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Research paper

Peripheral adiponectin levels in anxiety, mood, trauma- and stressor-related disorders: A systematic review and meta-analysis

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ABSTRACT

Background: Anxiety, mood, trauma- and stressor-related disorders confer increased risk for metabolic disease. Adiponectin, a cytokine released by adipose tissue is associated with these disorders and obesity via inflammatory processes. Available data describing associations with mental disorders remain limited and conflicted.

Methods: A systematic search was conducted for English, peer-reviewed articles from inception until February 2019 that assessed for serum or plasma adiponectin levels in adults with an anxiety, mood or trauma-related disorder. Diagnoses were determined by psychiatric interview, based on DSM-IV, DSM-5 or ICD-10 criteria. Analyses were performed using STATA 15 and Standardized mean difference (SMD) with 95% confidence interval was applied to pool the effect size of meta-analysis studies.

Results: In total 65 eligible studies were included in the systematic review and 30 studies in this meta-analysis. 19,178 participants (11,262 females and 7916 males), comprising healthy adults and adults with anxiety, mood and trauma-related disorders, were included. Overall results indicated an inverse association between adiponectin levels and examined mental disorders. Specifically, patients with an anxiety disorder (SMD = −1.18 μg/mL, 95% CI, −2.34; −0.01, p = 0.047); trauma or stressor-related disorder (SMD = −0.34 μg/mL, 95% CI, −0.52; −0.17, p = 0.0000) or bipolar disorder (SMD = −0.638 μg/mL, 95% CI, −1.16, −0.12, p = 0.017) had significant lower adiponectin levels compared to healthy adults.

Limitations: Heterogeneity, potential publication bias, and lack of control for important potential confounders were significant limitations.

Conclusion: Peripheral adiponectin levels appear to be inversely associated with anxiety, mood, trauma- and stressor related disorders and may be a promising biomarker for diagnosis and disease monitoring.

1. Background

Anxiety, mood (i.e. depressive, bipolar and related disorders), trauma- and stressor-related disorders are highly prevalent and associated with significant morbidity and mortality (American Psychiatric Association, 2013; Bandelow and Michaelis, 2015; Kessler et al., 2005). These disorders are multifactorial, complex and characterized by marked phenotypic and biological heterogeneity (Uher and Zwicker, 2017). Despite advances in treatment, tractable biomarkers for the prediction of disorder onset, the onset of comorbidity after the disorder has set in, and identifiers of treatment response are lacking (Boksa, 2013). Individual differences in peripheral biomarkers that are amenable to measurement may be useful in matching patients with drug treatments, and may serve as targets for the development of novel drugs that act through inflammatory and metabolic pathways (Herron et al., 2018).

Metabolic syndrome is a cluster of cardiometabolic conditions with an increased risk for adverse health outcomes such as cardiovascular disease, cancer, cognitive decline and mortality (Kaur, 2014). Metabolic syndrome is highly prevalent globally and especially comorbid with various psychiatric conditions including anxiety, mood, trauma- and stressor- related disorders (Milaneschi et al., 2018; Rosenbaum et al., 2015). Accumulating evidence suggests that these different psychiatric patient groups share features of dysregulation within the

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hypothalamic-pituitary-adrenal (HPA) axis and in the inflammatory response; both of these systems are also linked to the development of metabolic syndrome (Lopresti and Drummond, 2013; McNamara and Lotrich, 2012; Muneer, 2016). For example, depression has been characterized as a state of elevated inflammation, altered cardiovascular parameters and a deranged metabolic situation (Gans, 2006). Bipolar disorder (BD) is associated with chronic low-grade inflammation and several medical comorbidities (Muneer, 2016). Individuals with high anxiety levels and/or post-traumatic stress disorder (PTSD) are more likely to develop metabolic disease (Rosenbaum et al., 2015) as compared to those individuals without these disorders; with alterations shown in various pathways; including hypothalamic-pituitary-adrenal (HPA) and immune system dysregulation (Farr et al., 2014; Mellon et al., 2018; Michopoulos et al., 2016).). Yet our understanding of how these dysregulations contribute to metabolic syndrome-mental illness comorbidity remains incomplete. A potential mediator of the metabolic disease-mental illness association is an alteration in adipokine levels; biologically active proteins secreted by adipose tissue that participate in inflammatory processes (Ouchi et al., 2011).

The role of adipokines in mental disorders has been garnering more attention, given that adipose tissue also functions as a regulator of endocrine and metabolic activity (Ouchi et al., 2011). Adiponectin is the most abundant adipokine, secreted only by mature adipocytes and mainly produced in white adipose tissue (Stern et al., 2007a,b). Adiponectin, in contrast to other adipokines, is negatively correlated with obesity. In the presence of obesity, adiponectin release is down-regulated resulting in reduced circulating levels (Stern et al., 2007a,b). Low adiponectin has been shown to be closely associated with the clinical phenotype of metabolic syndrome (Mather and Goldberg, 2014; Stern et al., 2007a,b). Prospective studies have also shown the potential predictive value of serum adiponectin for identifying individuals at high risk of new onset metabolic syndrome (Kim et al., 2013; Liu et al., 2018; Yoon et al., 2016). Adiponectin has anti-atherogenic, anti-inflammatory and insulin-sensitizing properties which are thought to be key in explaining the interrelationship between adiposity, insulin resistance and inflammation (Ghadge et al., 2018; Kowalska, 2007). Although adiponectin is well known for its ability to regulate metabolic function, few studies have examined its association with mental health factors.

To date, most extant studies that have focused on the association between adiponectin and mental illness have been conducted among patients with major depressive disorder (MDD) and have yielded inconsistent results in the main (Carvalho et al., 2014; Hu et al., 2015). A meta-analysis by Hu et al. (2015) found that patients with MDD had lower adiponectin levels when compared to healthy patients in a European patient sample (Hu et al., 2015). Another meta-analysis emphasized that levels of adiponectin in patients with depression were not different from those in a healthy population, although levels have been shown to be higher or lower in subgroups of depressed subjects compared with controls (Carvalho et al., 2014). The most recent systematic review and meta-analysis (Cao et al., 2018) concluded that lower adiponectin levels may be associated with MDD, and that males expressing lower adiponectin-levels have an increased likelihood of developing MDD. There are limited studies on the association of adiponectin with anxiety, bipolar and trauma-related disorders. Barbosa et al. (2012) reported that patients with BD had increased plasma levels of adiponectin and leptin compared to healthy volunteers (Barbosa et al., 2012). Another study concluded that adiponectin levels, either directly or as a proxy of metabolic dysfunction, are independently associated with an unfavorable course of illness in BD (Mansur et al., 2016). There is increasing evidence that common mental disorders such as anxiety, mood, trauma- and stressor related disorders share common neurobiological underpinnings (Bandelow et al., 2016; Brainstorm Consortium et al., 2018) Adiponectin may be a useful metabolic-inflammatory marker for future identification and management of these common mental disorders as well as comorbid metabolic disease. Furthermore, adinopectin may serve as a potential target for the development of novel intervention strategies and as a predictor of treatment response (Furman et al., 2018).

This systematic review and meta-analysis aimed to synthesize and expand on existing literature by examining the association between peripheral adiponectin levels and common mental disorders that are (i) mechanistically linked and (ii) where peripheral adiponectin levels have been investigated as biomarker of the disease process of these disorders and/or as a biomarker of treatment response.

2. Methods

2.1. Criteria for considering studies for this review

We included all studies that assessed for peripheral serum or plasma adiponectin levels in adults with an anxiety, mood or trauma-related disorders, regardless of the sample size or the study population. Where the same dataset was analyzed in different publications, we only collected the most recent dataset and noted any potential overlap. For all studies, diagnoses were based on criteria for anxiety, mood and trauma-related disorders using a validated structured or semi-structured clinical interview (e.g., Composite International Diagnostic Interview [CIDI] (Wittchen, 1994) Structured Clinical Interview for DSM-IV [SCID-I] (Frist et al., 1996)), or a screening instrument based on DSM-IV, DSM-5, or ICD-10 criteria. The outcome of interest was either serum or plasma adiponectin expressed as μg/ml.

2.2. Search strategy, study selection and data-extraction

A systematic, computerized search was conducted on 15 February 2019 using the following databases: PubMed, EBSCOhost, Sciencedirect and Web of Science. The following search strategy was used: "(Adiponectin, OR adipocyte complement-related protein of 30 kDa OR Acrp30) AND ("acute stress disorder" OR "posttraumatic stress disorder" OR "ptsd" OR "anxiety" OR "generalized anxiety disorder" OR "social anxiety disorder" OR "agoraphobia" OR "panic" OR "stress" OR "specific phobia" OR "depression" OR "major depressive disorder" OR "bipolar disorder" OR "mood" OR "affective")". A broad search strategy with no restrictions placed on potential articles was used to include all relevant studies. As such, no restrictions were placed on the initial search. All available sources were included in the search irrespective of their date of publication. The search was undertaken independently, on the same day, by the first two authors (EV, JN). Terms related to psychiatric disorders were not included in the search to avoid being restrictive with regards to specific disorders. Also, no limit on the time-period was applied to be inclusive of relevant studies, however the search was restricted to English language studies and to human participants. We excluded literature reviews, book chapters, studies on animals or cell-lines or studies of genetic variation in ADP-related genes. Studies that included participants younger than 18 years of age were excluded (this extended to studies where the lower age limit for inclusion was below 18, even though the upper age range may have been over 18 years (e.g. 16–24 years). Studies comprised cross-sectional, case-control, cohort and intervention study designs. Two reviewers (EV, JN) independently analyzed the titles and abstracts retrieved from the search. All abstracts deemed potentially relevant were then reviewed in full text. Any disagreement between the reviewers regarding study inclusion was resolved by a third investigator (SS).

2.3. Data extraction and analyses

For each included article, data were extracted using a standard data extraction protocol to collect information on: (1) sample size; (2) country and setting (e.g. community or clinic sample); (3) gender; (4) age; (5) race / ethnicity; (6) medical comorbidity (7) smoking status; (8) fasting state; (9) type of blood specimen used for test (plasma versus

serum); (10) number of sample extraction (e.g., single, serial); (11) sample detection method (e.g., ELISA, RIA, other); (12) mean (SD) adiponectin level; (13) mental health outcome/s; (14) instrument/s used to measure the mental health outcome/s; (15) association of adiponectin with mental health outcome/s. If outcome data were missing, we contacted the corresponding authors by email. A study was excluded if (i) pertinent information to the review was missing, and (ii) if a reply was not received within 8 weeks, following a second email request. Of the 37 authors contacted, 9 responded and provided requested data.

2.4. Statistical analysis

Given the marked (i) clinical heterogeneity (differences in the patient populations that were examined in different studies and the differences in the treatments that were delivered), and (ii) methodological heterogeneity (differences in experimental design between studies), a decision was made to conduct a meta-analysis only on case-control studies in depressive-, bipolar-, anxiety- and trauma- and stressor-related disorders. Thus, we only included studies where a healthy control group was compared to a group of participants with an aforementioned mental disorder. We excluded cohort studies, intervention studies and studies where pertinent data for the qualitative analyses were missing (example adiponectin-value). In instances where >1 measurement was taken, only the baseline adiponectin level was included.

To estimate the association between adiponectin levels and mental disorder, the standardized mean difference (SMD) and 95% confidence interval (CI) from each study per disorder group was calculated using STATA 15. Pooled hazard ratios (HRs) (95% confidence intervals-CIs) were derived using fixed or random effects models, where appropriate, and expressed as one standard deviation (SD) increment of adiponectin. Heterogeneity across studies was assessed through the Q statistic. Whenever the heterogeneity between studies was not significant, fixed effects models were used to estimate Hedge's g.

We evaluated (i) the potential moderating effects of socio-demographic factors (% of females in overall sample, study-region), clinical variables (diagnostic instrument, rating scale), and adiponectin analysis information (assay type; fasting status, specimen type) and (ii) conducted subgroup analyses. Sensitivity analyses were performed to assess the robustness of the observed outcomes.

3. Results

The initial search identified $N = 6689$ studies of which $N = 37$ were duplicate studies and $N = 24$ were published in a language other than English. Following a review of titles and abstracts, 6597 articles were excluded following initial screening (see Fig. 1). Ninety-two full-text manuscripts were retrieved of which 27 were excluded after a full-text review and data extraction. For the systematic review, 65 studies on healthy adults and adults with anxiety, depression, bipolar and post-traumatic stress disorder were included and comprised 19,178 patients worldwide. Studies include 11 cohort, 36 case-control, 11 cross-sectional and 8 interventional studies (of which 3 were randomized controlled trials). See Tables 1 and 2 for a summary of included studies.

Thirty studies were included in the meta-analysis, Few studies were included for bipolar disorder ($N = 9$), trauma- and stressor- related disorders ($N = 2$) and anxiety disorders ($N = 3$) and the results of this meta-analysis should be considered as exploratory. 17 studies on depressive disorders were included in a separate meta-analysis.

4. Results

4.1. Measures of interest

4.1.1. Participants

A diverse range of participants were included. Studies came from high- and middle- income countries. No studies were available from Africa and from other low -income countries. Only 35 studies reported on the ethnicity/race of participants; of those studies that reported ethnicity, most participants were of Asian or Caucasian descent. In terms of gender, across the studies there were 11,262 females and 7916 males.

4.1.2. Covariates

4.1.2.1. Medical comorbidity. A wide range of comorbid medical illness was included, although the nature of medical illness was not always specified (Jeong et al., 2012). Some studies allowed for the inclusion of medical illness if participants were stable on treatment (Lee et al., 2014; Rapaport et al., 2016; Shelton et al., 2015a,b). One study further specified the exclusion of participants who had active medical illness (e.g. uncontrolled diabetes)that could be etiologically linked to ongoing depression as well as to immune and autoimmune conditions (Zeugmann et al., 2013) In the study by Barbosa et al. (2012), plasma levels of adipokines in bipolar patients did not differ according to the presence of medical comorbidities (i.e. arterial hypertension, diabetes mellitus, dyslipidemia or hypothyroidism) or medication use (i.e. lithium, anticonvulsants, antipsychotics, antihypertensives, antidiabetogenic drugs, antilipidemic drugs or thyroid hormones) (Barbosa et al., 2012).

4.1.2.2. Smoking status. Despite existing literature suggesting that the synthesis and secretion of adiponectin is influenced by several lifestyle factors such as diet, alcohol use, exercise and smoking status; only 25 of the 65 studies reported on or examined smoking status as covariate.

4.1.3. Adiponectin

Of the 65 studies reviewed, 48 examined fasting adiponectin, 7 examined non-fasting blood-samples, while in 10 studies fasting status was not reported. 37 studies analyzed plasma samples, 26 serum samples and 2 studies did not list sample type. Various assay methods to establish adiponectin values were employed, of which the most common were ELISA (46), followed by RIA (11) and other (Lincoplex, Luminex, Multiplex) (7). One study did not report on the analysis method. Of note, not all studies reported that ELISAs were done in duplicate, nor reported inter- and intra-assay coefficients. Furthermore, collected samples were centrifuged at varying rates per minute (rpm), for varying duration, and sera were stored at varying temperatures and for varying periods of time before analysis.

Adiponectin exists in a wide range of multimer complexes. Only 3 studies reported on adiponectin multimer distribution. In a small study in healthy elderly subjects without metabolic syndrome, the ratio of HMW to total adiponectin, and not absolute adiponectin levels, was negatively associated with depression severity. However, in Rao et al.'s study of individuals with PTSD, circulatory levels of HMW adiponectin were not significantly different between cases and controls (Rao et al., 2014). Lastly, in the study by Herder et al., only the ratio of HMW/total adiponectin was found to be associated with depressive symptoms in individuals recently diagnosed with type 2 diabetes (Herder et al., 2018).

4.1.3.1. Level of evidence. In healthy adults, the concentration of peripheral adiponectin levels ranged from 5 to 20 μg/ml (Matsuzawa, 2005). Across the studies included in the review, there was a significant variation in adiponectin levels (see Table 2), which is not surprising given the substantial differences in study populations and methods.

4.1.4. Mental health outcomes

Not all studies reported on the duration or severity of mental illness. Participants ranged from healthy (Adam et al., 2010; Narita, et al., 2006) to mentally illness and treatment naïve (Aliyazicioglu et al., 2011; Furman et al., 2018; Pinar et al., 2008; Soeiro-de-Souza et al., 2014) to mentally ill and medicated (Archer et al., 2018; Barbosa et al.,

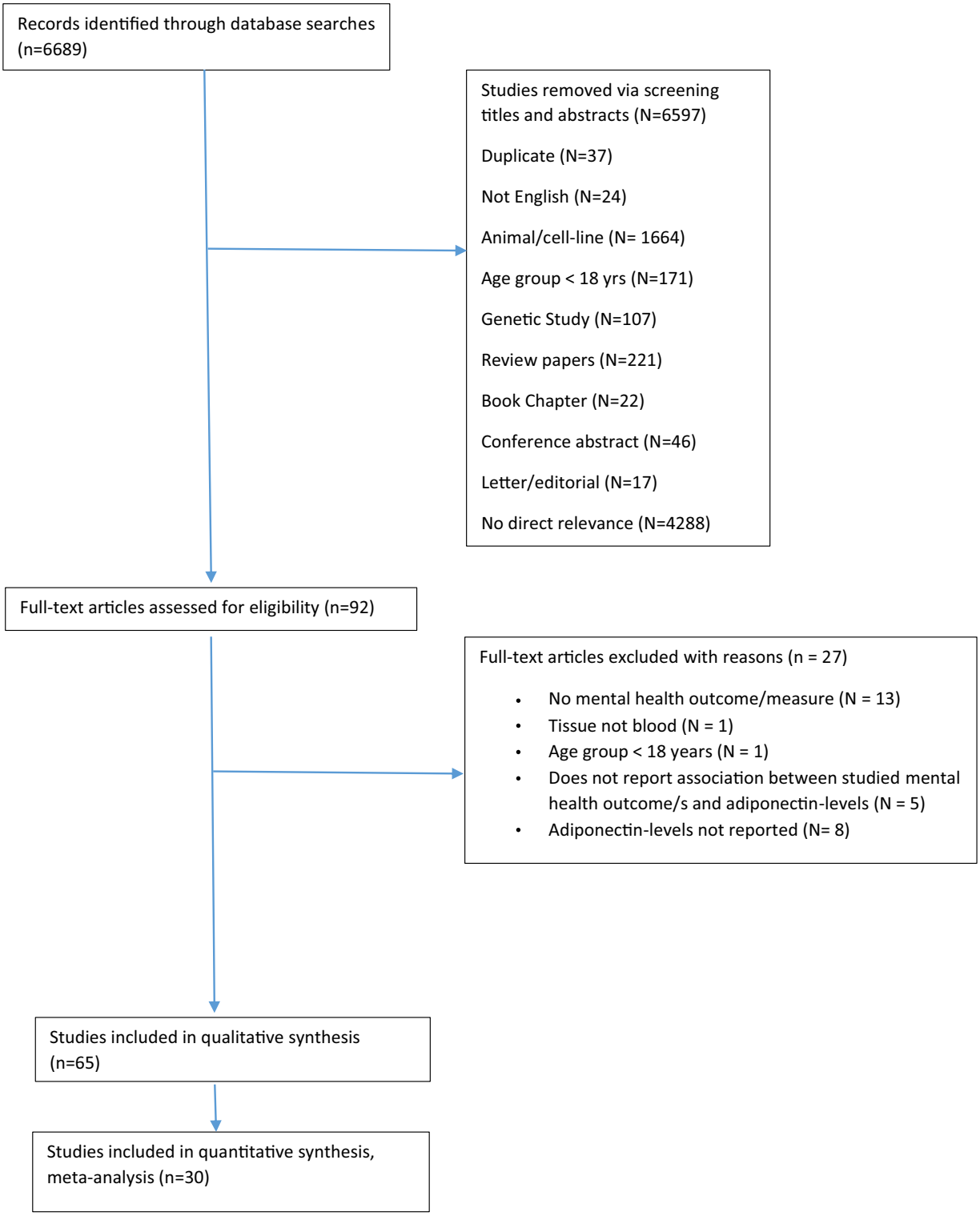

Fig. 1. Flow diagram of the review process.

2012; Mansur et al., 2017).

4.1.4.1. Medication use. Weber-Hamann et al. reported no change in plasma adiponectin levels of depressed patients over 6 weeks of antidepressant treatment (Weber-Hamann et al., 2007), whilst Archer et al. found no correlation between medication use and adiponectin levels in their study population of alcohol use disorder patients with a current depressive episode (Archer et al., 2018). A clinical trial by Pinar et al. of 40 unmedicated male participants diagnosed with depressive disorder who all started treatment with maprotiline (150 mg/day) found that total adiponectin levels decreased with maprotiline treatment (Pinar et al., 2008). In a clinical trial examining whether adiponectin moderated treatment outcomes (Furman et al., 2018), participants with low baseline adiponectin levels demonstrated a greater reduction in depressive symptoms over 12 weeks of treatment with Escitalopram/Buproprion than with Venlafaxine/Mirtazepine (Furman et al., 2018). Narita et al. conducted a cross-sectional study of participants, over the age of 40 years, who had experienced one or

Table 1
Summary of studies by psychiatric disorder.

First author (year)	Mental health outcome	Mental health measure/s	Study type and design	Sample	Setting and participants	Age in years mean (SD)	Gender (M/F)	Ethnicity
Adam et al. (2010)	Depression	SCID, PSS, PANAS	Cross-sectional, case-control (Study 2)	*N* = 48* A: Women with depressive disorder = 10 B: Women without depression = 38 (Study 2)	USA, community sample, participants were postmenopausal women with a range of stress levels captured by including women giving care to a relative diagnosed with dementia as well as non-caregiving women	Age range: 51–79 years (M age 61.87, SD = 6.51)	All participants female	Caucasian (majority), Hispanic/ Latina, Asian, black
Aliyazicioglu et al. (2011)	Depression	SCID	Cross-sectional, case-control	*N* = 142 A: Depressed patients = 78 B: Healthy control = 64	Turkey, unmedicated depressed patients recruited from hospital setting, and healthy controls from hospital staff.	A: 38 (11) B: 28 (9)	A 15/63 B 28/36	Not recorded
Archer et al. (2018)	Depression	MINI BDI MADRS AUDIT	Cross-sectional, prospective cohort	*N* = 242 A: AUD = 99 B: Non-AUD = 143	Finland, Outpatient recruitment, Majority medicated (>80%) participants were divided into two groups based on the baseline AUDIT-score, with Therapeutic intervention and 6 month follow-up All data were analysed between study groups and between genders.	A: 38.9 (18–62) B: 38.7 (17–64)	148/94	Caucasian
Bai et al. (2014)	Depression	MINI BDI-II DSSS	Cross-sectional, case-control	*N* = 235 A: Depressive disorder = 109 B: HC = 126	Taiwan, patients who met DSM-IV criteria for depressive disorder. 50 (45.9%) did not take antidepressants, and 59 treated with antidepressants. Age/gender/body mass index (BMI)-matched healthy subjects were enrolled.	A 41.96 (13.8) B 41.88 (10.0)	A 26/83 B 51/75	Asian
Chan et al. (2017)	Depression	HADS	Randomized, waitlist-controlled trial	*N* = 108 A: Exercise group = 46 B: Controls = 62	China, participants with Chronic Fatigue Syndrome-Like Illness were randomly assigned to either Qigong exercise or waitlist groups. Sixteen 1.5-h Qigong lessons were conducted. Outcome measures were taken at 3 time points	A:39.5 (33.5–45.3) B: 42.0 (32.5–47.0)	All participants female	Asian
Cizza et al. (2010)	Depression	Diagnosis: SCID, Severity: HAM-D HAM-A	Cross-sectional, case-control	*N* = 46 (23/23) A: Depressed = 23 B: HC = 23	United States, community controls were matched to subjects with MDD based on age ± 3.0 years and body mass index (BMI) ± 2.0 kg/m2 . The majority of women with MDD were taking antidepressants.	A: 35 ± 6.0 B: 35 ± 6.1	All participants female	Majority Caucasian
Diniz et al., 2012	Depression	Diagnosis: SCID Severity: HAM-D	Cross-sectional, case-control	*N* = 98 A: Depression =47 B: HC = 51	Brazil, elderly outpatients with a current major depressive episode (first or recurrent episode), comparison group were healthy volunteers recruited from an ongoing clinical cohort dedicated to the study of health and cognition in older adults All depressed patients unmedicated	A: 70.2 (4.7) B: 68.7 (5.6)	A: 10/37 B: 11/40	Not recorded
Domingues et al. (2015)	Depression Anxiety	BDI BAI	Cross-sectional, case-control	*N* = 96 A: Tension-type headache = 48 B: HC = 48	Brazil; cases are patients with tension-type-headaches, and controls had no history of headaches	A: 40.77 ± 18.13 B: 40.35 ± 14.38	A: 5/43 B: 5/43	Caucasian Mixed race Black
Duarte et al. (2014)	Depression Anxiety	BDI BAI	Cross-sectional, case-control	*N* = 133 A: Migraine = 68 B: HC = 65	Brazil; Sixty-eight migraine patients and sixty-five controls without headache were included	A: 40.8 ± 14.5 B: 44.7 ± 15.6	A: 5/63 B: 8/57	Caucasian Mixed race Black
Einvik et al. (2013)	Depression							Not recorded

(*continued on next page*)

Table 1 (*continued*)

First author (year)	Mental health outcome	Mental health measure/s	Study type and design	Sample	Setting and participants	Age in years mean (SD)	Gender (M/F)	Ethnicity
		Diagnosis: SCID Severity: BDI	Cross-sectional, case-control	*N* = 290 A: OSA = 34 B: HC = 256	Norway, participants part of the Akershus Sleep Apnea Project, a community-based study designed to investigate risk for OSA in the general population. Participants were invited to partake in depression assessment	A: 45 ± 9 B: 49 ± 11	A: 13/21 B: 142/114	
Everson-Rose et al. (2018)	Depression	Diagnosis: SCID Severity: CES-D	Cross-sectional, and longitudinal	Cross-sectional sample *N* = 575 A: Depressed = 146 B: Not depressed = 429 Longitudinal sample *N* = 262 A: Depressed = 70 B: Not depressed = 192	USA, his study uses data from the Study of Women's Health Across the Nation (SWAN), an ongoing community-based longitudinal study of the menopausal transition conducted at 7 clinical sites.	Cross-sectional sample A: 45.3 (2.3) B: 45.7 (2.6) Longitudinal sample A: 44.7 (2.1) B: 45.5 (2.5)	All participants female	Caucasian African-American
Fabregas et al. (2016)	Depression	Diagnosis: MINI-plus Severity: BDI, HAD, HAM-D, HAM-A	Case-control, longitudinal follow-up	*N* = 50 A: IFN treatment = 14 B: No IFN treatment = 36	Brazil, a convenience sample of HCV-monoinfected patients was performed at a public university-based outpatient service for infectious diseases. HCV monoinfected patients, with and without IFN treatment, were followed up for 18 months	A: 46.6 ± 12.3 B: 50.5 ± 12.4	A: 8/6 B: 16/20	Not recorded
Ferrari et al. (2018)	Depression	Diagnosis: CIDI Severity: BDI-I BDI-II	Cross-sectional, cohort	*N* = 173 A: No depressive symptoms = 151 B: Mild/Moderated depressive symptoms =22	Germany, participants were probands of a prospective monocenter observational study PPSDiab ("Prediction, Prevention and Sub-classification of type 2 Diabetes"), which recruited from November 2011 until May 2016 and consisted of women who had a recent pregnancy. Outpatient Recruitment and women were included within 15 months after delivery.	A: 35.4 ± 4.1 B: 35.6 ± 5.0	All female	Not reported
Furman et al. (2018)	Depression	HAM-D IDS-C	Single-blind, prospective, randomized clinical trial	*N* = 160 A: Escitalopram mono-therapy = 47 B: Escitalopram/Bupropion = 54 C: Venlafaxine/ Mirtazapine = 59	USA, the potential predictive effect of baseline adiponectin levels in index, unmedicated depressed patients undergoing 1 of 3 pharmacological treatments in the Combining Medications to Enhance Depression Outcomes clinical trial (CO-MED)	A: 46.8(11.8) B: 46.1 (12.2) C: 40.3 (11)	A: 14/33 B: 14/40 C: 18/41	White Black Hispanic Other
Herder et al. (2017)	Depression	ADS-L	Cross-sectional, cohort	*N* = 434 A: T1D =139 B: T2D =295	Germany, prospective observational study that evaluates the natural history and progression of recent-onset diabetes and its complications	A: 36.1 ± 12.5 B: 52.5 ± 10.5	A: 84/55 B: 197/98	Not recorded
Herder et al. (2018)	Depression	Diagnosis: CIDI Severity: CES-D	Longitudinal, cohort, follow-up, cross-sectional analysis of baseline data	*N* = 271 A: T1D = 168 B: T2D = 103	Germany, data were obtained from two matching randomized controlled trials addressing diabetes distress and depressive symptoms	A: 42.1 ± 12.1 B: 56.2 ± 8.2	A: 64/104 B: 60/43	Not recorded
Honkalampi et al. (2014)	Depression	BDI	Longitudinal population-base, for data-analysis: cross-sectional, case-control	*N* = 308 A: High Alexithymic features = 85 B: No Alexithymia features = 206	Finland, clinical data including laboratory assessments were obtained from a sub-sample (*n* = 308) of the Kuopio Depression Study general population study.	A: 55.4 ± 9.8 B: 56.5 ± 9.3	A: 40/45 B: 86/120	Not recorded

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Table 1 (*continued*)

First author (year)	Mental health outcome	Mental health measure/s	Study type and design	Sample	Setting and participants	Age in years mean (SD)	Gender (M/F)	Ethnicity
					Based on the Toronto Alexithymia Scale score in 1998, 1999, 2001 and 2005, a group of subjects with high alexithymic features (n = 85) was formed and compared with non-alexithymic controls (n = 206)			
Hung et al. (2007)	Depression	HAM-D BPRS	Cross-sectional, case-control	N = 64 (50/14) A: Major depressive disorder = 50 i) Reactive depression (RD) = 14 ii)Major depression (MD) = 21 ii)Bipolar disorder (BD) =15 B: HC = 14	Taiwan, patients were all young men with a primary diagnosis of major depressive disorder classified into subtypes of depressive disorder	A: i)RD 22•3 ± 0•9 ii)MD 22•9 ± 0•4 ii)BD 23•8 ± 0•7 B: 23•8 ± 0•6	All participants male	Asian
Jeong et al. (2012)	Depression	MINI GDS-K HAM-D	Cross-sectional, case-control, population-based	N = 785 A: Depression = 148 i) MDD = 41 ii)Minor depressive disorder (MnDD) = 46 iii)Subsyndromal depression (SSD) = 61 B: HC = 637	Korea, the participants enrolled in the present study were 785 subjects from 1000 randomly selected, community-dwelling Korean elders aged 65 years or over	A: i) 74.80 ± 8.39 ii) 77.30 ± 8.74 ii) 77.08 ± 8.46 B: 75.84 ± 8.30	A: i) 13/28 ii) 14/32 iii) 20/41 B: 307/330	Asian
Jong et al. (2017)	Depression	BDI	Cross-sectional, case-control	N = 129 A: BDI > 14 = 43 B: BDI < 14 = 86	Taiwan, patients on maintenance hemodialysis were enrolled in this cross-sectional study, which aimed at evaluating the relationship between symptoms of depression and ankle-brachial-index	A: 66.7 ± 10.1 B: 60.8 ± 13.9	A: 25/18 B: 50/36	Asian
Joung et al. (2014)	Depression	BDI-II	Cross-sectional, cohort	N = 95 Group comparison between 2 groups A: highest early life adversity = 34 B: no – moderate early life adversity = 61	USA, participants were recruited from the general population, Information on early-life adversity and psychosocial measurements was obtained via validated interview and questionnaires by trained interviewers	A: 47 (43– 49) B: 45 (43– 47)	A: 14/20 B: 29/32	53 (56.4%) were black/African American
Kaynar et al. (2013)	Depression	Diagnosis: SCID Severity: BDI, BAI	Cross-sectional, analytic	N = 150 A: 30 patients with normal kidney functions B: 30 patients on chronic hemodialysis program who never underwent a transplant C: 30 patients with chronic kidney disease stage 4 or 5 Group D: 30 patients on chronic peritoneal dialysis program who never underwent a transplant) E: 30 patients with functioning kidney allograft	Turkey, the aim of this study is to evaluate depression and anxiety scores among predialysis, hemodialysis, peritoneal dialysis and kidney transplantation patients and to search the changes of serum concentrations of these adipocytokines and ghrelin in these patients with respect to emotional disturbances.	A: 33.4 ± 9.4 B: 49.8 ± 16.1 C: 58.4 ± 15.2 D: 39.1 ± 13.4 E: 47.1 ± 13.1	A: 12/18 B: 20/10 C: 18/12 D: 16/14 E: 23/7	Not recorded
Laake et al. (2014)	Depression	PHQ-9	Population-based, cross-sectional	N = 1769 A: Depression case subjects (PHQ-	UK, participants in the South London Diabetes	A: 53.0 ± 10.40 B: 56.6 ± 11.05	A: 121/137 B: 855/656	A: White = 128 (49.6)

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Table 1 (*continued*)

First author (year)	Mental health outcome	Mental health measure/s	Study type and design	Sample	Setting and participants	Age in years mean (SD)	Gender (M/F)	Ethnicity
				9 >10) = 258 B: Nondepressed (PHQ-9 <10) = 1511	Study (SOUL-D), a prospective cohort study designed to test the relative effects of psychological and social factors on biomedical outcomes in people with newly diagnosed type 2 diabetes			Black = 95 (36.8) Asian/other = 35 (13.6) B: White = 750 (49.6) Black = 615 (40.7) Asian/other = 146 (9.7)
Lehto et al. (2012)	Depression	Diagnosis: SCID-I and SCID-II	Population-based cohort study, case-control	*N* = 147 A: Childhood maltreatment = 30 B: No childhood maltreatment = 117	Finland, part of the Kuopio Depression (KUDEP) four-phase general population study, which focused on the mental health of general population adults. 147 individuals with adverse mental symptoms participated and provided information on inter alia childhood maltreatment	A: 54.50 ± 46.75–60.00 B: 56.00 ± 49.00–63.00	A: 12/18 B: 49/68	Not recorded
Lehto et al. (2010)	Depression	Diagnosis: SCID-I Severity: HAM-D	Cross-sectional, case-control	*N* = 140 A: MDD = 70 B: HC = 70	Finland, this study part of the Kuopio Depression (KUDEP) general population study focusing on the mental health of general population adults. Participants were selected in 1998 via the National Population Register	A: 54.33 ± 9.32 B: 54.20 ± 9.20	A: 22/48 B: 22/48	Not recorded
Li et al. (2013)	Depression, anxiety	HADS POMS	Uncontrolled prospective interventional study. For data analysis cross-sectional, case-control	*N* = 30 A: MetS =12 B: Without MetS =18	Germany, a 2-week study and dietary intervention period consisted of 2 prefast days with moderate caloric restriction followed by 7 modified fasting followed by gradual reintroduction of ordinary food intake over 3 days	A: 53.6 ± 6.7 B: 45.9 ± 7.4	All participants female	Not recorded
Li et al. (2016)	Depression	Diagnosis: SCID for DSM-IV, MINI Severity: BDI	Cross-sectional, case-control	*N* = 60 A: MDD = 30 B: HC = 30	USA, participants were recruited through the Outpatient Clinical Research Program, to investigate whether glucose homeostasis and insulin sensitivity are impaired in MDD patients and its mechanisms.	A: 44.2 ± 2.2 B: 39.8 ± 1.9	A: 12/18 B: 9/21	Number of Caucasian: A: 16 B: 14
Machado-Vieira et al. (2017)	Depression Bipolar disorder	Diagnosis: SCID for DSM-IV Severity: MADRS, HAM-D	Cross-sectional, cohort, post intervention	*N* = 80 A: MDD = 49 B: BI-I/II = 31	USA, inpatients with either treatment-resistant MDD or BD-I/II who were currently experiencing a major depressive episode lasting at least 4 weeks were included in this study which combined data from three different double-blind, randomized, placebo-controlled, cross-over trials assessing the antidepressant efficacy of ketamine for treatment-resistant depression.	A: 43.1 ± 12.8 B: 46.1 ± 11.0	A: 28/21 B: 11/20	Not recorded
Marijnissen et al. (2013)	Depression	BDI-I	Cross-sectional, population-based survey	*N* = 1277 A: Males = 627 B: Females = 650	Netherlands, subjects aged 50–70 years who consented for an add-on study on non-invasive measurements of atherosclerosis	A:61.7 ± 5.9 B:60.4 ± 5.8	Total sample 627/650	> 95% Caucasian
Narita et al. (2008)	Depression							Asian

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Table 1 (*continued*)

First author (year)	Mental health outcome	Mental health measure/s	Study type and design	Sample	Setting and participants	Age in years mean (SD)	Gender (M/F)	Ethnicity
		Diagnosis: SCID for DSM-IV Severity: Zung Self-rating depressing scale	Cross-sectional, case-control, cohort	*N* = 36 A: Higher depressive score = 18 B: Lower depressive score = 18	Japan, healthy elderly subjects in their 50s–70 s were recruited from general inhabitants	A: 64.4 ± 4.6 B: 64.6 ± 4.9	A: 12/6 B: 8/10	
Narita et al. (2006)	Depression	HAM-D	Cross-sectional, case-control	*N* = 41 A: Remitted depression = 21 B: HC = 20	Japan, subjects were aged over 40 years, who had experienced one or more episodes of major depressive disorder which met DSM-IV diagnosis criteria. At the time of the examination, all subjects were in complete remission and had been receiving maintenance treatment with SSRI (fluvoxamine or paroxetine) or SNRI (milnacipran) for longer than 6 months.	A: 60.9 ± 7.1 B: 59.4 ± 4.6	A: 10/11 B: 10/10	Asian
Oh et al. (2018)	Depression	MINI GDS HDRS	Cohort, prospective	*N* = 261 A: Low tertile = 96 B: Middle tertile = 101 C: High tertile = 64	South-Korea, community-dwelling residents aged 65 years and older who participated in the Korean Longitudinal Study on Health and Aging. Participants divided into tertiles according adiponectin level.	A: 72.8 ± 6.8 B:72.0 ± 6.2 C: 75.2 ± 8.1	A: 58/38 B: 51/50 C: 18/46	Asian
Pan et al. (2008)	Depression	CES-D	Cross-sectional, case-control	*N* = 3289 A: Depressive symptoms = 312 B: HC = 2977	China, community residents aged 50–70 from Beijing and Shanghai who participated in the Nutrition and Health of Aging Population in China project investigated for depressive symptoms	A:58.3 ± 6.2 B: 58.6 ± 6.0	A: 98/214 B: 1360/1617	Asian
Pinar et al. (2008)	Depression	Diagnosis: SCID for DSM-IV Severity: HRSD	Cohort, interventional, follow-up	*N* = 40	Turkey, 40 unmedicated male subjects diagnosed with depressive disorder. Following enrolment, all patients started treatment with maprotiline (150 mg/day).	21.0 ± 1	All participants male	Not recorded
Rapaport et al. (2016)	Depression	Diagnosis: SCID Severity: HAM-D	Cohort, proof of concept interventional study	*N* = 150	USA, outpatients with MDD, ages 18–80, from through advertisements and outpatient referrals	46.1 ± 12.6	64/91	Caucasian = 104(67.1%) African-American = 29(18.7%) Other = 13 (8.5%) Not answered = 9(5.8%)
Rebelo et al. (2016)	Depression	EDPS	Prospective cohort	*N* = 159 A: High anxiety score = 30 B: Low anxiety score = 129	Brazil, healthy pregnant women, aged 20–40 years, were evaluated between gestational weeks 5–13, 22–26 and 30–36 and postpartum	The majority of the participants were between 20 and 29 years of age (72.3%)	All participants female	Skin Color White = 63 (26.9%) Brown = 121 (47.9%) Black =59 (25.2%)
Roberto et al. (2007)	Depression	Diagnosis: SCID-I Severity: HAM-D	Cross-sectional, case-control	*N* = 64 A: MDD = 32 B: HC = 32	Italy, subjects with mood disorders referred to the Department of Psychiatry. Participants were first-episode drug-naive major depression	A: 34.9 ± 5.9 B: 35.1 ± 5.2	A: 16/16 B: 15/17	Not recorded
Shelton et al. (2015a,b)	Depression	HDRS-17	Exploratory, interventional post-hoc analysis of	*N* = 185	USA, a multicentre, 60days doubleblind trial of daily methylfolate as adjunctive therapy for patients with SSRI-resistant MDD	All participants 43.2 ± 12.3	56/129	White = 56.8% African American =41.1% Asian = 1.1% Other = 1%

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Table 1 (*continued*)

First author (year)	Mental health outcome	Mental health measure/s	Study type and design	Sample	Setting and participants	Age in years mean (SD)	Gender (M/F)	Ethnicity
			randomised double-blind study					
Su et al. (2011)	Depression, bipolar disorder	Diagnosis: MINI SCID Severity: HAM-D BPRS	Cross-sectional, case-control	*N* = 61 A: RD = 13 B: MDD = 18 C: BD = 10 D: HC = 21	Taiwan, subjects were all inpatients recruited from the Tri-Service General Hospital. Patients were classified into subtypes of depressive disorder according to the presence of mood swings during the 4-week hospitalization course, past psychiatric history, and experience of stressful life events.	A:25.0 ± 3.0 B:22.2 ± 3.5 C:21.9 ± 2.0 D:22.7 ± 2.9	All participants male	Asian
Syk et al. (2018)	Depression	SCID-I MADRS-S MINI	Cross-sectional observation	*N* = 251 A: BN = 194 B: Controls = 57	Sweden, data and samples used in this study were obtained from the patient cohort "Uppsala Psychiatric Patient Samples" (UPP).	A: 21 (19; 23) B: Female 22 (20; 24) Male 24 (22; 26)	A: 43/151 B: 13/44	Not recorded
Toscana et al. (2018)	Depression	MINI HAM-D	Exploratory cross-sectional study	*N* = 80 A: TLE = 40 B: Controls = 40	Brazil, 40 patients with TLE who were recruited at a Epilepsy Outpatient Clinic 40 age and sex-matched controls were recruited from the local community.	A: 41.3 (11.5) B: 41.7 (9.4)	A:21/19 B:20/20	Not recorded
Weber-Hamman et al. (2007)	Depression	HDRS	Double-blind, randomized study	*N* = 37 A: Amitriptyline remitter = 7 B: Amitriptyline non-remitter = 6 C: Paroxetine remitter = 11 D: Paroxetine non-remitter = 13	Germany, depressed in-patients were treated with either amitriptyline or paroxetine over a period of five weeks. After six drug free days blood was drawn on day 1 and again 36 days after antidepressant treatment	A: 49.8 ± 17 B: 49.8 ± 20 C: 58.8 ± 15 D: 57.9 ± 16	12/25	Not recorded
Yildiz et al. (2017)	Depression	EPDS	Prospective, controlled	*N* = 244 A: PPD = 70 B: Non-PPD = 174	Turkey, a multicenter controlled trial. Women were evaluated at postpartum day 10. Participants were unmedicated	A: 25.9 ± 4.1 B: 26.4 ± 5.2	All participants female	Not recorded
Yang et al. (2019)	Depression	SCID HAM-D	Prospective, cohort	*N* = 255 A: Post-stroke depression = 69 B: No post-stroke depression = 186	China, patients with first-ever ischemic stroke and hospitalized within 24 h of symptoms onset were enrolled prospectively to investigate whether serum APN could predict poststroke depression at 3 months	A: 61.6 ± 9.0 B: 61.1 ± 10.0 C: 63.6 ± 9.5	A:57/28 B:40/45 C:41/44	Asian
Zeman et al. (2009)	Depression	HAM-D	Cross-sectional, case-control	*N* = 76 A: DD = 38 B: HC = 38	Czech Republic, medicated women suffering from DD, recruited from outpatient clinics, the control group consisted of healthy women (medical staff)	A: 59.2 ± 16.4 B: 57.8 ± 17.0	All participants female	Not recorded
Zeugmann et al. (2010)	Depression	Diagnosis: SCID-I Severity: HDRS	Cohort, cross-sectional	*N* = 70 A: MDD with metabolic syndrome =17 B: MDD without metabolic syndrome = 53	Germany, data for 70 inpatients with MDD (according to DSM-IV and ICD-10 and with or without metabolic syndrome was assessed 4 – 5 weeks following admission	A: 55.6 ± 13.5 B: 45.4 ± 13.1	A: 6/11 B:18/35	Not recorded
Barbosa et al. (2012)	Bipolar disorder	Diagnosis: MINI-plus Severity: YMRS, HDRS	Cross-sectional, case-control	*N* = 60 A: BD type 1 = 30 B: HC = 30	Brazil, this study included thirty euthymic BD type I patients and thirty controls matched by age, gender and educational level. Patients were recruited from	A: 49.0 ± 10.9 B: 47.1 ± 7.4	A: 12/18 B: 7/23	Not recorded

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Table 1 (*continued*)

First author (year)	Mental health outcome	Mental health measure/s	Study type and design	Sample	Setting and participants	Age in years mean (SD)	Gender (M/F)	Ethnicity
					an outpatient psychiatric clinic specialized in BD. All patients were medicated			
Elmslie et al. (2009)	Bipolar disorder	Diagnosis: SCID Severity: YMRS, MADRS	Cross-sectional, case-control	*N* = 120 A: BD = 60 B: HC = 60	New-Zealand, participants were overweight bipolar patients who had volunteered to take part in a weight reduction study and overweight volunteers without psychiatric illness. Bipolar patients who met the DSM-IV criteria for bipolar disorder and who had been taking sodium valproate for > 6 months, with clinically significant weight gain that appeared to be related to valproate treatment, were eligible for the study.	A: 42 ± 11 B: 44 ± 12	A: 11/49 B: 11/49	European, Maori, Asian
Lee et al. (2014)	Bipolar disorder	YMRS HAM-D	Cohort, cross-sectional	*N* = 94 A: Euthymic group = 50 B: Depressed group = 44	Korea, participants recruited from university outpatient clinic	A: 37.3 ± 12.1 B: 33.8 ± 10.08	A: 27/23 B: 13/31	Asian
Mansur et al. (2016)	Bipolar disorder	Diagnosis: SCID-I Severity: YMRS, HDRS	Cross-sectional, case-control	*N* = 87 A: BD = 59 B: HC = 29	Brazil, patients with BD type I/II were recruited from Outpatient Clinic	A: 43.1 ± 10.3 B: Not recorded	A: 13/46 B: 9/20	A: 35 (59.3%) were Caucasian.
Mansur et al. (2017)	Bipolar disorder	Diagnosis: SCID-I Severity: YMRS, HDRS	Cross-sectional, case-control	*N* = 76 A: BD = 55 B: HC = 21	Brazil, patients with BD type I/II (89% type 1 and 11% type 2) were recruited from an Outpatient Clinic	A: 43.5 ± 10.0 B: 38.6 ± 13.7	A: 11/44 B: 7/13	Caucasian A: 33 (61.1) B: 12 (57.1)
Platzer et al. (2018)	Bipolar disorder	Diagnosis: SCID-I Severity: YMRS BDI HAM-D	Cross-sectional, case-control	*N* = 188 A: Bipolar depression = 120 B: HC = 68	Austria, patients with BD type I or BD type II were recruited from Outpatient Clinic.	A: 42.20 ± 11.66 B: 36.92 ± 15.62	A: 63/57 B: 30/38	Not reported
Soeiro-de-Souza et al. (2014)	Bipolar disorder	Diagnosis: SCID Severity: HDRS, YMRS	Case-control, interventional, follow-up	*N* = 48 A: Acutely depressed BD individuals = 25 B: Healthy controls = 23	Brazil, outpatient based. 22 BD patients (88%) were drug-free for at least 6 weeks and 17 (68%) had never used a mood stabilizer or antipsychotic agent, i.e., were treatment-naive. At baseline, patients were started on lithium 450 mg/day, and subsequent flexible dosage adjustments were allowed, according to clinical response and serum lithium levels.	A: 28.5 ± 5.7 B: 27.1 ± 6.6	A: 6/19 B: 13/10	Not recorded
Tunçel et al. (2017)	Bipolar disorder	Diagnosis: SCID-I, SCID-II Severity: YMRS	Cross-sectional, case-control	*N* = 60 A: BD in the manic episode = 30 B: Control group = 30	Turkey, cases recruited from university research clinic. All patients were treated in the manic episode in the hospital and they were followed as outpatient during the euthymic episode	A: 35.0 ± 11.3 B: 34.4 ± 10.3	A: 11/19 B: 11/19	Not recorded
Vianna-Sulzbach et al. (2015)	Bipolar disorder	Diagnosis: SCID Severity:	Cross-sectional case-control	*N* = 82 A: BD = 34 B: HC = 48	Brazil, subjects were DSM-IV diagnosed BD patients and healthy controls. All patients	A: 44.91 ± 14.83 B: 46.38 ± 11.24	A: 17/31 B: 18/16	Not recorded

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Table 1 (*continued*)

First author (year)	Mental health outcome	Mental health measure/s	Study type and design	Sample	Setting and participants	Age in years mean (SD)	Gender (M/F)	Ethnicity
		YMRS, HAM-D			received pharmacological treatment by their psychiatrist according to clinical protocols.			
Ari et al. (2012)	Obsessive Compulsive Disorder	Y-BOCS	Case-control, cross-sectional	*N* = 60 A: OCD = 29 B: HC =31	Turkey, subjects with OCD according to DSM-IV and healthy controls. Case group composed of unmedicated patients who were diagnosed with OCD for the first time and whose obsessive compulsive symptoms were present at least for 1 year.	A: 27.7 ± 4.8 B: 28.7 ± 5.4	A: 13/16 B: 14/17	Not recorded
Atmaca et al. (2009)	Obsessive Compulsive Disorder	Y-BOCS HAM-D	Cross-sectional, case-control	*N* = 46 A: OCD = 23 B: HC = 23	Turkey, university research center. 3 of OCD patients (two females and one male) had comorbid depressive disorder according to DSM-IV, they were all unmedicated.	A: 28.6 ± 4.3 B: 30.8 ± 5.1	A 10/13 B 9/14	Not recorded
Brennan et al. (2009)	Phobic Anxiety	No diagnosic instrument Serverity: CCI	Cross-sectional, cohort	*N* = 984 A: No/Low anxiety = 288 B: Moderate anxiety = 318 C: High anxiety = 378	USA, The Nurses Health Study began in 1976 with the enrolment of 121,700 female nurses aged 30–55 years who received biennially mailed questionnaires on lifestyle factors and health outcomes Participants with type 2 diabetes from the Nurses' Health Study were classified as having low, moderate, or high phobic anxiety	A: 59.3 ± 6.5 B: 58.8 ± 6.7 C: 58.5 ± 6.7	All participants female	Majority Caucasian (>95%)
Narita et al. (2008) (a)	Anxiety	Diagnosis: SCID Severity: STAI	Pilot cross-sectional, cohort	*N* = 35 Healthy elderly participants	Japan, healthy elderly subjects in their 50s–70 s were recruited from general inhabitants	Males: 64.8 ± 5.1 Females: 64.2 ± 4.4	19/16	Asian
Rebelo et al. (2015)	Anxiety	STAI	Prospective cohort	*N* = 235 Women completing all 4 follow-up visits = 137	Brazil, healthy pregnant women aged 20–40 years with four waves of follow-up: 5–13th, 22–26th, and 30–36th gestational weeks and 30–45 days postpartum	The majority of the participants were between 20 and 29 years of age (72.3%)	All participants female	Skin Color White = 63 (26.9%) Brown = 121 (47.9%) Black =59 (25.2%)
Unsal et al. (2012)	Panic disorder	HDRS PAS	Cross-sectional, Case-control	*N* = 51 A: Panic disorder (PD) = 28 B: HC = 23	Turkey, the study group included 28 patients with PD according to DSM-IV, and age-, sex-matched healthy control group	A: 31.43 ± 6.13 B: 29.70 ± 5.13	A: 11/17 B: 13/10	Not recorded
Wagner et al. (2015)	Agoraphobia	Diagnosis: DIGS Severity: GAF	Cross-sectional Case-control	*N* = 2890 A: Agoraphobia = 124 B: HC = 2766	Switzerland, a random population sample.	A: 50.6 ± 8.4 B: 49.6 ± 8.8	On average 53% were female	Majority Caucasian (>92%)
Levandowski et al. (2013)	Trauma	Diagnosis: SCID Severity: CTQ	Case-control, cohort	*N* = 104 A: History of CM = 67 B: No CM = 37	Brazil, this follow-up study included 104 treatment-seeking crack cocaine female dependents. The CM+ group consisted of participants who reported having been exposed to at least one moderate-to-severe type of child abuse or neglect according to the Childhood Trauma Questionnaire (CTQ).	A: 26.0 ± 18.0–52.0 B: 26.5 ± 18.0–48.0	All participants female	Not recorded
Na et al. (2017)								Asian

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Table 1 (*continued*)

First author (year)	Mental health outcome	Mental health measure/s	Study type and design	Sample	Setting and participants	Age in years mean (SD)	Gender (M/F)	Ethnicity
	Post-traumatic stress disorder	IES-KR CES-D	Cross-sectional, case-control	*N* = 507 A: IES-R-*K* ≥ 25 = 139 B: Non-PTSD = 368	Korea, male firefighters were recruited. Participants completed the self-rated questionnaires, laboratory tests, and anthropometric tests. All participants had been working normally.	A: 41.39 ± 7.28 B: 37.67 ± 8.32	All participants male	
Rao et al. (2014)	Post-traumatic stress disorder	Diagnosis: SCID for DSM-IV Severity: CAPS	Case-control, cross-sectional	*N* = 93 A: PTSD = 44 B: Non-PTSD = 48	USA, subjects were enrolled in this case-control study with a 2 × 2 design (PTSD/control × male/female); All participants were free of medications	A: 30.5 ± 6.6 B: 30.5 ± 8.2	A: 22/22 B: 23/26	Caucasian Non-Caucasian

Male/Female (M/F), Cases (A), Controls (B); adiponectin (ADP), Bipolar (BD), Valproic Acid (VPA), Healthy Control Group (HCG), Depressive Disorder (DD), Postpartum Depression (PPD), Reactive depression (RD), Major Depressive disorder (MDD), Bipolar depression (BD), Childhood Maltreatment (CM), Interferon (IFN), Diabetes Mellitus Type 1 (TD1), Diabetes Mellitus Type 2 (TD2), Obsessive Compulsive Disorder (OCD), Metabolic Syndrome (MetS), Serotonergic Reuptake Inhibitor (SSRI), Alcohol Use Disorder (AUD).

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), Perceived Stress Scale (PSS), Becks Depressive Inventory (BDI-2), The Maudsley Obsessional-Compulsive Inventory (MOCI), The Positive and Negative Affect Schedule (PANAS), Depression and somatic symptoms scale (PSSS), Mini-international neuropsychiatric interview (MINI), Hamilton Anxiety and Depression Scale (HADS), Hamilton Anxiety Scale (HAM-A), Hamilton Depression Scale (HAM-D), Hamilton Depression Rating Scale (HDRS), Becks Anxiety Inventory (BAI), Allgemeine Depressionsskala, Langversion (ADS-L) questionnaire, the German version of the Center for Epidemiological Studies Depression scale (CES-D), Composite International Diagnostic Interview (CIDI); Brief Psychiatric Rating Scale (BPRS), Geriatric Depression Scale-Korean Version (GDS-K), The Beck Depression Inventory (BDI)-II, Clinician Administered PTSD Scale (CAPS), Korean version of the Impact Event Scale-Revised (IESR-K), Childhood trauma questionnaire (CTQ), Global Assessment of Functioning score (GAF score), Diagnostic Interview for Genetic Studies (DIGS), Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and Panic Agoraphobia Scales (PAS), State-Trait Anxiety Inventory (STAI), Crown Crisp Index (CCI), Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Young Mania Rating Scale (YMRS), The Montgomery–Åsberg Depression Rating Scale (MADRS), Profile of Mood States (POMS), Edinburgh Postnatal Depression Scale (EPDS), Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-16-SR), Inventory of Depressive Symptomatology- Clinician Rated (IDS-C30).

Potential overlap in samples in the following studies:

[a]Lehto et al. (2010, 2012): both studies included participants from the Kuopio Depression (KUDEP) four-phase general population study, potential overlap in sample.

[b]Mansur et al. (2016, 2017): both studies recruited participants from same Outpatient Clinic in São Paulo, Brazil, potential overlap in sample.

[c]Narita et al. 2018(a) & (b): Narita et al.(b) used *n* = 35 participants from Narita et al.(a) study.

Table 2
Summary of studies: Adiponectin assay and sampling methods and covariates.

First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
Adam et al. (2010)	Nil	Exclusion	Fasting	Plasma, samples were centrifuged, aliquoted and stored in polypropylene vials at −80 °C until analysis.	Single	Radioimmunoassay for human adiponectin (Millipore, MA)	A: 9.96 (1.5) B: 14.0 (0.73) $p < 0.02$ In postmenopausal women, negative mood was not associated with adiponectin cross-sectionally, but negative mood was a significant predictor for lower levels of adiponectin 1 year later, independent of initial adiponectin concentrations and changes in body mass index. Lastly, having a depressive disorder was related to lower adiponectin
Aliyazicioglu et al. (2011)	Nil	Not recorded	Fasting	Serum	Single	ELISA (Assay Pro, USA)	A: 10.27 (7.50) B: 5.84 (4.07) $p = 0.001$ Adiponectin was shown to be associated for MD patients, especially for overweight and obese patients with MD.
Archer et al. (2018)	Not recorded	Current Smokers All patients 103; Non-AUD patients 47; AUD patients 56; Men 45; Women 58. Cigarettes per day A: 12.78 (9.88) B: 5.38 (8.25)	Fasting	Serum, separated by centrifugation, and stored at –80 °C prior to analysis. All samples of this study were drawn in the morning in order to control for diurnal variation of the circulating mediators	Serial, baseline and at 6 months	ELISA (R&D Systems, Abingdon Science Park, UK)	*Baseline* A: 6.13 (3.22) B: 5.66 (2.68) p: NS Males: 5.40 (3.11) Females: 6.14 (2.74) p: NS *6 months* A: 5.01 (2.50) B: 5.82 (2.96) p: NS Males: 4.16 (2.48) Females: 6.28 (2.77) p: < 0.001
Bai et al. (2014)	Nil	Not recorded	Fasting	Serum, samples were collected using serum separator tubes (SST) and clotted for 30 min. All the samples were stored at 80 °C until use.	Single	ELISA (R&D systems, Minneapolis, MN, USA).	A: 7.57 (5.3) B: 6.6 (4.2) $p > 0.05$
Chan et al. (2017)	Nil	A: 1(2.2%) B: 2 (3.2%)	Not reported	Plasma, centrifugation (1000´g) at 4 °C for 15 min. The supernatants were transferred into new tubes and stored at −80 °C.	Serial, at 3-time points	ELISA (Antibody and Immunoassay Services, The University of Hong Kong, Hong Kong)	A: T0 = 11.5 (7.7–17.2) T1 = 11.6 (7.6–17.1) T2 = 10.5 (7.4–19.1) B: T0 = 11.1 (9.0–14.1) T1 = 10.1 (7.8–14.5) T2 = 12.1 (9.4–15.1) Compared with the waitlist group, the median adiponectin level of the Qigong group significantly increased following Qigong, from baseline to immediately postintervention (T1 − T0) (median = 0.8 mg/L

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Table 2 (*continued*)

First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
							for the Qigong group vs. −0.1 mg/L for the waitlist group; $p < 0.05$). The increase in plasma adiponectin levels following Qigong exercise was associated with the decrease in depression scores
Cizza et al. (2010)	Nil	Smokers in both study and control group	Fasting	Plasma	Serial	Linco Research, St. Charles, MO; radioimmunoassay (RIA)	A: 4.6 ± 1.9 B: 6.5 ± 2.9 $p = 0.0053$ Adiponectin remained lower in women with MDD over 24hr-period
Diniz et al. (2012)	Dyslipidemia Cardiovascular disease Diabetes Mellitus Hypertension	Not recorded	Fasting	Serum, the samples were stored at 80 C until adiponectin analysis	single	ELISA (R&D Systems, Minneapolis, USA).	A: 5.51 (4.03) B: 6.32 (4.26) $p < 0.001$ The correlation between adiponectin levels and HDRS scores remained statistically significant ($r = 0.44$, $p < 0.001$) after controlling for other variables.
Domingues et al. (2015)	Nil	Not recorded	Non-fasting	Serum was obtained after centrifugation and kept at −80 °C until analysis.	Single	ELISA (R&D Systems, Minneapolis, MN) All samples were assayed in duplicate, and analyses were blinded.	A: 31.1 (20.4–69.20) B: 37.8 (24.9–71.4) $p = 0.008$ The cases had higher rates of both depression (BDI = 7.5 (0–22) and anxiety (BAI = 8 (0–54) versus controls (BDI = 4 (0–31), $p = 0.041$), (BAI = 4 (0 – 19), $p = 0.014$) ADP levels were not influenced by BDI and BAI scores
Duarte et al. (2014)	Nil	Not recorded	Non-fasting	Serum was obtained after centrifugation and kept at −80 °C until analysis	Single	ELISA (R&D Systems, Minneapolis, MN) All samples were assayed in duplicate, and analyses were blinded.	A: 43.6 ± 11.8 B: 36.6 ± 9.7 $p < 0.0001$ Median BDI and BAI scores were significantly different between subjects with and without migraine ($p < 0.0001$ for both BDI and BAI). Cases had higher depression and anxiety scores than controls; however, no correlation was found between ADP levels and anxiety and depression scores. Also, the difference of ADP levels between patients with and without migraine persisted after multivariate analysis, suggesting that increased ADP levels in migraine are not a consequence of the

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Table 2 (*continued*)

First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
							psychiatric comorbidities
Einvik et al. (2013)	Diabetes Sleep apnea	A: 18 B: 69	Fasting	Serum	Single	S-adiponectin was determined by an in-house time-resolved immunofluorometric assay (TR-IFMA) based on two monoclonal antibodies and recombinant human adiponectin (R&D Systems, Abingdon, United Kingdom)	A: 7.26 (5.13–9.91) B: 7.39 (5.23–11.37) $P > 0.05$ NS The sum-score of BDI did not correlate with adiponectin levels ($r = 0.055$, $p = 0.210$)
Everson-Rose et al. (2018)	Nil	Cross-sectional Smoker =108 (19.0%) Non-smoker = 461 (81.0%) Longitudinal Smoker = 49 (18.9%) Non-smoker = 211 (81.1%)	Fasting	Serum, samples were maintained at 4 °C until separated and then frozen at −he °C and shipped on dry ice to a central laboratory	Cross-sectional sample: Single Longitudinal sample: serial (baseline, 1 yr, 3 yr and 5year followup)	Colorimetric enzyme immunoassay kits according to the manufacturer's instructions (Millipore, St. Charles, MO), assays done in duplicate)	*Cross-sectional* A: 9.09 (4.41) B: 10.17 (5.06) p: 0.015 *Longitudinal* A: 9.71 (4.10) B: 11.49 (5.33) p: 0.005 After adjusting for total caloric intake and physical activity but with BMI added to the model, the difference between women with high versus low CES-D scores was reduced to 6.9% (95% CI, −1.1%–14.3%; $p = 0.089$).
Fabregas et al. (2016)	Diabetes Hypertension	A: 1 B: 8	Not reported	Plasma	Single	ELISA (DuoSet; R&D Systems, Minneapolis, Minn., USA).	A: 23.4 ± 2.32 B: 24.4 ± 3.1 $p = 0.261$ Higher adiponectin levels at baseline did however protect against MD development during the follow-up.
Ferrari et al. (2018)	Diabetes	Not reported	Fasting	Plasma, samples were stored at −80 °C until assayed	Single	Not reported	A: 10.6 (7.7–15.5) B: 8.9 (6.3–13.0) p: 0.16
Furman et al. (2018)	Not reported	Not reported	Unknown	Plasma, stored at −80 °C until assayed	Serial, Baseline and 12 weeks	ELISA (EZHADP-61 K, EMD Millipore, Billerica, MA)	*Baseline* A: 8.58(4.7–15.7) B: 8.23 (5.9 – 10.3) C: 9.71 (5.6 – 14.0) $p = 0.358$ ADP levels did not correlate with baseline depression severity ($r = -0.0.03$, $p = 0.59$) *Baseline-to-exit change in adiponectin level by treatment group* A: 0.047 (−2.57, 1.05), $p = 0.57$ B: 0.447 (−0.95,1.83), $p = 0.286$ C: - 0.591 (−3.07, 0.76), $p = 0.0689$ ADP levels did not correlate with change in IDS-C with any treatment, and ADP-levels remained relatively steady

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Table 2 (*continued*)

First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
							between baseline and exit timepoints
Herder et al. (2017)	Nephropathy Neuropathy Myocardial infarction Stroke TIA	Not reported	Fasting	Serum, samples were stored at 80 C for 0.5–6.5 years prior to analysis	Single	ELISA	A: Total adiponectin: 5.97 (4.1; 7,9) .MW adiponectin: 2.75 (1.6; 4.3) HMW/total adiponectin 0.45 (0.12) B: Total adiponectin: 4.0 (2.99; 5.3 HMW adiponectin: 1.3 (1.0; 2.4) HMW/total adiponectin: 0.40 (0.11) $p < 0.001$ (for total and multimeric forms) The ratio HMW/total adiponectin was shown to be associated with depressive symptoms in individuals with recently diagnosed T2D
Herder et al. (2018)	Nephropathy Neuropathy Myocardial infarction Stroke TIA	Not recorded	Fasting	Serum, the same assays and control sera were used for samples from both study populations. Baseline and follow-up samples from patients were always assessed on the same plate to reduce measurement imprecision	Serial	ELISA	A: T0 = 9.74 (5.97; 14.78) T1 = 10.5 (6.96; 14.64) $p = 0.001$ B: T0 = 4.17 (2.66; 6.04) T1 = 4.36 (3.0; 6.33) $p = 0.001$ In patients with T2D, reductions in depressive symptoms were not associated with adiponectin. No significant associations between changes in adiponectin and changes in the CES-D scores.
Honkalampi et al. (2014)	Yes, coronary artery disease	A: 33.0 (29) B: 11.1 (24)	Fasting	Plasma, samples were immediately centrifuged and plasma stored at –80 °C. All samples were analysed at the same time to minimize the effect of batch variance	Single	Lincoplex kit (Millipore, Mass., USA) using a Bio-Plex Suspension Array system (Bio-Rad Laboratories Inc., Calif., USA	A: 12.9 ± 11.8 B: 17.8 ± 16.6 $p = 0.024$
Hung et al. (2007)	Nil	Not recorded	Fasting	Serum	Single	RIA established by Linco Research (St Charles, MO). Total adiponectin, in a range of high- to low-molecular weight multimeric forms, were included	A: i) RD 9•38 ± 0•46 μg/l, $p < 0•01$ ii) MD not recorded ii) BD 7•41 ± 0•45 μg/l B: 9•07 ± 0•54 μg/l, $p < 0•05$
Jeong et al. (2012)	Yes, though specific illnesses not listed	Not recorded	Fasting	Plasma	Single	ELISA (AdipoGen, Seoul, Korea)	HC: 9.27 (6.21) MDD: 10.37 (6.19) MnDD: 9.32 (5.88) SSD: 12.48 (8.38) $p = 0.002$ The concentration was highest in the SSD

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First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
							group, and the difference in plasma adiponectin level between the SSD and NC groups was statistically significant (p = 0.001, Tukey's post hoc comparison).
Jong et al. (2017)	Hepatitis C infection	Not recorded	Fasting	Plasma, samples were centrifuged at 1500 × g at 4 °C for 10 min for analysis	Single	ELISA (RayBiotech)	A: 5.7 ± 0.3 B: 5.6 ± 0.3 p = 0.063
Joung et al. (2014)	Nil	A: 12 (35.3) B: 15 (24.6)	Fasting	Serum	Single	RIA (Millipore)	A: 6.6 (3.8 – 8.6) B: 9.1 (5.4 –13.0) p = 0.03 No significant association between adiponectin levels and early-life adversity. Adiponectin levels were lower in the African American group versus Caucasians (p = 0.05) and higher in females versus males (p = 0.02)
Kaynar et al. (2013)	Nil	A: 5 (16.7) B: 19 (63.3) C: 14 (46.7) D: 13 (43.3) E: 15 (50)	Fasting	Plasma, aliquots were stored at 80 °C until analyzed	Single	ELISA (Sandwich) method with commercial ELISA kit manufactured by DRG	No actual adiponectin values reported, only associations Significant positive correlations were obtained between adiponectin levels and past history of depressive disorder (r = 0.234; p = 0.004). No significant relationship of adiponectin with BDI, BAI scores
Laake et al. (2014)	Macrovascular disease	Not recorded	Fasting	Serum	Single	ELISA (R&D Systems Europe, Oxon, U.K.)	A: 4.65 (3.27–6.65) B: 5.01 (3.29–7.61) p = 0.097 Adiponectin not found to be associated with depressive symptom scores
Lehto et al. (2012)	Coronary artery disease Rheumatoid arthritis Metabolic syndrome	A: 10 (33.3) B: 30 (25.6)	Fasting	Not reported	Single	LincoPlex kit (Millipore, MA, USA) using a Bio-Plex Suspension Array System (Bio-Rad Laboratories Pty Ltd; Hercules, CA, USA).	A: 8.07 (2.66–12.35) B: 11.58 (5.21–20.12) p = 0.007 Individuals with a history of childhood maltreatment had BMI levels equal to those without such childhood adversities. Nevertheless, regardless of the lack of obesity-related differences, lowered adiponectin levels were associated with childhood maltreatment
Lehto et al. (2010)	Coronary artery disease metabolic syndrome	A: 23 (32.9) B: 4 (5.7)	Fasting	Serum	Single	Human serum adipokine (Panel A) LincoPlex kit (Millipore, MA, USA) using a Bio-	A: 12.59 (11.14) B: 18.72 (16.32) p = 0.01 The MDD group participants

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First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
						Plex Suspension Array System (Bio-Rad Laboratories Pty Ltd; Hercules, CA, USA).	had lower adiponectin levels, higher depression scores, were more often smokers, and more often had CHD and MetS than the healthy controls. The MDD participants reporting antidepressant use (n = 23, 32.9%) presented no differences in the levels of adiponectin compared with the other MDD participants
Li et al. (2013)	Nil	Not recorded	Fasting	Plasma	Serial, samples were drawn in the morning of study day 4 and study day 11 (i.e. before and after fasting)	ELISA	A: Actual adiponectin values not reported Mean changes were for MetS patients: adiponectin: 3.5 g/ml (95% CI: 2.1; 4.9 g/ml), $p < 0.001$ B Actual values not reported For patients without MetS as: adiponectin: 1.9 g/ml (95% CI: 3.8; 0.0 g/ml); $p < 0.01$ Pairwise comparison between subjects in the two groups revealed that the MDD group had significantly lower levels of adiponectin
Li et al. (2016)	Nil	Not recorded	Fasting	Plasma, ten milliliters of blood were drawn from each participant by venipuncture in a tube containing EDTA. The blood was then centrifuged at 3000 g for 10 min, immediately divided into aliquots, and frozen at −80 °C until analysis.	Single	Elisa (Millipore, Billerica, MA). All samples were run in duplicate and the mean of the duplicate samples was reported.	Actual adiponectin values not reported, appear in graph Pairwise comparison between subjects in the two groups revealed that the MDD group had significantly lower levels of adiponectin $p < 0.05$
Machado-Vieira et al. (2017)	Nil	Not recorded	Not reported	Plasma, Samples were centrifuged at 3000 r.p.m. at 4 °C for 10 min and stored at − 80 °C until assay performance. Samples were diluted 1:10, measured in duplicate and blinded to clinical information	Serial, baseline, 230 min and 1 day	Multiplex Luminex immunoassay (xMAP Technology, Austin, TX, USA)	MDD Baseline: 2.12 230min: 2.13 1 day: 2.13 Bipolar Baseline: 1.91 230min: 2.01 1 day: 1.96 $p = 0.85$
Marijnissen et al. (2013)	Metabolic syndrome	Males: 101 (16) Females: 116 (17.9)	Fasting	Plasma	Single	ELISA (Elisadevelopment-System, Duoset, R&D Systems, Minneapolis, USA)	4.26 (2.43) A total of 213 (16.7%) persons suffered from clinically relevant depressive symptoms, i.e. 81 males and 132 females ($\chi^2 = 12.5$, df = 1, $p < 0.001$). Adiponectin showed

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First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
							neither a linear nor a U-shape association with depressive symptoms or symptom-profiles in the whole sample as well as when stratified for sex (all *p*-values >0.16).
Narita et al. (2008)	Nil	Not recorded	Fasting	Plasma	Single	ELISA (Daiichi Pure Chemicals Co., Ltd) Total plasma adiponectin and HMW, MMW and LMW adiponectin were measured	A: 5.3 ± 3.0 B: 5.9 ± 2.6 p = NS No significant association was observed between total adiponectin and depression score (r = −0.185, ns) However; HMW/total adiponectin and HMW/LMW were negatively associated with depression score (F = 10.965, p = 0.002 and F = 6.225, p = 0.018, respectively), and these associations remained significant after adjustment for BMI (F = 10.232, p = 0.003 and F = 5.322, p = 0.027, respectively).
Narita et al. (2006)	Nil	Not recorded	Fasting	Plasma	Single	ELISA (Daiichi Pure Chemicals Co., Ltd)	A: 12.19 ± 6.21 B: 8.66 ± 4.39 p < 0.05 The remitted depression group showed a significantly higher plasma adiponectin level than the control group Authors proposed that results together with previous experimental and clinical data, may indicate that maintenance antidepressant therapy promotes the production of adiponectin via the inhibition of TNF-α
Oh et al. (2018)	Not reported	Not recorded	Fasting	Plasma	Single	ELISA (Adipogen, Seoul, Korea)	A: 3.41 (1.25) B: 7.85 (1.38) C: 16.04 (5.31) p = 0.033 At 5-year follow-up of N = 261 euthymic participants, N = 2 from Group A, N = 7 from Group B and N = 8 from Group C developed incident depression
Pan et al. (2008)	Diabetes Cardiovascular disease Cerebrovascular disease	A: 77 (24%) B: 843 (28%)	Fasting	Plasma, blood samples were centrifuged at 4 °C, 3000 rpm for	Single	Luminex xMAPTM Technology (Linco Research Inc, St Charles, Mo) on a Bio-	A: 9.59 (8.81–10.44) B: 9.23 (8.79–9.70) p = 0.362

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First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
				15 min. After being frozen, the samples were shipped in dry ice and stored at −80 °C until analysis.		Rad Multiplex Suspension Array System	
Pinar et al. (2008)	Nil	Not recorded	Fasting	Plasma, blood was immediately chilled on ice and centrifuged, and serum aliquots were frozen at −80 °C until assayed	Serial, baseline (T0) and 30 days post intervention	RIA kit (Linco Research, Inc., St. Charles, MO).	T0: 29.66 ± 5.64 Day 30: 24.00 ± 6.26 $p < 0.001$ Total adiponectin levels decreased after maprotiline treatment
Rapaport et al. (2016)	Not recorded, unstable medical illness an exclusionary criterion	Smoking >10 cigarettes a day exclusionary	Not reported	Plasma	Single	ELISA (R&D Systems (Minneapolis, MN)	Males: 5.9 (4–22) Females: 9.7 (4–32)
Rebelo et al. (2016)	Nil	Not recorded	Fasting	Plasma, samples were centrifuged (5000 rpm/5 min) and the supernatant was separated, stored in cylinders containing liquid nitrogen and transported weekly to a 80 °C freezer, where they were stored until further analysis	Serial	ELISA (Millipore, St. Charles, MO, USA	Mean adiponectin value 1st trimester = 4.8 (3.57–6.69) 2nd Trimester = 4.7 (3.44–7.18) 3rd Trimester = 4.4 (3.41–6.49) Post-partum = 7.5 (4.76–10.61) There was no statistically significant association between the plasma adiponectin levels and the EPDS scores in the multiple model ($\beta = 0.07$; $p = 0.320$)
Roberto et al. (2007)	Nil	Nil, exclusionary factor for participation	Fasting	Plasma, all tubes were centrifuged at 2000 rpm for 20 min at 4 °C, then supernatant was collected and stored at −80 °C until analysis	Single	ELISA (Quantikine, R&D Systems)	A: 9.1 ± 4.3 B: 13.8 ± 5.4 $p < 0.001$ There was a significant gender effect on adiponectin levels: women had higher levels than men in both control group (14.9 ± 6.1 vs. 11.7 ± 5.1 μg/ml, $p < 0.01$) and MD patients (9.7 ± 4.1 vs. 7.3 ± 3.2 μg/ml, $p < 0.01$) A significant negative correlation was found between plasma adiponectin levels and HAM-D in MD group ($r = -0.757$, $p < 0.001$)
Shelton et al. (2015a,b)	Most medical illnesses were allowed if they were stably treated.	Not recorded	Non-fasting	Plasma	Single	Radioimmunoassay (EMD Millipore, Billerica, Massachusetts)	A: 8.38 (4.37) B: 12.42 (6.20) $p < 0.005$ Stratified by baseline BMI, those with BMI ≥30 had lower adiponectin values
Su et al. (2011)	Nil	Not recorded	Fasting	Serum	Single	Radioimmunoassay (Linco Research, St. Charles, MO). Total adiponectin, in a range of high- to low-molecular weight multimeric forms, was measured in an assay	A: 9.4(1.6) B: 8.9(3.3) C: 7.4(1.4) D: 9.5(2.3) $p < 0.05$ Plasma adiponectin was significantly lower in the BD subgroup of depressive

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Table 2 (*continued*)

First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
							patients compared to controls
Syk et al. (2018)	Exclusion criteria were cancer, systemic inflammatory disease, coeliac disorder, diabetes mellitus, treatment with testosterone, pregnancy	A: Female: 49 (32) Male: 3(7) B: Female:1(2) Male: 1(8) (Current smoker%)	Non-fasting	Plasma	Single	Total adiponectin, measured in duplicate with a solid phase two-site ELISA (Mercodia AB, Uppsala, Sweden) Assay sensitivity was 1.25 ng/mL for adiponectin	A: Female: 10.48 (8.41; 12.72) Male: 8.28 (6.18; 9.32) B: Female: 10.40 (8.87; 12.46) Male: 7.86 (5.65; 8.94) p:NS Adiponectin levels were not associated with depressive symptoms or current major depression.
Toscana et al. (2019)	Epilepsy, yet excluded if: i) recent seizures ii) any other neurological diseases, inflammatory diseases, or cancer; iii) recent use of immunosuppressive or immunomodulatory medication iv) recent surgery or major trauma; v) they presented renal or hepatic impairment or pregnancy	Not recorded	Not reported	Plasma	Single	Blood samples were centrifuged at 3000 rpm, 4 °C, for 10 min for plasma obtaining. and stored at −70 °C until analysis. Plasma samples were thawed for the analysis by enzyme-linked immunoassay (ELISA) sandwich kit, following the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). The analyses were performed blinded and in duplicate.	A: 13.89 ± 1.72 (13.82) B: 18.76 ± 4.92 (17.75) $p < 0.0001$ People with TLE presented lower adiponectin levels in comparison with controls; with no correlation between adiponectin level and HAM-D scores.
Weber-Hamman et al. (2007)	Not recorded	Not recorded	Fasting	Not reported	Serial, day 1, day 35	Radioimmunoassay (Linco Research Inc., St. Louis, MO)	A: Day1: 10.34 ± 3 Day35: 10.6 ± 4.1 B: Day 1: 10.18 ± 3.4 Day 35: 9.48 ± 4.4 C: Day 1: 9.52 ± 5.6 Day 35: 10.3 ± 5.1 D: Day 1: 9.46 ± 3.2 Day 35: 9.6 ± 4.4 p = NS Higher values in female compared to male patients ($p < 0.01$). However, when female and male patients were analyzed separately no changes in adiponectin concentrations were found
Yildiz et al. (2017)	Nil	Not recorded	Fasting	Serum, samples were taken in tubes containing anticoagulant (sodium EDTA 1.8 mg/ml + aprotinin 500 U/ml blood kallikrein inactivator; Sigma Aldrich, St Louis, MO). Samples were centrifuged and	Single	ELISA (Thermo Scientific Multiskan FC, 2011-06 USA)	A: 14.85 (6,71) B: 10.96 (6,63) $p = 0.001$ Adiponectin levels were found to be significantly higher in PPD subjects compared to controls ($p < 0.05$).

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Table 2 (*continued*)

First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
				stored at −80 °C until analysis			
Yang et al. (2019)	Hypertension Diabetes Coronary Artery Disease Hyperlipidemia	A: 33 (38.8) B: 40 (47.1) C: 33 (38.8)	Not reported	Serum, samples were obtained from each subject within 24 h after admission. The specimens were centrifuged at 1500*g* for 10 min and the isolated serum frozen at −80 °C for later analysis. The variation coefficients of intra- and interassay for the biochemical assays were 3.0 − 8.8% and 1.8 − 6.1%, respectively.	Single	ELISA kits (EZHMWA-64 K, Merck Millipore, Burlington, MA).	A: 3.5 [2.5–6.3] mg/mL B: 6.2 [3.5–8.0] mg/mL, $p = 0.001$ The ROC curve analysis demonstrated the optimal cut-off value of serum APN level as a 3-month PSD indicator was estimated to be 3.5 mg/mL, which yielded a sensitivity of 74.7% and a specificity of 52.5%, with the area under curve at 0.640 (95% CI, 0.565–0.746).
Zeman et al. (2009)	Nil	Not recorded	Fasting	Serum	Single	RIA method (LINCO Res., Mo., USA)	A: 13.07 (6.43) B: 14.98 (4.88) $p > 0.05$ In this study no differences in the parameters investigated were seen between the drug free depressive women or those treated with or escitalopram alone or in the combination with mirtazapine
Zeugmann et al. (2010)	Active medical illness that could be etiologically related to ongoing depression (eg uncontrolled diabetes) as well as immune and autoimmune conditions were exclusionary criteria	Not recorded	Fasting	Plasma, centrifuged at 3000 g for 10 min, immediately divided into aliquots and frozen at −70 °C until analysis	Serial T1 = *a* few days after referral to clinic T2 = 4–5 weeks after inpatient treatment	ELISA (R&D systems)	A: T1 = 7.2 (4.1) T2 = 4.5(2.1) B: T1 = 10.4(6.2) T2 = 10.3(8.1) $p < 0.05$
Barbosa et al. (2012)	In cases and controls: Arterial hypertension Diabetes Mellitus Dyslipidemia Hypothyroidism	Not recorded	Non-fasting	Plasma, the blood was immediately centrifuged at 3000 g for 10 min, 4 C, twice. The plasma was collected and stored at 80 C until assayed	Single	ELISA (DuoSet, R&D Systems, Minneapolis, MN, USA) All samples were assayed in duplicate	A: 3,70 (4,1) B: 8,28 (5,3) $p < 0.001$ Plasma levels of adipokines were not correlated with age, years of study, length of illness, BMI, YMRS, HDRS
Elmslie et al. (2009)	Diabetes Hypertension Dyslipidemia	A: 29 B: 19	Fasting	Plasma	Single	Measured in duplicate on radioimmunoassay (Linco Research, St Charles, MO, USA)	A: 9.6(5.9) B: 7.4(4.3) $p = 0.03$ Adiponectin levels were higher in patients than in a well-matched control group despite comparable BMI and waist circumference
Lee et al. (2014)	Not listed, unstable medical conditions exclusionary factor for participation	A: 12 (24%) B: 15 (34%)	Fasting	Serum, blood was centrifuged, and serum samples were separated in small aliquots and frozen at - 70 °C until use	Single	Human Adipokine Panel A multiplex immunoassay kit (HADK1-61K-A03; Millipore)	A: 7.8(6.07) B: 9.4(7.83) $p = 0.276$ Males: 5.91(2.82) Females: 10.51 (8.37) $p = 0.001$
Mansur et al. (2017)	Metabolic syndrome	Not recorded	Fasting	Plasma, EDTA tubes were centrifuged at	Single	ELISA (Cloud-Clone Corporation,	

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First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
				280 g for 5 min in a refrigerated centrifuge, aliquoted, and kept at −80 °C until further analyzed.		Katy, TX, USA,) Samples were run in Duplicate and blinded to staff	A: 7.77 (5.51) B: 8.53 (8.95) $p = 0.451$
Mansur et al. (2016)	Nil	A: 17 (29%)	Fasting	Plasma, Blood collected in EDTA tubes were kept in ice until processing, for plasma isolation EDTA tubes were centrifuged at 1500 rpm for 5 min in a refrigerated centrifuge, aliquoted and kept at 80 C until further analyzed.	Single	ELISA (EMD Millipore Corporation, USA. Cat. #EZHADP-61K	A: 8.08 (0.52) B: 9.17 (0.84) $p = 0.283$ Adiponectin and leptin levels were higher in females than males ($p = 0.002$), and there was no effect of ethnicity $p = 0.821$). Within individuals with BD, there was no effect of mood state on adiponectin concentrations ($p = 0.610$). Finally, there was no association between adiponectin and use of psychotropic medication. After adjustment for age, gender and BMI, individuals with BD and low adiponectin levels (i.e. <7.5 mg/ml), had a higher number of mood episodes ($p < 0.001$), lower number of psychiatric hospitalizations ($p = 0.007$), higher depressive symptoms ($p < 0.001$) and lower levels of functioning ($p < 0.020$).
Platzer et al. (2018)	Cardiovascular disease, diabetes, metabolic syndrome. Severe medical or neurological conditions were exclusionary	Smoking, current (%) A: 53.80 B: 26.60	Fasting	Plasma, samples were stored immediately at –80 C and later thawed for further analyses	Single	ELISA (BioVendor, BrnoRe ckovice, Czech Republic)	*Whole sample* A: 7.95 (2.95) B: 9.06 (3.16) $p = 0.317$ *Females* A: 8.40 (3.18) B: 10.66 (2.96) $p = 0.034$ *Males* A: 7.53 (2.68) B: 6.95 (1.95) $p = 0.189$
Soeiro-de-Souza et al. (2014)	Nil	A: 7 (28%) B: 6 (26%)	Fasting	Plasma, blood was immediately centrifuged at 3000 g for 10 min, 40 C, twice. The plasma was collected and stored at −80 °C until assayed	Serial, blood samples were collected at baseline and at endpoint (week 6), while healthy controls had only one-point sample collection at baseline	ELISA (DuoSet, R&D Systems, Minneapolis, MN, USA). All samples were assayed in duplicate.	A: Pre-treatment = 10,2 (1,7) Post-treatment = 8.9 (2.5) Overall, baseline levels of adiponectin were similar between patients and control. Baseline levels of adiponectin did not predict remission (ns)
Tunçel et al. (2017)	Nil	Not recorded	Fasting	Plasma	Serial	ELISA (Biovendor Heidelberg, Germany, Lot no: E13-052)	A: Manic episode = 12.8 (4.8) Euthymic episode = 12.4 (5.0)

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Table 2 (*continued*)

First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
							B: 11.2 (4.4) p = NS No difference shown in the adiponectin level
Vianna-Sulzbach et al. (2015)	Not recorded	Not recorded	Not reported	Serum was obtained by centrifugation at 300 g for 5 min and kept frozen at 70 °C for up to 6 months, until the assay.	Single	Sandwich-ELISA (Quantikine, R&D Systems, Minneapolis, Minn., USA). All samples were assayed in duplicates	A: 4.33 (9.5) B: 3.97 (10.4) p = 0.080 There was no difference between patients and controls in adiponectin median
Ari et al. (2012)	Nil	Not recorded	Fasting	Serum, blood samples for adiponectin were drawn from a forearm vein. Then, the samples were centrifuged at 1600 × g for 15 min at 4 °C. The separated serum was stored at −80 °C until the time of assay.	Single	ELISA (RayBiotech, Inc. Norcross GA, USA)	A: 11.92 ± 2.04 B: 18.81 ± 5.24 p < 0.001 There was a negative correlation between adiponectin level and Y-BOCS scores in patient group (r = −0.385, p = 0.039) and in control group (r = −0.442, p = 0.020).
Atmaca et al. (2009)	Nil	Not recorded	Fasting	Serum, sera were stored at −20 °C until thawed for glucose and adiponectin assays	Single	ELISA (Cehmicon International, USA)	A: 11.1 ± 2.2 B: 17.6 ± 2.9 p < 0.001 There was a negative correlation between adiponectin levels and Y-BOCS scores of the patient group (r = −0.67, p = 0.006).
Brennan et al. (2009)	Diabetes	A: 29 (10.2%) B: 47 (14.9%) C: 60 (15.9%)	Non-fasting	Plasma	Single	Radioimmunoassay (Linco)	A: 5.3 (1.0–31.7) B: 6.1 (1.3–38.4) C: 5.4 (1.2–41.8) p = 0.35 There was no association between phobic anxiety and adiponectin levels
Narita et al. (2008) (a)	Nil	Not recorded	Fasting	Plasma	Single	ELISA	Males: 6.5(3.7) Females: 9.7(4.0) p < 0.05 Severity of trait anxiety score was negatively associated with adiponectin-serum-levels
Rebelo et al. (2015)	Nil	Not recorded	Fasting	Plasma was separated after 5 min of centrifugation (5000 rpm) and subsequently stored at −80 °C for later analysis.	Serial, at all gestational trimesters (weeks 5–13, 20–26 and 30–36	ELISA (Millipore, St. Charles, Missouri, USA)	A: First trimester = 9.4 (8.0–10.7) Second trimester = 8.2 (7.0–9.3) Third trimester = 7.9 (7.0–8.9) B: First trimester = 10.1 (9.3–10.9) Second trimester = 11.3 (9.1–13.4) Third trimester = 9.9 (9.1–10.7) p-values: 0.208; 0.086; 0.014 Adiponectin concentrations in the

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Table 2 (*continued*)

First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
							highest tertile during the 3rd trimester of pregnancy represented a protective factor against the occurrence of high antenatal anxiety (OR = 0.32 [0.11–0.98]; $p = 0.045$). Plasma adiponectin in the first and second trimesters was not significantly associated with antenatal anxiety. The correlation between third trimester adiponectin levels and the anxiety score was −0.155 (p-value = 0.051) As opposed to women with low anxiety levels, women with high anxiety during the 3rd trimester, had a significant decrease in plasma adiponectin concentrations throughout pregnancy ($p = 0.01$)
Unsal et al. (2012)	Not recorded	Not recorded	Fasting	Serum	Single	ELISA (Linco ELISA Kit)	A: 2.7 ± 1.0 B: 3.87 ± 2.3 $p < 0.05$
Wagner et al. (2015)	Nil	A: 86 (69.3%) B: 1664 (60.2%)	Fasting	Serum	Serial	ELISA (R&D Systems, Inc, Minneapolis, USA)	Baseline A: 9.1(2.8) B: 8.9(3.0) $p = 0.610$ Follow-up A: 5.6(3.4) B: 5.8(3.0) $p = 0.533$ Adiponectin was significantly lower in persons with than those without agoraphobia after adjustment for covariates ($\beta = -0.053$ (95%-CI −0.101 to −0.005; $p = 0.032$))
Levandowski et al. (2013)	Nil	Not recorded	Fasted – 3hours	Plasma	Serial	ELISA All samples were assayed in duplicate.	Actual adiponectin values not reported Crack users reporting childhood maltreatment exhibited a significant reduction in plasma levels of adiponectin when compared to CM- group. $p = 0.036$. In addition, only CM- participants plasma levels of adiponectin increased during detoxification
Na et al. (2017)	Nil	Not recorded	Non-fasting	Plasma	Single	Sandwich ELISA kit with a TMB microwell	A: 8.26 (4.90) B: 10.43 (6.54)

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Table 2 (*continued*)

First Author (year)	Medical comorbidity	Smoking status	Fasting state	Blood sample type, extraction & storage	Single/serial sample	Adiponectin (ADP) assay technique	Total ADP levels (μg/ml); where applicable cases versus controls (mean, SD, p-value)
						peroxidase substrate solution.	$p < 0.0001$ The plasma adiponectin level was inversely correlated with the IES-R-K scores after adjusting for age and waist circumference. However, adiponectin had no relationship with depression. There were no significant differences in the plasma adiponectin levels in depressive symptoms group. There was also no correlation between adiponectin levels and CES-D total scores.
Rao et al. (2014)	Nil	A: 11(25%) B: 9 (19%)	Fasting	Serum, blood sampling was performed every 30 min for 8 h while subjects slept through an indwelling catheter in the antecubital vein. Samples were processed in real time and stored at −70 °C.	Single	ELISA (ALPCO Diagnostics Inc, Salem, NH) Total and high-molecular weight (HMW) adiponectin were assayed on serum samples	A: HMW Adiponectin 3.36 (0.02–13.3) Total Adiponectin 6.88 (1.92–21.3) B: HMW Adiponectin 3.93 (0.96–14.6) Total Adiponectin 8.99 (2.35–29.6)

A: Cases, B: Controls, Confidence interval (CI); enzyme-linked immunosorbent assay (ELISA); radio-immunoassay (RIA); not significant (NS).

more episodes of major depressive disorder, were in complete remission at the time of examination, and had been receiving maintenance treatment with an SSRI (fluvoxamine or paroxetine) or SNRI (milnacipran) for more than 6 months (Narita et al., 2006). The authors found that plasma adiponectin levels were higher in depressed patients treated with antidepressants for more than 12 months compared to healthy matched controls (Narita et al., 2006). In sum, these results suggest that medication-induced alterations in adiponectin-values may be antidepressant-class and time-dependent.

4.1.4.2. Mental health measures. Mental health measures differed across the studies, as did cut-off scores that were applied. For depression, the most common measure of illness severity was the 17-item Hamilton Rating Scale for Depression (HAMD-17) (Leucht et al., 2013), followed by the Beck Depression Inventory (BDI) (Beck et al., 1961). For studies of bipolar disorder; the most commonly used measures of severity were the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the HAMD-17.

4.1.4.3. Mental health outcomes. Of the 65 studies included in the review, the majority examined depression ($N = 46$), followed by bipolar disorder ($N = 9$), anxiety ($N = 7$) and trauma-related disorders ($N = 3$). Six studies examined more than 1 mental health outcome (e.g., depression and anxiety or depression and bipolar disorder). See Table 1.

4.1.4.3.1. Depressive disorders. Of the studies on depressive disorder, 34 included both male and female participants, 9 studies only female participants, and 3 studies only male participants.

4.1.4.3.2. Studies with both male and female participants. Of the 34 studies that included both genders, 17 found significant associations and 17 no associations. Most of the studies that found significant associations ($N = 14$) demonstrated an inverse association of adiponectin levels and depression. Only 3 studies documented higher adiponectin levels among depressed patients.

Among studies that found no significant associations, a study in Taiwan (Bai et al., 2014) included both medicated and unmedicated depressive disorder patients without medical comorbid disorders and found no difference in serum adiponectin levels between cases and controls (Bai et al., 2014). In a small case-control study in Brazil, differences in adiponectin levels between participants with temporal lobe epilepsy (TLE) and controls remained statistically significant after controlling for current major depressive episode diagnosis, with the authors concluding that plasma levels of adiponectin were independently associated with TLE, with no influence of sex, age, or depression diagnosis (Toscana et al. 2019). Of note, all patients were medicated and antiepileptic drugs, especially valproate and topiramate, have been shown to decrease adiponectin levels. In a Norwegian a cross-sectional, community-based study designed to investigate the risk for obstructive sleep apnea in the general population, no association was found between circulating adiponectin levels and depression (both when evaluated by self-reported symptoms or by diagnostic criteria). Total score on the Beck Depression Inventory (BDI) also did not correlate with adiponectin levels ($r = 0.055$, $p = 0.210$) (Einvik et al., 2013). This study, however, mainly included men and more obese participants with a higher prevalence of CVD risk factors. The authors noted that the high BMI of the sample may have masked the potential weaker independent effect of depression on adiponectin concentrations. In a double-blind, randomized trial by Weber-Hamman et al. (2007) conducted in Germany, adiponectin concentrations did not change significantly over the six weeks of antidepressant treatment in remitting and non-remitting depressed patients. This study was limited by the lack of inclusion of a healthy control group. Higher adiponectin values have been documented in female compared to male patients ($p < 0.01$) (Weber-Hamann et al., 2007). Finally, in a cohort of young adults with

depression in Sweden (Syk et al. 2018), plasma adiponectin was not significantly correlated with total MADRS-S scores in women or men and there was no significant difference in total MADRS-S scores between quartiles of plasma adiponectin among females in the study. Similarly, plasma adiponectin levels also did not differ between patients with current MDD and controls (Syk et al. 2018).

A Brazilian study of elderly outpatients with a current major depressive episode (first or recurrent episode), but unmedicated, found significantly *lower* serum-adiponectin levels among cases versus controls (Diniz et al., 2012). In a multicenter, 60-day, double-blind trial of daily methylfolate for patients with SSRI-resistant MDD, undertaken in the USA, lower serum-adiponectin levels were observed among MDD participants compared with controls. When further stratified by baseline body mass index (BMI), those with BMI ≥30 had lower adiponectin values (Shelton et al., 2015a,b). Further, a proof of concept interventional study utilizing omega-3 supplementation in outpatients with MDD, also conducted in the USA, found significantly lower serum adiponectin levels among the female versus male MDD participants (Jeong et al., 2012). An interesting Chinese cohort study demonstrated that low serum adiponectin could predict the onset of poststroke depression (PSD) at 3 months in patients following acute ischaemic stroke (Yang et al. 2019). Archer et al.'s group followed up an alcohol use disorder (AUD) and non-AUD group with comorbid depression for 6 months and while they found similar baseline adiponectin levels in both study groups and genders, levels of adiponectin was strikingly low in men after 6 months of treatment. All groups in the aforementioned study had a significant decrease in Montgomery–Ashberg Depression Rating Scale (MADRS) score at follow-up, but the MADRS score in men remained higher than that in women. The authors hypothesized that the higher MADRS score and thus depression severity may perhaps serve to explain the smaller increase in adiponectin among male participants (Archer et al., 2018).

In a Turkish study of 78 unmedicated patients with depression recruited from a hospital setting, and 64 healthy controls, serum adiponectin levels were found to be significantly *higher* among cases versus controls (MDD = 10.27 ± 7.50 (7.67); healthy controls = 5.84 ± 4.07 (4.42); $p = 0.001$) (Aliyazicioglu et al., 2011). Interestingly when the MDD-group were further subdivided by BMI, the "lean" subgroup with a low BMI had higher adiponectin levels as compared with the "normal" and "obese" subgroups ($p = 0.053$) (Aliyazicioglu et al., 2011). Similarly, in a study of community-dwelling Korean elders aged 65 years and older, stratified according to depressive subtypes, higher plasma adiponectin values were found among the diagnostic groups ($df = 3$, $F = 4.928$, $p = 0.002$). The concentration was highest in the subsyndromal depressive (SSD) group, and the difference in plasma adiponectin levels between SSD and healthy control groups was statistically significant ($p = 0.001$). Notably, when men and women were analyzed separately, the differences in plasma adiponectin levels among the diagnostic groups remained significant in men ($df = 3$, $F = 5.045$, $P = 0.002$) but not in women ($df = 3$, $F = 1.188$, $p = 0.314$) (Jeong et al., 2012). Another large study of community-dwelling South-Korean elderly ($N = 613$) found that those participants who had higher adiponectin levels at baseline were at the highest risk of developing incident depression 5 years later, even after adjusting for age, BMI, sex, burden of chronic medical illness and the Mini-Mental State Examination Score (odds ratio = 10.64, 95% CI, 1.21–93.84, $p = 0.033$) (Oh et al. 2018).

4.1.4.3.3. Studies with only female participants. Among the 9 studies that only included female participants, 6 studies found statistically significant associations and 3 studies found no associations between adiponectin levels and depression. Five studies demonstrated lower levels of adiponectin, whilst only 1 study found higher adiponectin levels among female depressed patients.

A Turkish multicenter controlled trial of two hundred and forty-four- women participants evaluated at 10 days postpartum found statistically significant *higher* serum adiponectin levels in women with postpartum depression (PPD). Mean serum adiponectin level was 14.845 ng/mL in the group with PPD and 10.960 ng/mL in the group without depression ($p = 0.001$). PPD participants were unmedicated, had no previous depressive episodes or other psychiatric illness and had a similar BMI to the non-PPD participants (Yildiz et al., 2017).

In a study of postmenopausal women conducted in the USA (Adam et al., 2010), women with a depressive disorder had significantly *lower* adiponectin than the group without a depressive diagnosis (M adiponectin = 9.96, SD = 1.5 vs. 14.0, SD = 0.73, $F(2,53) = 5.6$, $p < 0.02$), however the comparison groups were very small ($N = 10$; $N = 38$). In another USA-based study among mostly medicated female participants with MDD versus healthy controls, adiponectin levels remained lower in women with MDD measured serially over a 24hr period (Cizza et al., 2010). In a Chinese randomized, waitlist-controlled trial ($N = 108$) of Baduanjin Qigong; a Chinese medicine exercise intervention which combines meditative and physically active elements, was evaluated among females with Chronic Fatigue Syndrome-Like Illness (Chan et al., 2017). Not only did Baduanjin Qigong exercise significantly increase adiponectin levels in participants, but the increase in the adiponectin levels was associated with a reduction in depression scores. After adjusting for covariates (age, alcohol drinking, daily smoking, regular exercise, BMI, and waist circumference), linear regression analysis further predicted Qigong exercise and a change in adiponectin following Qigong exercise was a significant factor for ameliorating depression symptoms immediately after intervention. In a study investigating whether glucose homeostasis and insulin sensitivity were impaired among MDD patients, adiponectin levels were found to be decreased in the MDD patients. In addition, insulin sensitivity was correlated with adiponectin levels, indicating that reduced insulin sensitivity and inflammatory processes are linked among MDD patients (Li et al., 2016). Everson-Rose and colleagues from the USA demonstrated that among healthy middle-aged women, higher levels of depressive symptoms were consistently associated with lower concentrations of adiponectin in both cross-sectional and longitudinal analyses. The authors found that average baseline values of adiponectin for women with a current MDD episode were lower (mean (SD) = 8.9 (4.3) μg/ml) than either women with a history of, but no current, MDD diagnosis (10.1 (4.8) μg/ml) or women with no MDD history (10.0 (5.1) μg/ml). Notably, in this analyses, depressive symptoms remained inversely related to adiponectin after taking into consideration age, adiposity, hormonal and behavioral risk factors (diet, smoking status, alcohol consumption, physical exercise), all of which are potentially important confounders.

Among the studies that reported no statistically significant associations; a Brazilian prospective cohort study of healthy pregnant women aged 20–40 years with four follow-up points during the perinatal period found that plasma adiponectin levels were not associated with depressive symptoms (Rebelo et al., 2016). Interestingly, the women who remained non-depressed throughout the study tended to have higher values of adiponectin throughout pregnancy and in the postpartum period compared to those who had depressive symptoms at least once, but this difference was not statistically significant ($\beta = 0.14$; $p = 0.071$). The authors cautioned about the interpretation of their results, because of the different assays used during the study and in acknowledgement of the perinatal period being characterized by very specific metabolic changes and mental health issues. Furthermore, adiponectin levels tend to be lower in pregnant women compared to nonpregnant women. The authors concluded that although the associations reported in the present study were not statistically significant and, therefore, should be regarded as inconclusive, they believed that more research was warranted (Rebelo et al., 2016). Although the group of Ferrari et al. demonstrated lower adiponectin levels in their study group of postpartum women with mild to moderate depressive symptoms versus an asymptomatic group, this effect disappeared after BMI adjustment. Women with depressive symptoms had a higher BMI which is known to affect adiponectin levels. The authors noted that their

sample might have been too small to detect an effect (Ferrari et al., 2018). In a study of women with depressive disorder (DD) in the Czech Republic, women with DD differed from the control group with regards to the leptin-to-adiponectin ratio ($p < 0.05$), but not adiponectin levels (p = NS). The authors suggested that the significant increase of the leptin-to-adiponectin ratio in depressive women compared to healthy controls might be another common feature of both depression and MetS. The Hamilton Depression Scale (HAM-D) score of these women did, however, correlate negatively with adiponectin ($r = -0.3505$; $p < 0.05$), independent of insulin resistance (HOMA-IR) (Zeman et al., 2009).

4.1.4.3.4. Studies with only male participants. Lastly among the 3 studies that included only male participants, all 3 found significant associations, Specifically, in all 3 studies adiponectin was inversely associated with depression.

A study conducted in Taiwan among young men with different subtypes of depressive disorder found *lower* plasma adiponectin levels in the bipolar depression group as compared to the control and reactive depression groups (7.41 ± 0.45 μg/ml vs. 9.07 ± 0.54 μ/ml and 9.38 ± 0.46 μ/ml; $p < 0.05$ and $p < 0.01$, respectively) (Hung et al., 2007). Similarly, in a cohort of young men with various subtypes of depression, plasma adiponectin was significantly lower in the bipolar depression subgroup of patients compared to controls (Su et al., 2011).

4.1.4.3.5. Results of the meta-analysis. Tests for heterogeneity were first performed ($I^2 = 87.0\%$, $p = 0.000$) followed by a random-effects model (SMD, −0.198 μg/mL, 95% CI, −0.41, −0.01, $p = 0.061$) (Fig. 2). Subgroup analyses were carried out according to blood sample and gender: serum ($I^2 = 80.3\%$, $p = 0000$); SMD, −0.024 μg/mL, 95% CI, −0.29, −0.29, $p = 0.858$) and plasma ($I^2 = 90.8\%$, $p = 0000$); SMD, −0.198 μg/mL, 95% CI, −0.41, −0.01, $p = 0.858$) (Fig. 3); gender according to male and female ($I^2 = 80.1\%$, $p = 0000$); SMD, −0.015 μg/mL, 95% CI, −0.18, −0.21, $p = 0.880$) and female only ($I^2 = 80.3\%$, $p = 0000$); SMD, −0.655 μg/mL, 95% CI, −0.41, −0.01, $p = 0.012$) (Fig. 4).

4.1.4.3.6. Bipolar disorders.

4.1.4.3.7. Qualitative review. All 9 of the bipolar disorder studies included both male and female participants. Five studies found significant associations, of which 4 found lower adiponectin levels among bipolar disorder patients. Four studies found no association.

A small case-control study ($N = 60$) conducted in Brazil among medicated euthymic BD type 1 patients and healthy controls found significantly *lower* plasma adiponectin levels among BD patients (BD: 3.70 μg/l, controls: 8.28 μg/l, $p < 0.001$ (Barbosa et al., 2012). Mansur's study of Brazilian BD outpatients found that among female participants, adiponectin was lower in BD, relative to healthy controls ($p < 0.017$) (Mansur et al., 2016). In a relatively large cross-sectional study ($N = 188$) of outpatient participants with bipolar depression, depressive patients with BD exhibited significantly lower adiponectin levels compared to euthymic patients as well as controls. These findings suggest that different mood states in bipolar disorder can have differing effects on adiponectin levels. Furthermore, among women with BD, lower adiponectin levels were significantly associated with more depressive symptoms (Platzer et al., 2018).

Conversely in a study by Elmsie et al. in New Zealand, data were collected from 60 overweight bipolar patients who had experienced clinically significant weight gain thought to be related to sodium

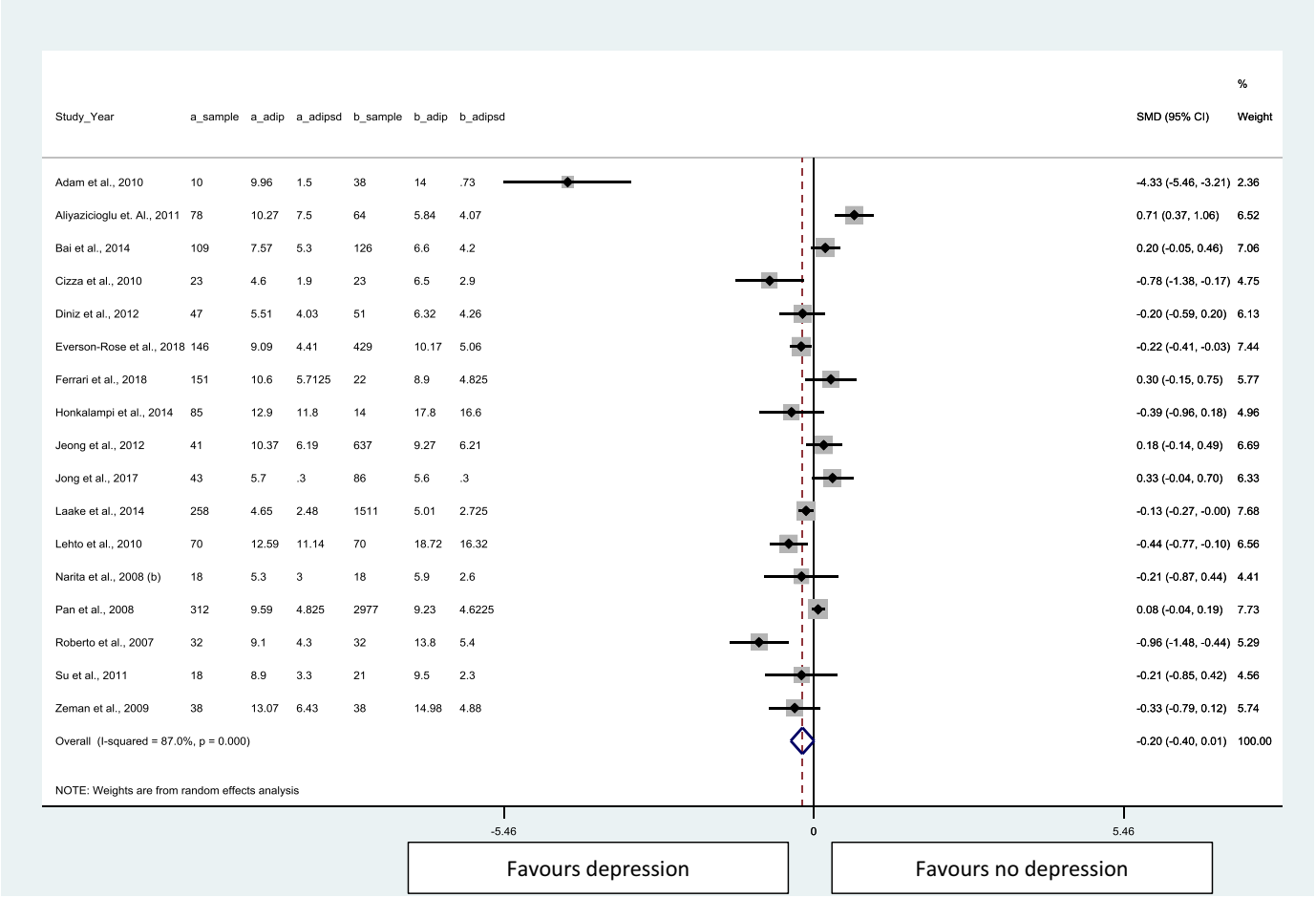

Fig. 2. Meta-analysis of the association of adinopectin levels in patients with depressive disorders and healthy controls. SMD, standard mean difference; CI, confidence interval; a, cases, b, controls; adp, mean adiponectin level, adpsd, standard deviation.

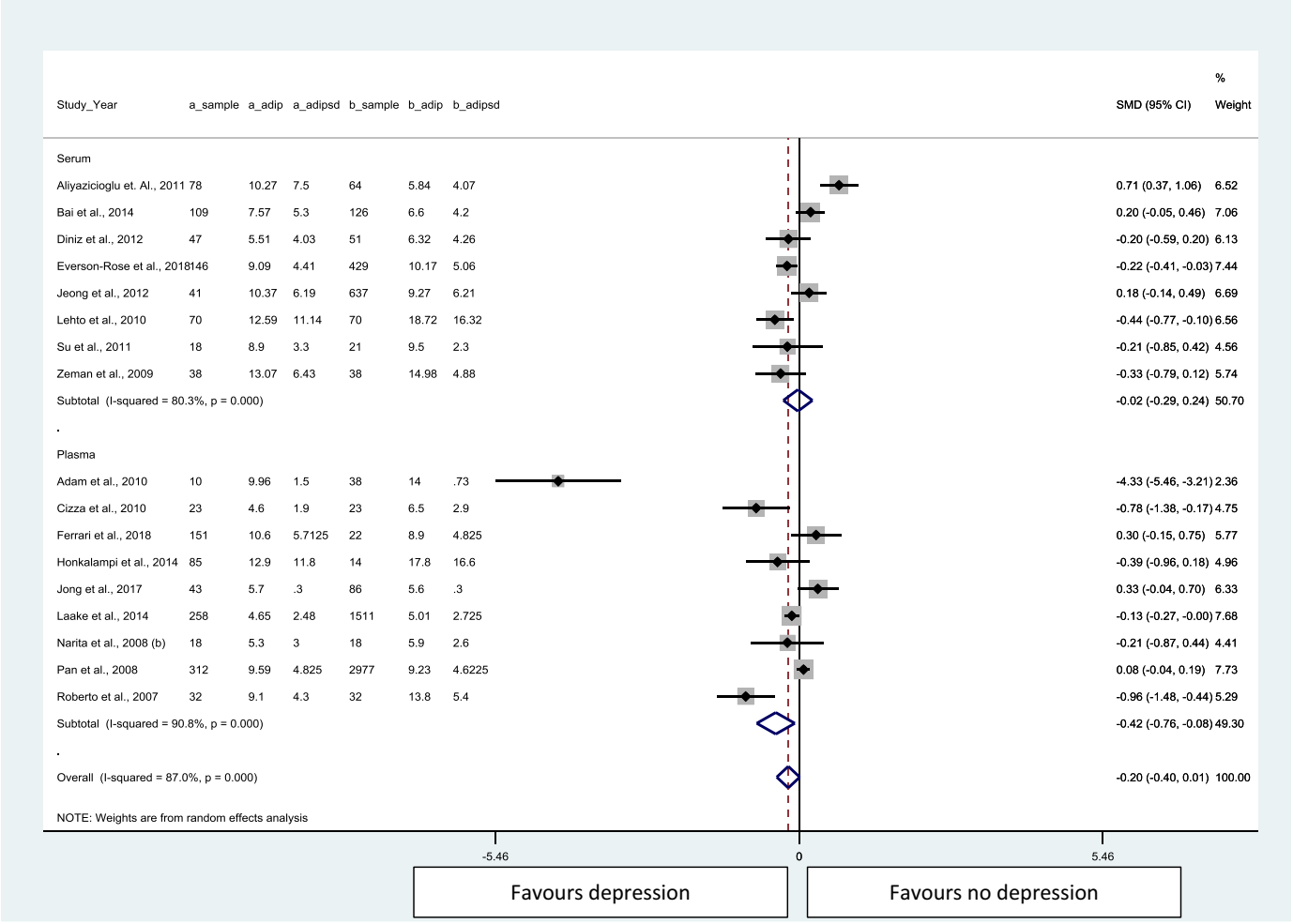

Fig. 3. Meta-analysis of the association of adiponectin levels in patients with depressive disorder and healthy controls, separated by blood sample type. SMD, standard mean difference; CI, confidence interval; a, cases, b, controls; adp, mean adiponectin level, adpsd, standard deviation.

valproate treatment and from 60 control subjects without psychiatric illness matched for age, gender, body mass index and ethnicity. *Higher* adiponectin levels were documented among medicated BD patients as compared to a well-matched control group despite comparable BMI and waist circumference levels (Elmslie et al., 2009). Two of the studies that did not report significant differences between cases and controls still found significant gender differences in measured adiponectin levels with higher adiponectin levels observed among female participants (Lee et al., 2014; Mansur et al., 2016). In a Turkish study in which patients were treated during a manic episode in hospital and then followed up as outpatients whilst euthymic, no difference in adiponectin was observed in terms of different mood states (Tunçel et al., 2018). In an interventional study using flexible dosing of Lithium in a group of acutely depressed BD individuals (the majority unmedicated), baseline levels of adiponectin were similar between patients and controls and baseline levels of adiponectin did not predict remission (Soeiro-de-Souza et al., 2014). Lastly, a Korean study of 94 BD outpatients also found no statistically significant difference in adiponectin values when comparing euthymic patients with depressed bipolar patients, however the study did demonstrate higher adiponectin levels (10.51 ± 8.37 vs. 5.91 ± 2.82 μg/ml; $p = 0.001$) in female compared with male patients (Lee et al., 2014).

4.1.4.3.8. Results of the meta-analysis. In the present continuous variable meta-analysis, tests for heterogeneity were first performed (I^2 = 90.5%, $p = 0.000$) followed by a random-effects model (SMD, −0.638 μg/mL, 95% CI, −1.16, −0.12, $p = 0.017$) (Fig. 5). Subgroup analysis was carried out for assay-method: ELISA (SMD, −0.440 μg/mL, 95% CI, −0.94, −0.06, $p = 0.082$) and RIA (SMD, −1.263 μg/mL, 95% CI, −3.126, −0.601, $p = 0.184$), overall $p = 0.017$ (Fig. 6).

4.1.4.3.9. Anxiety disorders.

4.1.4.3.10. Qualitative review. The following specific anxiety disorders were evaluated: obsessive-compulsive disorder (OCD), phobic anxiety, and panic disorder. All but 1 of the 7 studies included both genders. Most of the studies found significant associations ($N = 6$) and in most of these ($N = 5$) an inverse association of adiponectin levels and anxiety.

In one study of individuals with phobic anxiety, no significant association was found between the presence of phobic anxiety and adiponectin levels (Brennan et al., 2009). In the 2 studies of OCD, adiponectin values were found in both to be negatively correlated with Y-BOCS scores in the patient groups. Both studies also found adiponectin values to be significantly *lower* among patients with OCD versus healthy controls ($p < 0.001$) (Ari et al., 2012; Atmaca et al., 2009). Similarly, in a pilot cross-sectional study among healthy elderly patients aged 50 to 70 years, the severity of trait anxiety scores was negatively associated with serum adiponectin levels (Narita et al., 2008). In a prospective cohort of 235 pregnant women followed up at 4-time points during the perinatal period, women with high anxiety levels as opposed to women with low anxiety levels during the 3rd trimester, had a significant decrease in plasma adiponectin concentrations throughout pregnancy ($p = 0.01$) (Rebelo et al., 2016). In a study of participants with panic disorder, mean adiponectin levels were significantly lower in the patient group (26.96 ± 9.92 ng/ml) compared to controls

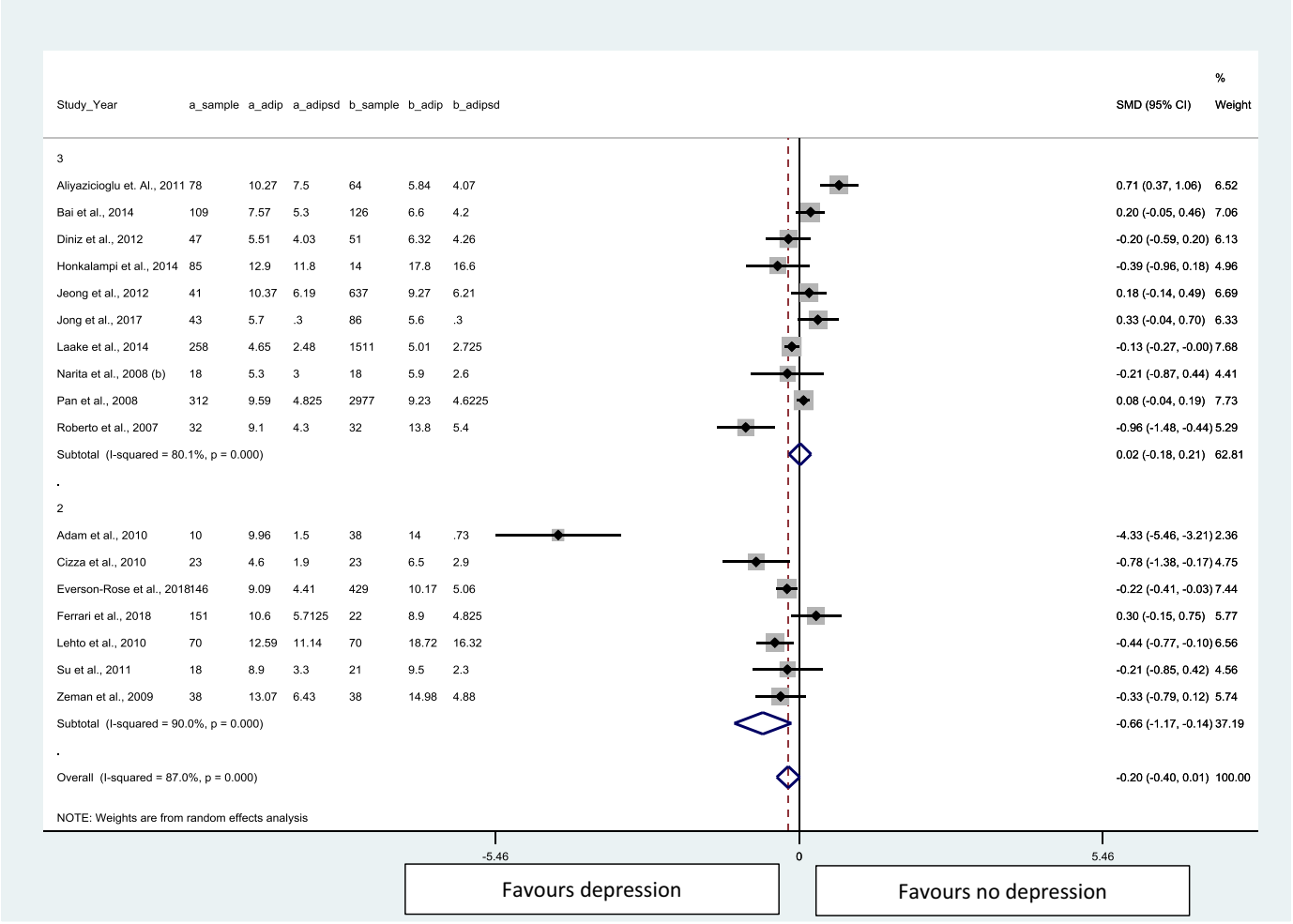

Fig. 4. Meta-analysis of the association of adiponectin levels in patients with depressive disorders and healthy controls, separated by gender. 3 = males and females; 2 = female only SMD, standard mean difference; CI, confidence interval; a, cases, b, controls; adp, mean adiponectin level, adpsd, standard deviation.

(37.63 ± 23.17 ng/ml) ($t = -2.21$; $p = 0.032$) (Unsal et al., 2012). Lastly, among participants with agoraphobia, adiponectin was significantly lower in persons with agoraphobia than those without, even after adjustment for covariates (β = −0.053 (95% CI −0.101 to −0.005; $p = 0.032$)) (Wagner et al., 2015). Of note the only study that did not demonstrate any association between anxiety and adiponectin included only female participants and measured anxiety with a self-rated questionnaire only (Brennan et al. 2009).

4.1.4.3.11. Results of the meta-analysis. For the anxiety disorder group, tests for heterogeneity were first performed ($I^2 = 95.7\%$, $p = 0.000$) and subsequently a random-effects model (SMD = −1.18 μg/mL, 95% CI, −2.34; −0.01, $p = 0.047$) (Fig. 7)

4.1.4.3.12. Trauma-related disorders.

4.1.4.3.13. Qualitative review. 2 of the 3 trauma studies found significant associations, both an inverse association of adiponectin to trauma-related disorders, 1 study was among male and the other female participants only.

In the Rao et al. study of 92 age- and gender- matched participants, *no* difference in either total or high molecular weight (HMW)-adiponectin values were found between healthy controls and individuals with PTSD following an oral glucose challenge test and overnight sampling (Rao et al., 2014). The investigators did, however, demonstrate a hyperinsulinemic response among participants with PTSD (Rao, 2014). Conversely, in a sample of 507 male firefighters, the PTSD symptom group had *lower* plasma adiponectin levels than controls ($p < 0.0001$), with an inverse correlation between plasma adiponectin levels and PTSD severity observed. Interestingly, there was no correlation between adiponectin levels and depression, though adiponectin levels were associated with the presence of PTSD symptoms (odds ratio = 0.955, 95% CI = 0.920–0.991) (Na et al., 2017). In another study among crack-cocaine dependent females during early abstinence, those reporting childhood maltreatment (CM) exhibited a significant reduction in plasma levels of adiponectin when compared to the CM- group ($p = 0.036$). In addition, plasma levels of adiponectin increased during detoxification in only the CM- group (Levandowski et al., 2013).

4.1.4.3.14. Results of the meta-analysis. Tests for heterogeneity were first preformed ($I^2 = 0.0\%$, $p = 0.818$) followed by a random-effects model (SMD = −0.34 μg/mL, 95% CI, −0.52; −0.17, $p = 0.0000$), (Fig. 8).

5. Discussion

This systematic review and meta-analysis synthesize current evidence on the association of peripheral adiponectin levels and anxiety, mood and trauma-related disorders.

Findings of adiponectin, whilst intriguing, need to be interpreted against the background of several methodological limitations inherent in the included studies, which also extend to known and unexplored confounders. Although most studies considered the potential influence of age, sex and adiposity on adiponectin levels, previous research has shown that factors like fasting status, ethnicity, medication, comorbid medical conditions and psychosocial stress can also influence adiponectin-levels (Feizollahzadeh et al., 2014; Murphy et al., 2016; Won et al., 2014). Variables such as duration of illness, patient selection,

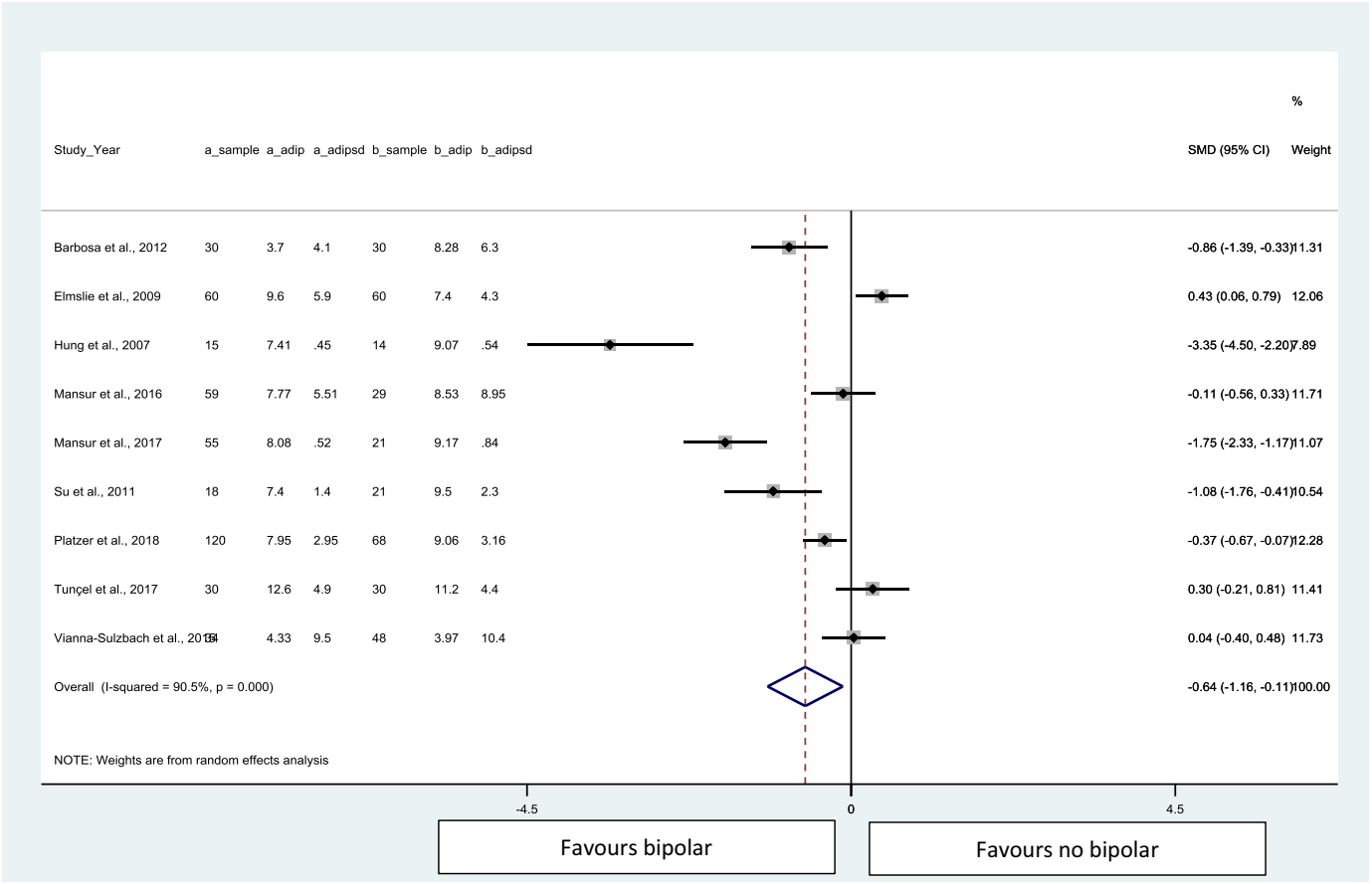

Fig. 5. Meta-analysis of the association of adiponectin levels in patients with bipolar disorder and healthy controls. SMD, standard mean difference; CI, confidence interval; a, cases, b, controls; adp, mean adiponectin level, adpsd, standard deviation.

illness subtype, assessment tool and cut-off scores employed, comorbid illness and psychotropic treatment should all be considered when interpreting findings from studies of adiponectin as they all have been shown to affect circulating levels. In this review among the bipolar disorders, the different mood states (euthymic versus depressed) were shown to have differing effects on adiponectin levels. Furthermore, among the studies included in the review, medical illness was either not assessed or participants with medical illness were characterized by heterogeneous medical histories. Some studies specified the exclusion of comorbid acute or chronic inflammatory conditions, while others did not take this into consideration. Adherence to medication was not assessed and so the risk of residual confounding cannot be ignored. Adiponectin levels could also be influenced by psychopharmacological agents which influence lipid metabolism and induce weight gain. In some of the studies included in the review, patients were receiving concomitant benzodiazepines whose effects on the inflammatory system are unclear. Future large prospective studies in participants treated with psychotropic medications are needed to clarify the effects of maintenance therapy on adiponectin.

Across studies included in the review, the effects of gender were evident. This is in keeping with much of the existing literature. Lower adiponectin levels in men compared with women have been observed in general population samples (Obata et al. 2013, Isobe et al. 2005). The reasons for this gender difference have not been fully elucidated, but Cnop et al. (2002) suggested that both the number of adipocytes and their size are different in men compared to women which may determine adiponectin production. Nishizawa et al. have proposed that low adiponectin levels in males are most likely due to an inhibitory effect of androgen (Nishizawa et al., 2002). Few of the included studies considered ethnicity as a covariate. In a study by Young et al. of depressed individuals who had experienced early life adversity, adiponectin levels were lower in African American participants compared to Caucasian participants ($p = 0.05$) (Joung et al., 2014), whilst in a study by Mansur et al. participants with BD no effect of ethnicity was observed ($p = 0.821$)(Mansur et al., 2016). Other studies have also demonstrated that ethnicity was an independent factor affecting adiponectin levels (Carvalho-Ferreira et al., 2015; Meshkini et al., 2018). The extent to which gender, adiposity and lifestyle factors influence adiponectin concentrations may also vary by ethnicity and requires further investigation.

Mental disorders are often underpinned by stress and lifestyle factors, including smoking, low physical activity levels, alcohol use and unhealthy nutrition. These factors can of themselves have inflammatory effects; however in most of the included studies these confounding factors were not assessed. Few studies examined physical activity, which has previously been shown to impact proinflammatory cytokines, and specifically to increase adiponectin concentrations (Nurnazahiah et al., 2016). Adherence to healthy dietary patterns, such as a Mediterranean diet (Izadi and Azadbakht, 2015), has been shown to increase adiponectin concentrations, though other studies have reported this difference to be gender-dependent, with only men experiencing an increase (Bédard et al., 2014). Alcohol use has been shown to increase inflammation and reduce adiponectin secretion (Harwood, 2012), whilst decreased adiponectin concentrations in current smokers has been shown to reverse after smoking cessation (Kotani et al., 2012). Among the few studies that examined smoking status in this review, categories of smoking status studied were not always identical (example: current versus past smoking)

To summarize, most studies did not assess lifestyle factors and when these were assessed objective and calibrated tools or measures (e.g.

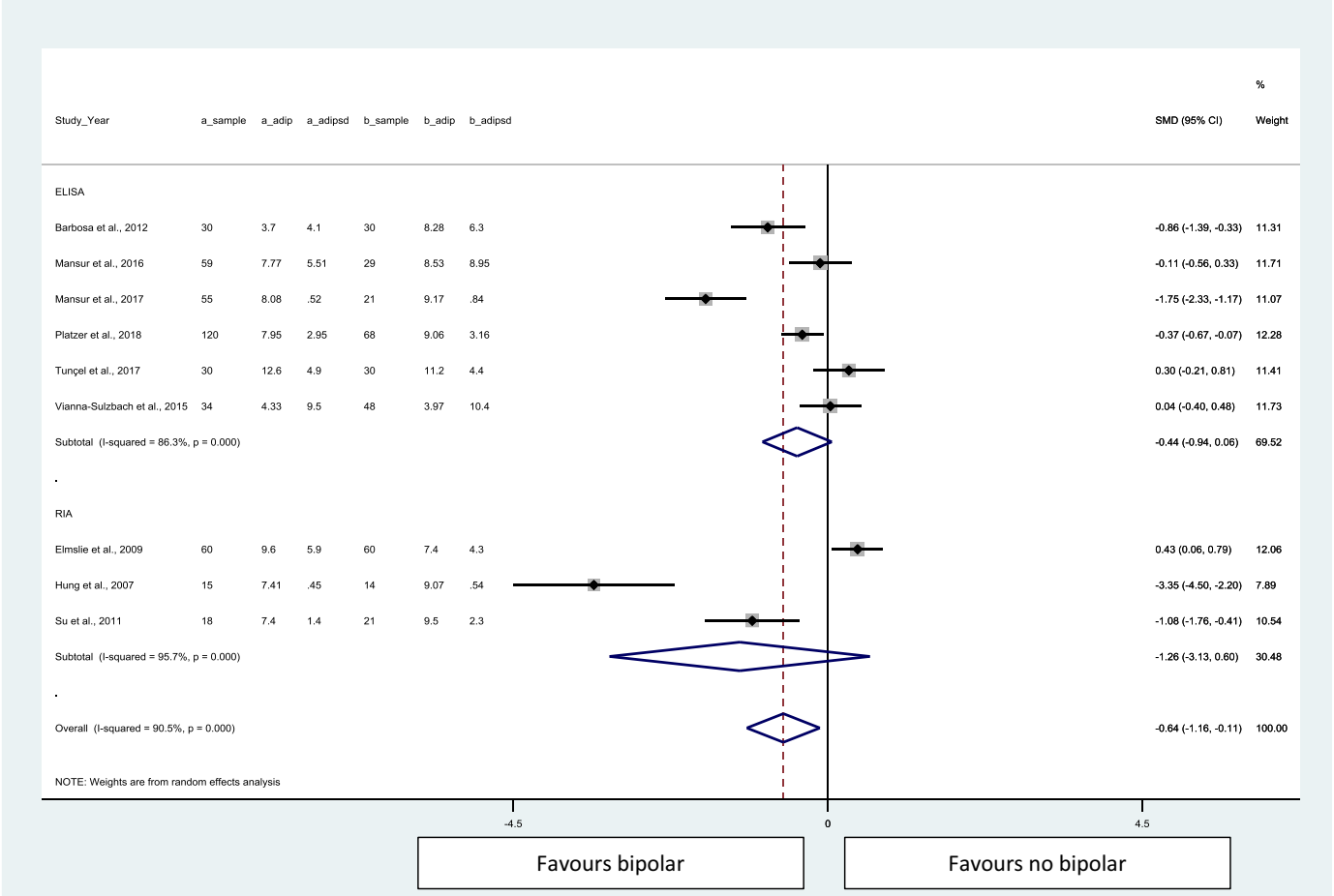

Fig. 6. Meta-analysis of the association of adiponectin levels in patients with bipolar disorder and healthy controls, separated by assay type. SMD, standard mean difference; CI, confidence interval; a, cases, b, controls; adp, mean adiponectin level, adpsd, standard deviation.

urine cotinine-levels, accelerometers or pedometers, breathalyser) were not employed. In addition, findings observed in these studies may be explained by other factors, such as blood sample type, fasting state, blood collection time, and the assay system used. Since some studies used non-fasting serum/plasma samples to measure adiponectin, it will be important to clarify the impact of fasting on circulating adiponectin levels in mental illness, specifically. Studies in other populations have observed minor or no diurnal variation in adiponectin concentrations in humans and no influence of fasting on adiponectin concentrations (Hotta et al., 2000; Merl et al., 2005; Shand et al., 2006). Comparing absolute values between studies is difficult since differences in the type of analysis kit used, kit lot number and standard curves can all affect measured levels of cytokines. The assay system used to measure circulating adiponectin differed across the studies in this review, as did blood sample type (plasma versus serum) and extraction/storage method. The meta-analysis by Carvalho et al. revealed that peripheral adiponectin levels were significantly lower in MDD patients than in controls when assayed with radioimmunoassay (RIA), but not with ELISA (Carvalho et al., 2014). In this review, adiponectin-levels were lower among MDD patients versus controls when plasma samples versus serum were used; whilst adiponectin levels were lower in Bipolar patients versus controls whether assayed with RIA or ELISA. Adiponectin circulates in serum as three oligomeric complexes known as high, medium and low molecular weight forms; the HMW isoform is believed to be more active in glucose metabolism than other isoforms (Wang et al., 2010) and an important factor in explaining the metabolic syndrome (Lara-Castro et al., 2006). The studies that did report adiponectin multimer distribution reported varying results. Overall, the results suggest that the assessment of total adiponectin may be insufficient and that analysis of the levels of the multimeric forms should be favourable to assess the significance of adiponectin. Further studies could improve on current results by analyzing the multiple isoforms of adiponectin. To clarify the causal relationship between mental disorders and multimeric complexes of adiponectin, prospective investigation in adequately powered samples should be undertaken.

Potential bias might result from uncontrolled methodological quality in some studies. Regarding study design, most of the included studies were cross-sectional thereby limiting inferences on causality; and reference to possible mechanisms should be cautiously regarded. Most of the studies were single site studies with small samples and groups were not homogenous with respect to age, smoking status and educational level, factors which may have an influence on symptoms of mental illness. Although the systematic review was conducted using multiple databases, it has some limitations. Firstly, the search was restricted to the English language; secondly, despite several attempts to contact the authors of the published articles with missing data by email, some studies were excluded due to non-response ($N = 16$). Most of the studies were observational (case-control or cross-sectional) and vulnerable to methodological biases. Limitations of the meta-analysis include a small number of eligible case-control studies as well as 'measured heterogeneity'. Adiponectin as a candidate biomarker needs to be evaluated in larger clinical cohort and clinical trial designs to identify its clinical utility as a biomarker. Enhanced methodological rigor may be achieved through addressing issues of homogeneity, comparability, larger samples, multiple points of assessment and incorporation of essential covariates (e.g. metabolic aspects, lifestyle factors, sampling and analyses method). Moreover, cross-cultural and cross-geographical replication studies are needed.

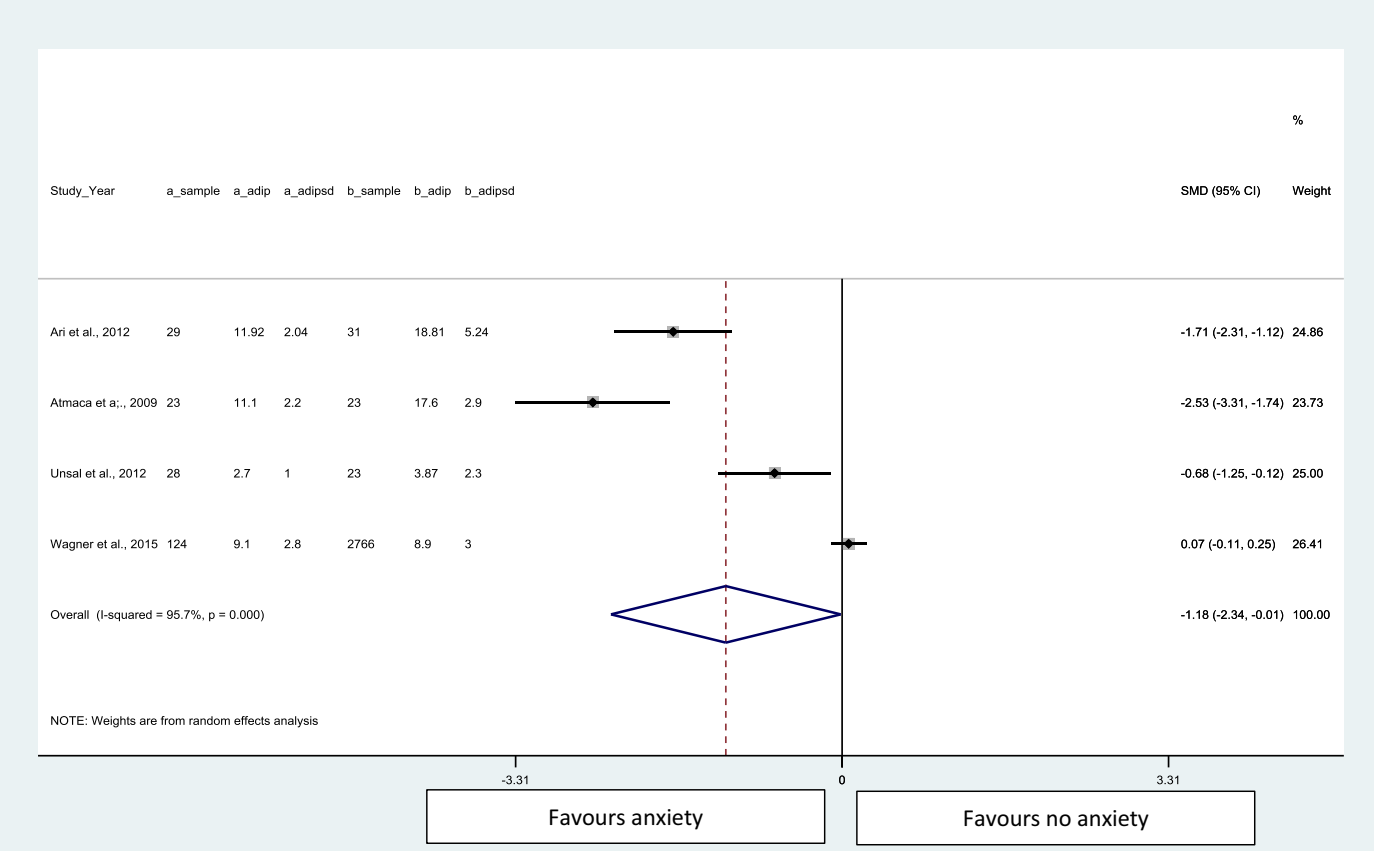

Fig. 7. Meta-analysis of the association of adiponectin levels in patients with anxiety disorders and healthy controls . SMD, standard mean difference; CI, confidence interval; a, cases, b, controls; adp, mean adiponectin level, adpsd, standard deviation.

The functional mechanisms and neuronal circuits underlying adiponectin's action within the central nervous system have not yet been completely elucidated. Several hypotheses have been investigated to explain the link between metabolic disease and common mental disorders via adiponectin. The adiponectin-hypothesis suggests that the link between metabolic disease and psychopathology directly links to hypoadiponectinemia (Yilmaz, 2008). Inflammation is the process generally invoked to explain decreased production of adiponectin in metabolic disease and its co-morbidities. Briefly, expansion of adipose tissue in obesity, with or without additional contributions from cardiovascular disease and/or insulin resistance, leads to development of chronic inflammation, which in turn contributes to inhibition of adiponectin (Fantuzzi, 2013). The regulation of several pro- and anti-inflammatory cytokines is another possible biological mechanism that may be involved. Adiponectin regulates the expression of several key pro- and anti-inflammatory cytokines, including reducing secretion of TNF-alpha and inducing the production of anti-inflammatory cytokines such as IL-1 (Mancuso, 2016; Ouchi et al., 2011). Immune hyperactivation and dysregulated cytokine production and signaling have been described in all the common mental disorders included in the current study (Hou et al., 2017; Rosenblat and McIntyre, 2017; Speer et al., 2018; Zou et al., 2018). Low adiponectin levels may reflect a chronic inflammatory state because of its anti-inflammatory properties (Fantuzzi, 2013). Adiponectin insufficiency has been shown to increase susceptibility to stress-induced depressive behaviors and impair function of the HPA axis (Lo Sauro et al., 2008). Another possibility relates to an altered hypothalamic-pituitary-adrenal (HPA) axis, which plays a regulatory role with adiponectin, with robust evidence demonstrating a dysfunctional hypothalamic-pituitary-adrenal (HPA) axis in the pathophysiology of depression (Vreeburg et al., 2009), bipolar (Murray), anxiety (Faravelli et al., 2012) and trauma-related disorders (Kinlein et al., 2015; Sherin and Nemeroff, 2011).

In the brain, adiponectin signaling occurs through its receptors, AdipoR1 and AdipoR2, and directly influences important brain functions such as energy homeostasis, hippocampal neurogenesis and synaptic plasticity (Thundyil et al., 2012). AdipoR1 and AdipoR2 receptors have been shown to be expressed in mood-related brain-areas; more specifically, AdipoR1 mRNA has been shown to be highly expressed in limbic forebrain areas such as the medial frontal cortex, hippocampus and amygdala, suggesting a possible physiological role for these receptors (Psilopanagioti et al., 2009). Adiponectin stimulates hippocampal neurogenesis which been implicated in the mechanism of action for antidepressant treatment (Segi-Nishida, 2017) and intracerebral administration of adiponectin has also been found to have antidepressant properties in rat-models (Liu et al., 2012). A recent preclinical study investigated the adiponergic system as a potential treatment target against depression related to metabolic dysfunction (Nicolas et al., 2018). The researchers found that daily treatment of AdipoRon, a potent adiponectin receptor agonist, not only prevented corticosterone-induced early onset of moderate obesity and metabolic syndromes, but also successfully reversed the corticosterone-induced depression-like state in the mice-models (Nicolas et al., 2018). The researchers reported that AdipoRon exerted its pleiotropic actions on various systems including hippocampal neurogenesis, serotonergic neurotransmission, neuroinflammation, and the tryptophan metabolic pathway, which could explain its antidepressant properties (Nicolas et al., 2018, Nicolas, 2018). In summary, these links between adiponectin, HPA-axis dysregulation and inflammation highlight biologically plausible mechanisms linking adiponectin to mental illness and metabolic disease.

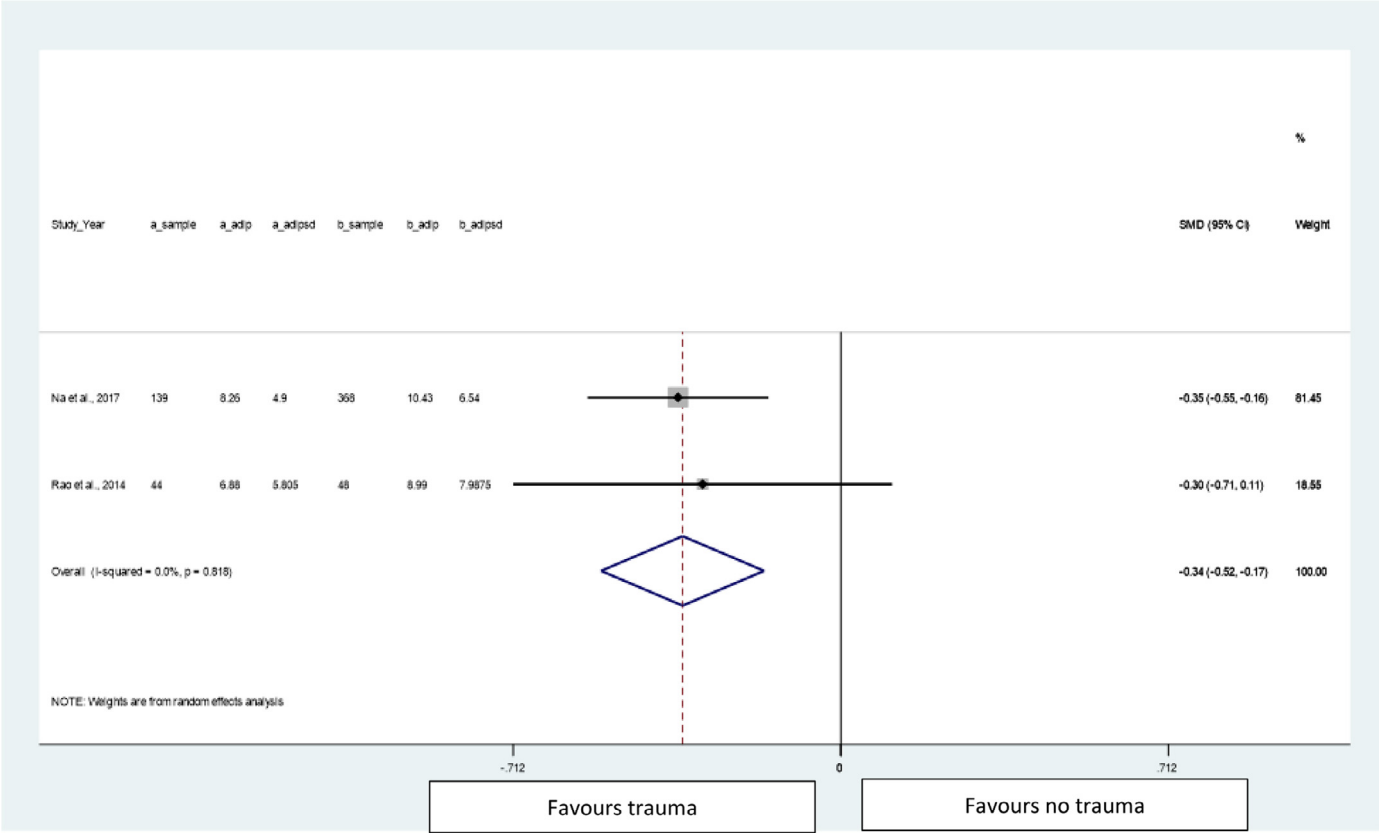

Fig. 8. Meta-analysis of the association of adiponectin levels in patients with trauma- and stressor- related disorders and healthy controls. SMD, standard mean difference; CI, confidence interval; a, cases, b, controls; SD, standard deviation.

6. Conclusion

Our systematic review and meta-analysis suggest that anxiety, mood and trauma- and stressor related disorders are associated with differences in circulating adiponectin levels. Specifically, inverse (hypoadiponectinemia) and gender dimorphic effects are evident. Although these studies do not explain causality, the consistency of the associations across diverse populations suggests that circulating adiponectin may be a promising biomarker for the diagnosis and monitoring of common mental health disorders. Additional research is needed to further explore whether lowered adiponectin is a critical physiologic pathway by which common mental illness contributes to metabolic dysregulation and increasing cardiometabolic disease. Adiponectin and its signaling pathways may represent innovative therapeutic strategies, especially where mental illness-metabolic disease comorbidity exists. Whilst current available evidence is suggestive but not conclusive, further exploration of this area of research should be supported and gender should be taken into consideration in this evaluation.

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Declaration of Competing Interest

This original research article complies with ethical standards and authors report no potential conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.09.050.

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