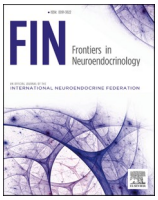
Frontiers in Neuroendocrinology 67 (2022) 101013

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne



Appetite-regulating hormones in bipolar disorder: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Mood disorder
Depression
Adiposity
Obesity
Overweight

ABSTRACT

Impaired hormonal regulation of appetite may contribute to higher cardiovascular risk in bipolar disorder (BD). We performed a systematic review and meta-analysis of studies investigating peripheral blood levels of appetite-regulating hormones in BD and controls. A total of 32 studies were included. Leptin and insulin levels were significantly elevated in patients with BD during euthymia, but not in other mood states. Greater differences in the number of male participants between patients with BD and healthy controls were associated with higher effect size estimates for the levels of insulin. There were significant positive correlations of effect size estimates for the levels of adiponectin with the percentage of individuals with type I BD and duration of BD. Our findings point to the mechanisms underlying high rates of cardiometabolic comorbidities in BD. Moreover, they suggest that investigating hormonal regulation of appetite might help to understand differences in the neurobiology of BD types.

1. Introduction

Bipolar disorder (BD) is a chronic mental condition characterized by recurrence of mood episodes that affects up to 5% of the world population (Belmaker, 2004). Patients with BD have increased risk of developing metabolic syndrome in comparison with the general population (Bartoli et al., 2013; McIntyre et al., 2010). Metabolic syndrome is a cluster of conditions that occur together, increasing the risk of cardiovascular complications. These conditions include diabetes and/or raised fasting plasma glucose, dyslipidemia, abdominal obesity, and high blood pressure. Epidemiological and clinical studies have shown that more than half of individuals with BD are either overweight or obese (Liu et al., 2022; McElroy et al., 2002), and increased weight might be associated with BD regardless of treatment with antipsychotics and mood stabilizers (Maina et al., 2008).

There is evidence that obesity and its metabolic consequences are associated with certain unfavourable outcomes in patients with BD, including treatment resistance, increased number of mood episodes and inpatient admissions, as well as progression into a non-responsive chronic course of illness (Cairns et al., 2018; Calkin, 2019; Charles et al., 2016). Additionally, obesity in patients with BD has been associated with longer illness duration, greater disability, poor global functioning, and worse response to lithium (Calkin et al., 2009). Moreover, it has been reported that with every unit-increase of BMI, the likelihood of response to any bipolar treatment and the likelihood of remission decrease by around 7% (Kemp et al., 2010). Finally, overweight and obesity in BD have been associated with poor cognitive functioning and more pronounced neurostructural abnormalities (Bora et al., 2019; Depp et al., 2014; Yim et al., 2012).

Neurobiological mechanisms underlying the relationship between

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https://doi.org/10.1016/j.yfrne.2022.101013
Received 18 March 2022; Received in revised form 21 June 2022; Accepted 29 June 2022
Available online 2 July 2022

metabolic alterations and mood dysregulations remain unclear. However, there are studies showing the importance of endocrine dysregulation, neurotransmission imbalance, mitochondrial alterations, dysregulated inflammatory pathways, as well as oxidative and nitrosative stress (Maletic and Raison, 2014; Scaini et al., 2016; Soczynska et al., 2011) In recent years, the role of appetite-regulating hormones in the onset and clinical progression of BD has widely been investigated. These hormones can be divided into appetite suppressing (anorexigenic) peptides (i.e., leptin, insulin, peptide YY or cholecystokinin) and appetite stimulating (orexigenic) peptides (i.e., neuropeptide Y, orexins, agouti-related peptide, galanin or ghrelin) (Atkinson, 2008). Although the majority of these hormones are produced by adipose tissue (i.e., adiponectin, resistin, leptin, visfatin, vaspin), some of them are also produced by enteroendocrine cells of the gastrointestinal tract (i.e., glucagon-like peptide 1, ghrelin, peptide YY, cholecystokinin, insulin). Appetite-regulating hormones play important role in insulin sensitivity and energetic homeostasis (Williams et al., 2016). They mediate ingestion in the central nervous system by being released to the peripheral blood system or indirectly via vagal afferents. The arcuate nucleus in the hypothalamus plays a key role in regulating food intake. Due to its unique morphology, appetite-regulating hormones are able to reach this nucleus without crossing the blood–brain brain barrier (Yu and Kim, 2012). However, the brain rewarding system in the midbrain, where leptin acts on dopaminergic neurons, is also important in the context of highly palatable food desire (Hommel et al., 2006). The levels of appetite-regulating hormones can also be regulated by gut microbial metabolites, including short-chain fatty acids, amino acids, bile acids and lipopolysaccharide (Han et al., 2021). A recent systematic review showed that lower levels of bacterial genera that produce short-chain fatty acids (e.g., butyrate) can be observed in patients with severe mental disorders, including BD (McGuinness et al., 2022). Additionally, these hormones have been shown to regulate processes and behaviours that might be impaired in BD, including sleep-wake cycle (Shea et al., 2005) and sexual behaviours (Cicero et al., 2011). Moreover, some appetite-regulating hormones impact immune-inflammatory responses, known to be dysregulated in BD (Misiak et al., 2020; Munkholm et al., 2013). To date, several studies have aimed to address alterations in the levels of appetite-regulating hormones in patients with BD; however, only some of them have been subjected to qualitative and quantitative synthesis (Fernandes et al., 2016; Misiak et al., 2019). Therefore, in this study we aimed to perform a systematic review and meta-analysis of studies investigating peripheral blood levels of appetite-regulating hormones in patients with BD and in healthy controls.

2. Material and methods

2.1. Search strategy

Two authors (BS and DF) independently searched online databases (MEDLINE, ERIC, CINAHL Complete, International Pharmaceutical Abstracts as well as the Academic Search Ultimate and the Health Source: Nursing/Academic Edition) with no time limits (until 16th Dec 2021). Online searches were performed using the following keywords: "adiponectin" OR "agouti-related peptide" OR "agrp" OR "amylin" OR "cart" OR "cocaine- and amphetamine-regulated transcript" OR "cholecystokinine" OR "galanin" OR "gastric inhibitory peptide" OR "gip" OR "ghrelin" OR "glp-1" OR "glucagon" OR "glucagon-like peptide-1" OR "insulin" OR "leptin" OR "neuropeptide Y" OR "npy" OR "orexin" OR "oxyntomodulin" OR "pancreatic polypeptide" OR "peptide YY" OR "pomc" OR "proopiomelanocortin" OR "pyy" OR "visfatin" OR "obesity" OR "overweight" OR "diabet*" OR "hypertens*" AND "bipolar" OR "psychosis" OR "mania" OR "manic". Additionally, references of eligible publications were reviewed. Disagreements about inclusion or exclusion of specific studies were resolved through discussion with the third author (BM). The search strategy was designed in agreement with the PRISMA guidelines (Page et al., 2021). The PRISMA checklist is provided in Supplementary Table 1. The protocol of this systematic review and meta-analysis was registered in the PROSPERO database (CRD42022310000).

2.2. Eligibility criteria

Inclusion criteria were as follows: 1) studies comparing serum or plasma levels of appetite-regulating hormones between individuals with BD and healthy controls; 2) necessary data (sample size, descriptive statistics for the levels of hormones) were available in the manuscript or upon request (if needed the corresponding authors were contacted to obtain relevant data) and 3) full-text articles published in English. In case of overlapping samples, the publication reporting data from the largest sample of participants was included. The following exclusion criteria were applied: 1) studies reporting mRNA levels of appetite-regulating hormones; 2) studies of individuals with BD without healthy controls; 3) animal model studies; 4) case reports; 5) non-original studies (e.g., reviews, editorials and commentaries) and 6) publications not reporting necessary data to perform meta-analysis.

2.3. Data extraction

Extracted data included: 1) age; 2) sex; 3) BMI; 4) the levels of appetite-regulating hormones; 5) information regarding the use of psychotropic medications 6) illness duration; 7) percentage of individuals with BD type I and type II; 8) the severity of depressive and manic symptoms; 9) type of assay and biological material (serum or plasma) used to measure the levels of appetite-regulating hormones. In case of data provided as median and interquartile range (IQR), relevant conversion methods were applied. The median was included as the approximation of the mean (Higgins and Green, 2011). The IQR was divided by 1.35 to estimate SD (Hozo et al., 2005).

2.4. Quality assessment

Quality of studies was assessed using the Newcastle-Ottawa Scale (NOS). The NOS is a checklist that enables to evaluate three categories of quality, including the selection (the maximum score is 4 points) and the comparability of study groups (the maximum score is 2 points), and the ascertainment of exposure or outcome of interest (the maximum score is 3 points). For the purpose of this study, points for comparability of exposure were allocated in case of non-significant differences between individuals with BD and healthy controls in terms of age and sex.

2.5. Data analyses

Main outcomes included differences in appetite-regulating hormones between individuals with BD and healthy controls. Due to anticipated between-study heterogeneity, random-effects models and the restricted maximum likelihood estimator were used to pool effect size estimates calculated as Hedges' g. Random-effects models are recommended if included studies are characterized by methodological heterogeneity, and thus we did not deem as reasonable to assume that they could share a common effect (Tufanaru et al., 2015). The Knapp-Hartung adjustments were applied to calculate the confidence interval around pooled effect, since these are known to reduce the chance of obtaining false positive findings, especially in case of low number of studies (Inthout et al., 2014; Langan et al., 2019). Effect sizes were pooled for appetite-regulating hormones measured by at least two studies. The number of effect size estimates included in each analysis was reported as the "k" measure. Heterogeneity was assessed using the I^2 statistics. Heterogeneity was considered to be low, moderate or high according to I^2 values of 25%, 50% and 75%, respectively (Higgins et al., 2003). In order to check if any single study accounted for heterogeneity, a leave-one-out sensitivity analysis was performed. Meta-regression analyses were carried out for continuous variables assessed by at least six studies (Fu et al.,

Table 1
General characteristics of eligible studies.

Study	Patients with BD					Healthy controls			Hormones	Matching	Assay	Biological material	NOS
	N	Age	% males	Mood state	Medications	N	Age	% males					
Barbosa et al. (2012)	30	49.0 ± 10.9	23.3	Euthymia	Li, AEs, FGAs, SGAs	30	47.1 ± 7.36	40.0	Adiponectin, leptin, resistin	Age, sex, educational level	ELISA	Plasma	5
Bond et al. (2017)	53	23.1 ± 4.6	45.3	Euthymia, mania, depression	MSs, SGAs, ADs, drug-free	22	25.0 ± 5.2	40.9	Adiponectin	Age, sex	Luminex xMAP	Serum	5
Chang et al. (2019)	62	35.9 ± 12.7	38.7	Euthymia	AEs, FGAs, SGAs, Li	62	34.2 ± 12	38.7	Insulin	Age, sex, BMI	NK	Serum	4
Chen et al. (2020)	94	39.6 ± 11.6	29.8	Euthymia	NK	40	38.8 ± 8.87	37.5	Adiponectin, ghrelin, insulin, leptin	Age, sex	RIA (ghrelin, insulin), ELISA (adiponectin, leptin)	Serum	4
Coello et al. (2019)	206	29.5 ± 9.6	38.8	Euthymia, mania, depression	Li, AEs, FGAs, SGAs, ADs, drug-free	109	28 ± 9.3	39.4	Insulin	Age, sex	NK	Plasma	5
Cordas et al. (2015)	33	26.9 ± 5.3	33.3	Depression	Mostly unmedicated	103	26.6 ± 5.2	33.3	Leptin	Age, sex, BMI, educational level, ethnicity	ELISA	Serum	6
da Silva et al. (2017)	31	41.7 ± 11.8	25	Euthymia	APs, MSs, ADs drug-free	33	41 ± 11.9	27	Insulin	Age, sex	ELISA	Serum	4
Dolab et al. (2020)	56	42.9 ± 13.3	64.3	NK	Li, AEs	31	42.2 ± 10.1	51.6	Adiponectin, leptin	Age, sex	ELISA (adiponectin), LDN kit (leptin)	Serum	3
Dolapoglu et al. (2021)	40	49.4 ± 11.2	50	Euthymia	Li, AEs	40	45.8 ± 6.9	50	AgRP	Age, sex	ELISA	Serum	4
Elmslie et al., (2009)	60	42.0 ± 11	18.3	NK	Valproate	60	44.0 ± 12	16.7	Adiponectin, insulin	Age, sex, BMI, ethnicity	RIA	Plasma	3
Fleet-Michaliszyn et al. (2008)	18	41.4 ± 2.1	0	Euthymia	Li, AEs, FGAs, SGAs, ADs	17	40.9 ± 2.3	0	Insulin	Age, sex, BMI, ethnicity	RIA	NK	5
Gergerlioglu et al. (2006)	61	25.1 ± 3.8	50.8	Euthymia	SGAs, MSs	45	24.1 ± 2.8	53.3	Leptin	Age, sex, BMI	ELISA	Serum	4
Guha et al., (2014)	55	43.2 ± 10.6	45.5	Various mood states	Drug-free (>6 months)	25	44.7 ± 9.8	48	Insulin	Age, sex, ethnicity	NK	Pasma	5
Huang et al. (2021)	33	38.2 ± 9.6	33.3	Depression	Medicated	50	35.6 ± 8.8	40.0	Adiponectin, ghrelin, insulin, leptin	Age, esx	RIA	Serum	3
Hung et al. (2007)	15	23.8 ± 2.7	100.0	Depression	Drug-free (>1 week)	14	23.8 ± 2.2	100.0	Adiponectin, insulin	Age, BMI, sex	ELISA	Plasma	5
Juster et al. (2018)	20	52.4 ± 10.8	35	Various mood states	MSs, ADs, APs	202	40.1 ± 11.8	29.2	Insulin	Age, sex	NK	Serum	2
Mansur et al., (2016)	59	43.1 ± 10.2	22	Depression, euthymia	Li, SGAs, FGAs, ADs, AEs	28	38.6 ± 13.6	26.8	Adiponectin, leptin	Age, BMI, sex	ELISA	Plasma	5
Mansur et al., (2019)	190	41.7 ± 10.8	32.1	Various mood states	Li, SGAs, FGAs, ADs, AEs	213	37.9 ± 7.2	29.6	Insulin	Age, sex	NK	Plasma	3
Parlak et al. (2018)	82	35.4 ± 9.1	53.6	Euthymia, mania	Li, AEs, SGAs	30	35.6 ± 9.7	60	AgRP, leptin	Age, sex, BMI, marital status	ELISA	Serum	4
Platzer et al., (2018)	120	42.2 ± 17	52.5	Depression, euthymia	Li, AEs, SGAs, ADs and BZDs	68	36.9 ± 15.6	44.1	Adiponectin	Age, BMI, sex	ELISA	Plasma	4
Platzer et al., (2021)	139	45.3 ± 13.9	53.2	Euthymia	Li, SGAs, FGAs, ADs, AEs	93	38.7 ± 15.4	37.6	Ghrelin, leptin	–	ELISA	Serum	2
Ragson et al., (2010)	103	32 ± 6.7	0	Various mood states	Li, SGAs, ADs, AEs	36	31 ± 7.1	0	Insulin	Age, sex	ELISA	Plasma	5
Rosso et al. (2015)	57	50.2 ± 14.2	31.6	NK	Li, valproate	49	32 ± 5.1	51	Ghrelin, insulin, leptin, resistin	Age, sex, BMI	Luminex × MAP	Serum	4
	25		24	Depression	Li and drug-free	23		56.5	Adiponectin		ELISA	Plasma	5

(*continued on next page*)

Table 1 (*continued*)

Study	Patients with BD					Healthy controls			Hormones	Matching	Assay	Biological material	NOS
	N	Age	% males	Mood state	Medications	N	Age	% males					
Soeiro-de Souza et al., (2015)		28.5 ± 5.7					27.1 ± 6.6			Age, sex, BMI, cigarette smoking			
Su et al., (2011)	10	22.7 ± 2.9	100	Depression	Drug-free (>1 month) except ADs	21	25.0 ± 3.0	100.0	Adiponectin	Age, sex, gender	ELISA	Plasma	4
Syk et al. (2019)	31	21.5 ± 2.3	30.7	Euthymia, depression	Drug-free, MSs, ADs	57	22.7 ± 2.5	22.8	Adiponectin, leptin	Age, sex, BMI	ELISA	Plasma	6
Tsai et al. (2012)	33	31.6 ± 6	63.6	Euthymia, mania (the same patients	Li, SGAs, FGAs, AEs	33	28.9 ± 3.9	63.6	Insulin, leptin	Age, sex	RIA	Plasma	5
Tsai et al. (2014)	32	31.8 ± 8.3	53.1	Euthymia, depression (the same patients)	Li, SGAs, FGAs, AEs	32	31.5 ± 5.2	53.1	Insulin, leptin	Age, sex	RIA	Plasma	5
Tuncel et al. (2017)	30	34.4 ± 10.3	36.7	Euthymia,mania (the same patients)	Li, FGAs, SGAs, valproate	30	35.0 ± 11.3	36.7	Adiponectin, ghrelin, insulin, leptin, resistin	Age, sex	ELISA	Plasma	6
Vargas et al. (2014)	49	NK	35	NK	NK	201	NK	29.2	Insulin	Age	UK	Plasma	3
Vianna-Sulzbach et al. (2015)	34	44.9 ± 14.8	33.8	Euthymia	Medicated	48	46.4 ± 11.2	35.4	Adiponectin	Age, sex, BMI, years of education	ELISA	Serum	4
Wei et al. (2020)	123	28.1 ± 8.6	41.5	NK	MSs, ADs, drug-free	325	29.2 ± 9.9	40.6	Leptin	Age, sex, BMI	Magnetic Luminex Assay	Plasma	6

Abbreviations: ADs – antidepressants, AEs – antiepileptics, AgRP – Agouti-related peptide, APs - antipsychotics, BD – bipolar disorder, BMI – body mass index, BZDs - benzodiazepines, ELISA – enzyme-linked immunosorbent assay FGAs – first-generation antipsychotics, Li – lithium, MSs – mood stabilizers, NK – not known, NOS – the Newcastle-Ottawa Scale, RIA – radioimmunoassay, SGAs – second-generation antipsychotics.

2011). Additionally, subgroup analyses taking into consideration mood states (mania, depression and euthymia) were carried out. Publication bias was tested using the Egger's test for appetite-regulating hormones determined by at least 10 studies (Sterne et al., 2008). Results of statistical analysis were considered significant if the p-value was lower than 0.05. Data analyses were carried out using the IBM SPSS software, version 28.

3. Results

3.1. General characteristics of eligible studies

There were 1914 publication records initially identified through systematic searches (Fig. 1). Finally, 32 studies were included in systematic review and meta-analysis (Barbosa et al., 2012; Bond et al., 2017; Chang et al., 2021; Chen et al., 2021; Coello et al., 2019; Cordas et al., 2015; da Silva et al., 2017; Dolab et al., 2020; Dolapoğlu et al., 2021; Elmslie et al., 2009; Fleet-Michaliszyn et al., 2008; Gergerlioglu et al., 2006; Guha et al., 2014; Huang et al., 2021; Hung et al., 2007; Juster et al., 2018; Mansur et al., 2020, 2016; Parlak et al., 2018; Platzer et al., 2020, 2019; Rasgon et al., 2010; Rosso et al., 2015; Soeiro-de-Souza et al., 2014; Su et al., 2011; Syk et al., 2019; Tsai et al., 2014, 2012; Tunçel et al., 2018; Vargas et al., 2014; Vianna-Sulzbach et al., 2015; Wei et al., 2020). Overview of included studies is shown in Table 1. Altogether, these studies included 1984 individuals with BD and 2170 healthy controls. In the vast majority of studies, individuals with BD and healthy controls were matched for age and sex. The NOS score ranged between 2 and 6 (4.31 ± 1.09). There was a sufficient number of studies to perform meta-analysis for the levels of leptin, adiponectin, insulin, AgRP, resistin and ghrelin (Table 2).

3.2. Leptin

The levels of leptin were determined by 16 studies (Barbosa et al., 2012; Chen et al., 2021; Cordas et al., 2015; Dolab et al., 2020; Gergerlioglu et al., 2006; Huang et al., 2021; Mansur et al., 2016; Parlak et al., 2018; Platzer et al., 2020; Rosso et al., 2015; Syk et al., 2019; Tsai et al., 2014, 2012; Tunçel et al., 2018; Vianna-Sulzbach et al., 2015; Wei et al., 2020). Forrest plot for the analysis of leptin levels is shown in Supplementary Fig. 1. Leptin levels were significantly higher in subjects with BD in pooled analysis ($k = 21$, $g = 0.36$, 95 %CI: 0.14 – 0.58, $p = 0.003$, $I^2 = 79.7\%$) and subgroup analysis of euthymic patients ($k = 10$, $g = 0.35$, 95 %CI: 0.03 – 0.68, $p = 0.036$, $I^2 = 74.2\%$). There were no significant between-group differences in leptin levels in the subgroup analysis of patients with mania ($k = 3$, $g = 0.41$, 95 %CI: −1.08 – 0.89, $p = 0.360$, $I^2 = 82.4\%$) and those with depression ($k = 4$, $g = 0.12$, 95 %CI: −0.95 – 1.19, $p = 0.739$, $I^2 = 88.2\%$). Sensitivity analysis revealed that no single study accounted for high between-study heterogeneity in pooled analysis and subgroup analysis of patients with depression (Supplementary Table 3). However, there were no significant between-group differences in leptin levels in the subgroup analysis of euthymic patients after removing single studies (Barbosa et al., 2012; Mansur et al., 2016; Parlak et al., 2018; Tunçel et al., 2018). Results of the Egger's test revealed no evidence of publication bias (coefficient = 3.097, SE = 2.193, t = 1.412, p = 0.174). Meta-regression analyses (Table 3) showed significant associations of effect size estimates with type of biological material (serum vs. plasma: $k = 21$, $\beta = -0.547$, 95 % CI: −0.88 - −0.22, $p = 0.001$) and the NOS score ($k = 21$, $\beta = 0.174$, 95 %CI: 0.01 – 0.34, $p = 0.040$).

3.3. Adiponectin

The levels of adiponectin were investigated by 14 studies (Barbosa et al., 2012; Bond et al., 2017; Chen et al., 2021; Dolab et al., 2020; Elmslie et al., 2009; Huang et al., 2021; Hung et al., 2007; Mansur et al., 2016; Platzer et al., 2019; Soeiro-de-Souza et al., 2014; Su et al., 2011;

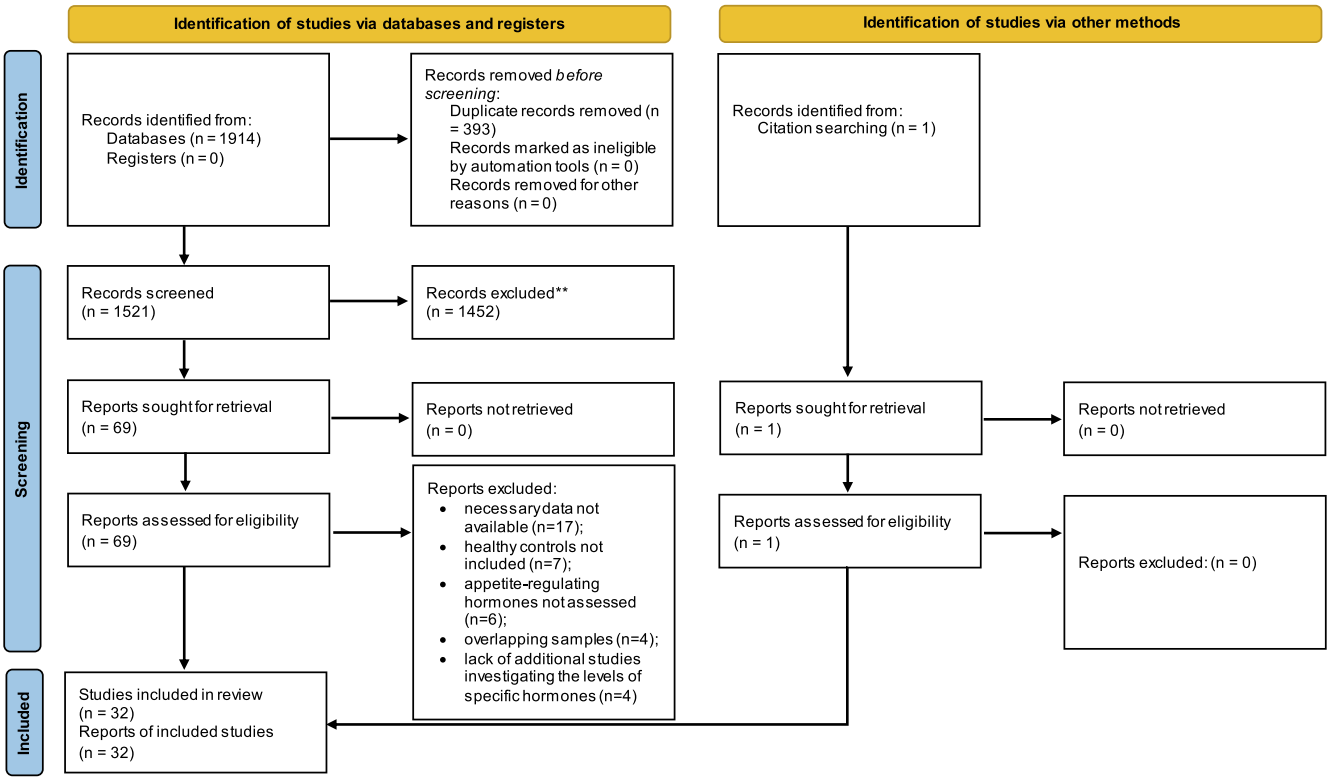

Fig. 1. Search strategy (Page et al., 2021).

Table 2
Summary of main findings.

Hormone	Mood state	k	g	95 %CI	p	I^2
Leptin	Pooled analysis	21	0.36	0.14–0.58	**0.003**	79.7%
	Euthymia	10	0.35	0.03–0.68	**0.036**	74.2%
	Depression	4	0.12	−0.95–1.19	0.739	88.2%
	Mania	3	0.41	−1.08–0.89	0.360	82.4%
Adiponectin	Pooled analysis	17	0.24	−0.49–0.98	0.492	96.8%
	Euthymia	6	1.02	−1.46–3.50	0.340	98.9%
	Depression	6	−0.35	−0.91–0.21	0.172	74.1%
Insulin	Pooled analysis	20	0.39	0.22–0.55	**< 0.001**	67.4%
	Euthymia	7	0.28	0.11–0.46	**0.007**	0%
	Depression	3	0.53	−1.06–2.12	0.287	80.8%
	Mania	2	0.43	−0.01–0.88	0.051	0%
AgRP	Pooled analysis	3	−0.29	−1.48–0.91	0.412	75.9%
	Euthymia	2	−0.01	−0.24–0.22	0.638	0%
Resistin	Pooled analysis	4	0.25	−0.69–1.19	0.465	83.2%
	Euthymia	2	0.16	−3.65–3.96	0.689	63.3%
Ghrelin	Pooled analysis	6	0.22	−0.40–0.84	0.398	88.1%
	Euthymia	3	0.35	−0.93–1.63	0.360	87.0%

Significant differences ($p < 0.05$) were marked with bold characters.
k refers to the number of effect size estimates.

Syk et al., 2019; Tunçel et al., 2018; Vianna-Sulzbach et al., 2015). Forrest plot for the analysis of adiponectin levels is shown in Supplementary Figure 2. There were no significant between-group differences in adiponectin levels in the pooled analysis (k = 17, g = 0.24, 95 %CI: −0.49 – 0.98, p = 0.492, I^2 = 96.8%) as well as the subgroup analyses of depressed (k = 6, g = -0.35, 95 %CI: −0.91 – 0.21, p = 0.172, I^2 = 74.2%) and euthymic patients with BD (k = 6, g = 1.02, 95 %CI: −1.46 – 3.50, p = 0.340, I^2 = 98.9%). The subgroup analysis of adiponectin levels in patients with mania was not performed due to low number of studies. Sensitivity analyses demonstrated that these differences remained not significant after removing any single study (Supplementary Table 3). Removal of the study by Barbosa et al. (2012) reduced heterogeneity to moderate level in the pooled analysis (I^2 = 63.8%) and low level in the subgroup analysis of euthymic patients (I^2 = 48.4%). Results of the Egger's test were significant (coefficient = 8.949, SE = 2.848, t = 3.142, p = 0.007) indicating the possibility of publication bias. Meta-regression analyses demonstrated significant positive correlations of the percentage of individuals with type I BD (k = 7, β = 0.047, 95 %CI: 0.005 – 0.09, p = 0.030) and illness duration (k = 11, β = 0.097, 95 %CI: 0.02 – 0.17, p = 0.012) with effect size estimates of adiponectin levels.

3.4. Insulin

The levels of insulin were measured by 17 studies (Chang et al., 2021; Chen et al., 2021; Coello et al., 2019; da Silva et al., 2017; Elmslie et al., 2009; Fleet-Michaliszyn et al., 2008; Guha et al., 2014; Huang et al., 2021; Hung et al., 2007; Juster et al., 2018; Mansur et al., 2016; Rasgon et al., 2010; Rosso et al., 2015; Tsai et al., 2014, 2012; Tunçel et al., 2018; Vargas et al., 2014). Forrest plot for the analysis of insulin levels is shown in Supplementary Figure 3. The levels of insulin were significantly higher in patients with BD in the pooled analysis (k = 20, g = 0.39, 95 %CI: 0.22 – 0.55, p < 0.001, I^2 = 67.4%) and the subgroup analysis of euthymic patients (k = 7, g = 0.28, 95 %CI: 0.11 – 0.46, p 0.007, I^2 = 0%). No significant between-group differences were found in the subgroup analyses of patients with mania (k = 2, g = 0.43, 95 %CI: −0.01 – 0.88, p = 0.051, I^2 = 0%) and those with depression (k = 3, g = 0.53, 95 %CI: −1.06 – 2.12, p = 0.287, I^2 = 80.8%). Sensitivity analysis demonstrated that these differences remained significant after excluding any single study (Supplementary Table 3). Similarly, between-group differences in the levels of insulin remained not significant after removing any single study from the subgroup analysis of patients with depression. Results of the Egger's test were not significant (coefficient =

Table 3
Results of meta-regression analyses.

Hormone	Moderator	k	β	95 %CI	p	R^2
Leptin	Mean difference in age	21	0.007	−0.04–0.05	0.778	0
	Mean difference in % males	21	−0.015	−0.04–0.01	0.163	0
	Mean difference in % cigarette smokers	7	−0.003	−0.03–0.02	0.806	0
	Mean difference in BMI	21	−0.037	−0.19–0.11	0.626	0
	Serum vs. plasma	21	−0.547	−0.88 - −0.22	**0.001**	0.44
	NOS	21	0.174	0.01–0.34	**0.040**	0.12
	Patients with type I BD (%)	9	0.000	−0.01–0.01	0.994	0
	Illness duration	16	0.027	−0.01–0.06	0.099	0
	HDRS	8	0.010	−0.02–0.04	0.549	0
	YMRS	11	−0.002	−0.02–0.02	0.828	0
Adiponectin	Mean difference in age	17	−0.010	−0.14–0.12	0.877	0
	Mean difference in % males	15	−0.026	−0.06–0	0.881	0
	Mean difference in % cigarette smokers	6	−0.020	−0.04–0	0.075	0.38
	Mean difference in BMI	16	−0.061	−0.28–0.15	0.574	0
	Serum vs. plasma	17	−0.278	−0.99–0.43	0.445	0
	NOS	17	0.071	−0.28–0.42	0.697	0
	Patients with type I BD (%)	7	0.047	0.005–0.09	**0.030**	0
	Illness duration	11	0.097	0.02–0.17	**0.012**	0
	HDRS	6	−0.089	−0.18–0	0.064	0
	YMRS	9	−0.007	−0.07–0.06	0.824	0
Insulin	Mean difference in age	19	−0.002	−0.03–0.03	0.904	0
	Mean difference in % males	20	0.024	0.002–0.047	**0.038**	0.35
	Mean difference in BMI	17	0.050	−0.04–0.14	0.291	0.21
	Serum or plasma	19	−0.145	−0.49–0.20	0.417	0
	NOS	20	0.034	−0.13–0.19	0.683	0
	Patients with type I BD (%)	6	−0.007	−0.004 – 0.02	0.213	0.01
	Illness duration	11	−0.007	−0.05–0.03	0.745	0
	HDRS	6	−0.004	−0.04–0.03	0.815	0
	YMRS	9	0.004	−0.02–0.3	0.754	0

Abbreviations: BD – bipolar disorder, BMI – body mass index, HDRS – the Hamilton Depression Rating Scale, NOS – the Newcastle Ottawa Scale, YMRS – the Young Mania Rating Scale.

0.481, SE = 1.366, t = 0.352, p = 0.729), indicating no evidence of publication bias. Meta-regression analyses showed a significant positive correlation of between-group differences in the percentage of males with effect size estimates for the levels of insulin (k = 20, β = 0.024, 95 %CI: 0.002 – 0.047, p = 0.038).

3.5. AgRP

The levels of AgRP were determined by only two studies (Dolapoğlu et al., 2021; Parlak et al., 2018). Forrest plot for the analysis of AgRP levels is shown in Supplementary Figure 4. There were no significant between-group differences in the levels of AgRP in the pooled analysis (k = 3, −0.29, g = -0.29, 95 %CI: −1.48 – 0.91, p = 0.412, I^2 = 75.9%) and the subgroup analysis of euthymic patients (k = 2, g = -0.01, 95 %CI = -0.24 – 0.22, p = 0.639, I^2 = 0%). Sensitivity analyses revealed that these differences remained not significant after removing any single study (Supplementary Table 3). Due to low number of studies, other analyses were not performed.

3.6. Resistin

The levels of resistin were assessed by three studies (Barbosa et al., 2012; Rosso et al., 2015; Tunçel et al., 2018). Forrest plot for the analysis of resistin levels is shown in Supplementary Figure 5. No significant between-group differences in the levels of resistin in the pooled analysis (k = 4, g = 0.25, 95 %CI: −0.69 – 1.19, p = 0.465, I^2 = 83.2%) and the subgroup analysis of euthymic patients (k = 2, g = 0.16, 95 %CI: −3.65 – 3.96, p = 0.689, I^2 = 63.3%) were found. Sensitivity analyses showed that between-group differences remained not significant after removing any single study. Due to low number of studies, other analyses were not carried out.

3.7. Ghrelin

The levels of ghrelin were determined by five studies (Chen et al., 2021; Huang et al., 2021; Platzer et al., 2020; Rosso et al., 2015; Tunçel et al., 2018). Forrest plot for the analysis of ghrelin levels is shown in Supplementary Figure 6. There were no significant between-group differences in the levels of ghrelin in the pooled analysis (k = 6, g = 0.22, 95 %CI: −0.40 – 0.84, p = 0.398, I^2 = 88.1%) and the subgroup analysis of euthymic patients (k = 3, g = 0.35, 95 %CI: −0.93 – 1.63, p = 0.360, I^2 = 87.0%). Sensitivity analyses demonstrated that these differences were not significant after removing any single study. Due to low number of studies, other analyses were not performed.

4. Discussion

Main findings of the present systematic review and meta-analysis indicate that levels of insulin and leptin, albeit with small effect size estimates, are elevated among people with BD, as compared with healthy controls. As for insulin levels, heterogeneity was moderate in pooled analysis and it might be partially explained by the effect of mood state. Indeed, we found that elevated levels of insulin occur only in subjects with BD during euthymia with no evidence of heterogeneity (I^2 = 0%). Meta-regression analyses revealed larger effects size estimates in studies with greater between-group differences in the number of males between individuals with BD and healthy controls. Similarly, we demonstrated elevated levels of leptin during euthymia, but not in other mood states. However, it should be noted that heterogeneity was large in this subgroup analysis, and after removing single studies in sensitivity analyses, between-group differences in leptin levels appeared to be not significant. Moreover, higher quality of studies was associated with greater effect size estimates. No significant alterations of other appetite-regulating hormones were found in subjects with BD. However; except for adiponectin, there was a low number of studies investigating the levels of AgRP, ghrelin and resistin. Importantly, meta-regression analyses showed that higher adiponectin levels might be associated with a diagnosis of type I BD and longer illness duration. The association of the percentage of patients with specific BD types with effect size estimates of leptin and insulin was not significant. Unfortunately, the majority of studies investigating appetite-regulating hormones did not report the number of patients with BD subtypes that could enable to further

investigate differences between type I and type II of BD.

In case of leptin, there was high between-study heterogeneity, and the difference in its level between euthymic individuals with BD compared to controls was not significant after removing single studies in sensitivity analysis. Meta-regression also demonstrated that higher quality of studies is associated with greater effect size estimates of between-group differences in leptin levels. Leptin is a hormone secreted by adipose tissue cells, that elicits pro-inflammatory activity by increasing the secretion of interleukin-6 and tumor necrosis factor-α (Lee et al., 2014). Physiologically, leptin interacts with its receptors in the arcuate nucleus of the hypothalamus and reduces appetite. According to the adipoinsular axis, leptin decreases insulin synthesis and secretion by pancreatic cells, and increases hepatic metabolism of insulin (Paz-Filho et al., 2012). Furthermore, leptin exerts neuroprotective activity by binding to its receptors located within the cerebral cortex, hippocampus, basal ganglia and cerebellum (Tang, 2008; Venkatasubramanian et al., 2010). Elevated levels of leptin and insulin suggest that individuals with BD might show dysregulation of adipoinsular axis interactions between leptin and insulin signaling (Kieffer and Habener, 2000). In the physiological state, insulin acts as the major adipogenic hormone. With the increasing storage of fatty tissue, rising levels of leptin reduce the secretion of insulin through interactions with the autonomic nervous system and its receptors expressed by pancreatic β-cells. Furthermore, increased level of leptin in euthymic patients may also play protective role by suppressing the hypothalamic–pituitaryadrenal axis activity which is known to be hyperactivated in BD (Belvederi Murri et al., 2016; Roubos et al., 2012). It is also important to note that the type of biological material was significantly associated with effect size estimates for leptin levels. Specifically, effect size estimates were significantly higher in studies that measured leptin levels in plasma samples. In agreement with this observation, plasma samples have been shown most accurate for the measurement of leptin due to high coefficient of variation in serum samples (Gröschl et al., 2000). Previous meta-analysis did not demonstrate significant differences in leptin levels between individuals with BD across various mood states compared to healthy controls, but it included lower number of studies (Fernandes et al., 2016).

Importantly, our findings from previous meta-analysis (Misiak et al., 2019), in which we observed higher levels of adiponectin in euthymic patients with BD, became not significant after including latest research (Chen et al., 2021). However, results of the Egger's test indicated the possibility of publication bias. In agreement with our previous meta-analysis, we found that longer illness duration and greater percentage of individuals with type I BD are associated with higher effect size estimates. Taking into account these findings, adiponectin might be considered as a marker of illness progression. Indeed, staging model of BD suggests exacerbation of oxidative stress, deficiency of neurotrophins and inflammation during illness progression (Kauer-Sant'Anna et al., 2009). It should also noted that adiponectin levels play different roles depending on age, as it has been shown that lower levels of adiponectin in young and healthy adults are associated with higher incidence of cardiovascular diseases (Sattar et al., 2006), while in older adults, higher adiponectin levels might be related to greater risk of stroke and mortality (Kizer et al., 2012). On the other site, in line with the observation of higher adiponectin level in patients with type I BD, it has been found that the levels of pro-inflammatory cytokines are elevated in patients with type I BD compared to those with type II BD (Bai et al., 2014; Wang et al., 2016). The genetic overlap between type I and type II BD, based on genome-wide association studies, has been estimated at approximately 78%, and suggests several shared biological mechanisms contributing to each BD subtype, but also indicates specific neurobiological characteristics underlying BD types (Wendt et al., 2020). A recent large study demonstrated that type I and type II BD differ not only with respect to the course of illness and psychopathological manifestation, but also with respect to BMI and rates of nutritional, endocrine and metabolic diseases that might be higher in patients with type I BD (Karanti et al., 2020). Transcriptomic studies have also shown differences in the underlying neurobiology of BD with respect to its types that might be of importance to our findings. For instance, it has been reported that down-regulation of type 1 diabetes mellitus pathway appears in type II BD, but not in type I BD (Dmitrzak-Weglarz et al., 2021). Emerging evidence also suggests differences in gut microbiota composition with greater abundance of *Collinsella* in type II BD in comparison with type I BD (McIntyre et al., 2019). Higher abundance of *Collinsella* has also been associated with greater insulin resistance (Gomez-Arango et al., 2018). Additionally, eating disorders might be significantly more prevalent in patients with type II BD compared to those with type I BD (Fornaro et al., 2021). Moreover, a recent systematic review with network meta-analysis has shown differences in response to treatment between type I and type II BD (Bahji et al., 2021). The choice of treatment may further influence differences in adiponectin levels as antidepressive medications influence appetite and weight gain.

Specific mechanisms underlying altered levels of insulin in euthymic individuals with BD, but not in those at other mood states, remain unclear. First, it cannot be ruled out that euthymic state simply reflects greater exposure to medications used in the treatment of BD. Indeed, there is evidence that various medications, including mood stabilizers, antipsychotics and antidepressants contribute to weight gain with its metabolic consequences (Mazereel et al., 2020). Second, our findings should be considered in light of various types of insulin feedback loop dysregulations. Indeed, two relevant glucose homeostasis dysregulations have been found: insulin resistance characterized by elevated insulin levels as well as glucotoxicity manifesting in increased fasting glucose and reduced insulin secretion (Lindmark et al., 2006). There are studies showing that glucotoxicity, but not insulin resistance, is associated with worse cognitive performance (Geijselaers et al., 2017). Moreover, preclinical studies have demonstrated that insulin resistance, especially among overweight or obese patients, might be a physiological reaction against metabolic stress through mitochondrial superoxide balance (Hoehn et al., 2009; Nolan et al., 2015). Interestingly, the study by Mansur et al. (2020), included in our meta-analysis, found that increased BMI is associated with better cognitive performance and lower self-reported anhedonia in insulin-resistant patients with BD. In our meta-analysis, effect size estimates of differences in insulin levels were not moderated by BMI; however, in studies included in the present meta-analysis, individuals with BD and healthy controls were matched for BMI. The hypothesis of "protective" role of insulin resistance might explain as to why we found elevated levels of insulin in euthymic patients but not in those during other mood states. It is also important to notice that elevated levels of insulin may not reflect insulin resistance. Indeed, there is evidence that insulin exerts neurotrophic and neuroprotective activities (Blázquez et al., 2014; Gray et al., 2014). Notably, results of meta-regression analysis suggest the existence of sex differences with respect to insulin alterations in patients with BD. Specifically, we found that higher effect size estimates for between-group differences in the levels of insulin in studies with higher number of males among patients with BD. Epidemiological studies have demonstrated that the prevalence of diabetes is significantly higher in men (Chen et al., 2012). There is evidence that males are more prone to develop visceral obesity compared to females (Nordström et al., 2016). Studies also show that women present higher insulin and incretin responses as well as greater capacities for insulin secretion compared to men, likely due to protective effects of estrogens (Tramunt et al., 2020). This observation might be of particular relevance to our findings that are based on studies with relatively young individuals with BD considering menopausal age (mean age across studies: 36.45 years).

There are several limitations of this meta-analysis that need to be considered. First, sample size of most studies was relatively small and non-representative. Considering their cross-sectional design, causal associations cannot be established. In this regard, it cannot also be established what is the clinical relevance of altered adiponectin levels with respect to BD types. Additionally, there was a limited number of

studies reporting the levels of appetite-regulating hormones in individuals during mania as well as studies investigating the levels of AgRP, resistin and ghrelin that were found to be eligible. Nevertheless, the severity of manic symptoms was not associated with effect size estimates in meta-regression analyses of studies that measured the levels of insulin, adiponectin and leptin. Another point is that heterogeneity was high for most of analyses and factors explaining this observation were not fully identified. It should also be noted that the analysis of adiponectin levels might be characterized by publication bias. Finally, we were not able to investigate the effects of potential confounding factors related to the use of various medications, dietary habits, physical activity, substance use and comorbid physical health impairments (e.g., diabetes and cardiovascular disease).

In sum, the present meta-analysis implies that individuals with BD, especially those during euthymia, might show elevated levels of insulin and leptin. However, additional studies, especially those including patients with mania, are still needed to understand dynamics of appetite regulation across various mood states. Future studies also need to adopt longitudinal designs in order to unravel causal associations. Moreover, future studies exploring appetite-regulating hormones with respect to BD types, could further contribute to their differentiation irrespective of euthymic, manic or depressive phase. Nevertheless, the present findings might be informative for clinical practice and raise awareness of higher diabetes risk in BD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Authors are deeply grateful to the following authors of eligible studies for providing necessary data to perform this systematic review and meta-analysis: Klara Coello (University of Copenhagen, Copenhagen, Denmark), Frederike Fellendorf (Medical University Graz, Graz, Austria), Clarissa S. Gama (Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil), Robert-Paul Juster (University of Montreal, Montreal, Canada), Rodrigo B. Mansur (Universidade Federal de São Paulo, São Paulo, Brazil and University of Toronto, Toronto, Canada) and Mikaela Syk (Uppsala University, Uppsala, Sweden). This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2022.101013.

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