias given equal distribution of studies reporting both positive and negative effect sizes (Fig. S5). However, supplementary Egger's test identified significant publication bias when assessing global cognition ($p = 0.0002$) and attention domains ($p = 0.002$) due to the large effect size of one outlier that was removed as part of the sensitivity analysis. No significant publication bias was reported for visual memory, verbal memory, executive function, processing speed, or working memory outcomes ($p > 0.05$).

Sensitivity analysis

A sensitivity analysis was performed by removing eight studies with an indication of a history of a confounding variable (Downer et al., 2016; Kontari & Smith, 2019; Marijnissen et al.,

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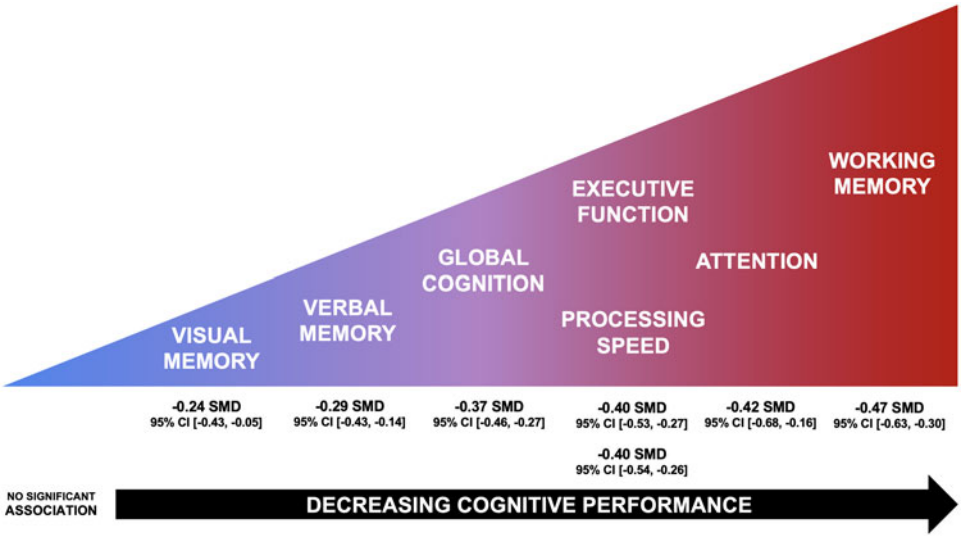

Figure 4. Summary of the association between metabolic dysregulation and different cognitive domains in individuals with mood disorders.

2017; Ng et al., 2009; Salvi et al., 2020; Silveira et al., 2014; Tsai et al., 2007) or large effect size (Janocha et al., 2010) (Fig. S6–7). The overall effect size remained significant for global cognition (−0.37 SMD, 95% CI [−0.47 to −0.27], $p < 0.00001$, $I^2 = 77\%$, $n = 4539$, $k = 17$) in the pooled population and within the BD and MDD subgroups, but not in the depressive symptoms subgroup due to removal of many studies. Similar results were produced for the individual metabolic domain subgroups; however, peripheral insulin resistance and hypertension effect sizes could not be calculated due to fewer than two studies included in these subgroups. The sensitivity analysis for the attention subgroup remained significant (−0.27 SMD, 95% CI [−0.44 to −0.09], $p < 0.003$, $I^2 = 58\%$, $n = 1419$, $k = 6$). Reassessment of publication bias using the Egger's test for the global cognition outcome was no longer significant ($p = 0.383$; Fig. S5g).

Certainty of evidence

The GRADE framework identified very low certainty of evidence for verbal and visual memory due to both positive and negative findings within individual studies and high overall heterogeneity (I^2>75%), and similarly for global cognition and attention due to publication bias. A low certainty of evidence was assigned to executive function, processing speed, and working memory outcomes due to residual confounding such as the impact of pharmacotherapy on the outcomes of interest, differences between family history/genetic predispositions to mood or metabolic disorders, variance in cognitive measures, and no measurement of state *v.* trait characteristics of mood disorders (Table S4).

Discussion

This review is the first of its scope to explore the association between metabolic dysfunction and various cognitive outcomes in a diverse mood disorder population. Global cognitive performance was significantly lower among individuals with BD, MDD, and depressive symptoms experiencing comorbid metabolic dysregulation in comparison to metabolically healthy mood disorder populations, and the effect size did not differ significantly among the mood disorder subgroups. These relationships with cognition were strongest (in descending order) in mood disorder populations with T2D, peripheral insulin resistance, a BMI ⩾25, and MetS/multiple cardiometabolic risk factors. In analyzing individual cognitive domains, worse cognitive performance was most prominent for working memory, followed by attention, executive function/processing speed, global cognition, verbal memory, and visual memory. The association between high triglyceride levels and hypertension with cognitive outcomes could not be assessed because of the limited number of studies reporting on these parameters.

Overall, these findings which explore the impact of several metabolic parameters in multiple mood disorders correspond to trends that are in line with what has been reported in BD (Bora et al., 2019), as well as beyond the mood disorder population, including schizophrenia (Bora et al., 2017). Our results parallel and complement the associations explored from an alternate perspective, whereby depressive symptoms are associated with cognitive impairment in individuals with diabetes (Chow et al., 2022). Similar associations were reported for bariatric patients with MDD, whose cognitive performance was impaired compared to bariatric patients without psychiatric illness (Restivo et al., 2017). Therefore, this bidirectional relationship between metabolic dysfunction and mental health disorders permeates multiple populations, suggesting shared mechanisms in relation to their effect on cognitive outcomes. Some proposed biological underpinnings of these complex interactions include inflammation, hyperactivity of the hypothalamic-pituitary-adrenal axis, disrupted insulin signaling, and dysregulated glucose homeostasis (Korczak, Pereira, Koulajian, Matejcek, & Giacca, 2011).

Identification of this multifaceted relationship between metabolic dysregulation, mood disorders, and cognition provides a novel framework for addressing cognitive decline in this population. For example, intervention studies have utilized anti-diabetic drugs such as liraglutide and metformin to revert metabolic dysfunction in MDD and BD patients, and demonstrated improvements in cognitive outcomes following the trials (Guo et al., 2014; Mansur et al., 2017). Therefore, targeting the metabolic domain may serve as an alternative treatment option as current first-line interventions often fail to treat cognitive deficits (Hamer et al., 2019). This is of importance as cognitive

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impairment is associated with worse adherence to treatment in individuals with mood disorders (Corréard et al., 2017; Martinez-Aran et al., 2009). As a result, this may exacerbate pre-existing symptoms and cost the healthcare system an additional $3252–$19 363 per patient, annually (Cutler, Fernandez-Llimos, Frommer, Benrimoj, & Garcia-Cardenas, 2018). Furthermore, due to the strong socioeconomic influence on metabolic health (Mohammed et al., 2019) and mental illness (Mann, Heesch, Rachele, Burton, & Turrell, 2022), this may disproportionately increase the risk for cognitive dysfunction among individuals of low socioeconomic status (Wang et al., 2023). Therefore, when cognitive impairments persist despite the use of standard treatments in mood disorder populations, they may exacerbate the burden at both the individual patient and global healthcare level.

This review synthesizes evidence which outlines the significant negative association between metabolic dysregulation and cognition in the context of mood disorders, with low inter-subgroup variability. Furthermore, it does so in a representative population by being inclusive of those experiencing depression who may not have a formal diagnosis due to stigma or limited access to mental health services. Despite this, there are several limitations that must be considered.

The results of this review must be interpreted with care as the differences observed in cognitive performance do not confirm cognitive impairment. The comparisons drawn between cognitive outcomes in individuals with mood disorders, with or without metabolic dysfunction, rather highlight the importance of assessing cognition in this population, and the close relationship between these domains. Further studies must be conducted with the use of standardized cognitive score thresholds to assess the clinical relevance of these associations. Additionally, it must be noted that cognitive data used for this analysis were sourced from heterogeneous populations that vary in age, sex ratio, medical comorbidities, clinical severity, and medication use. Although the meta-regressions did not identify any significant trends between cognitive outcomes and some of these parameters, they still serve as confounding variables that may influence the associations that were reported. Specifically, the prevalence of psychotropic medication use within studies was high. Due to the independent effect of these medications on metabolic parameters (Pillinger et al., 2020), it is difficult to discern their effects from other underlying physiological mechanisms. Although these elements are more representative of populations that are seen in clinic, they may dampen the effects reported in the results. However, the reported medications were also used by the control group, such that matching allows for better interpretation of these associations. Furthermore, the medication-free/naïve populations outlined in this review reported similar trends, whereby a multitude of metabolic parameters were associated with worse cognition/greater risk for cognitive impairment (Qiu et al., 2022; Zhuo et al., 2022). Therefore, further validation of these associations in medication-free/naïve populations is necessary to eliminate confounding factors.

In addition to the variability between study populations, there was also significant heterogeneity in the cognitive assessment tools employed and domains assessed within studies. As there is no standardized method to assess this outcome, this limits comparability of cognition between studies. Similarly, different assessments were used to measure depression severity, but SMD was computed to be able to compare these elements. Since there was no significant difference in depression symptom severity between the two comparison groups, this suggests that the associations with cognitive outcomes were predominantly driven by the metabolic parameters being studied. However, similar regressions could not be performed for assessments of mania, apathy, and avolition due to limited reporting of these outcomes. Furthermore, many studies also did not report on race, ethnicity, and socioeconomic status making it unclear how results generalize across these variables. Finally, small sample sizes with large margins of errors may have affected the strength of evidence and inclusion of mostly cross-sectional study designs limits the interpretation of causality. Therefore, large-scale longitudinal studies are necessary to explore the directionality of these relationships.

In conclusion, this review and meta-analysis demonstrates the negative association between metabolic dysregulation and cognition in individuals with mood disorders. T2D was demonstrated to have the strongest association with cognitive outcomes in this population. Of all cognitive domains, working memory performance was lowest in mood disorder populations with comorbid metabolic dysfunction *v.* metabolically healthy comparators. Further research is required to understand the underlying mechanisms of this interplay between mood disorders, metabolism, and cognition.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000345.

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Author contributions. All authors contributed to the synthesis and revision of the final manuscript. K. M. and S. M. A. were involved in the concept and design of the study, and planning formal analysis. K. M. was involved in conducting the systematic search, screening articles, data extraction, risk of bias and GRADE assessment, and statistical analysis. Z. H. contributed to article screening, data extraction, and risk of bias assessment. N. S., F. P., and J. G. contributed to article screening and data extraction. R. D., E. S., and A. H. contributed to article screening. M. K. H. was involved in planning formal analysis and revision of the manuscript. B. I. G., D. K., and A. G.-G revised the work and offered feedback for improvement.

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