Biomarkers in cerebrospinal fluid of patients with bipolar disorder versus healthy individuals: A systematic review

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ABSTRACT

Background: The pathophysiological processes of bipolar disorder (BD) may be detectable by the use of cerebrospinal fluid (CSF) biomarkers. Biomarkers for BD may in time assist with diagnosis, prediction of disease course, or identification of response outcome to treatments. Explorative biomarkers have been proposed in many studies but no CSF biomarkers are integrated into routine clinical practice.

Aim: We aimed for the first time to review studies of CSF biomarkers in patients with BD compared to healthy control individuals (HC). We investigated the effect of diagnosis, age, gender, clinical state, medication, technical characteristics of tests, fasting state and, cognitive function if applicable.

Method: We did a systematic review according to the PRISMA Statement based on comprehensive database searches for studies on cerebrospinal biomarkers in patients with bipolar disorder versus HC. Risk of bias was systematically assessed.

Results: The search strategy identified X studies of which thirty-four fulfilled the inclusion criteria. A total of 117 unique biomarkers were investigated. Forty biomarkers showed statistically significant differences between BD and HC. Eleven biomarkers were evaluated in more than one study. Only the findings of elevated homovanillic acid and 5-hydroxy-indoleacetic acid were replicated across studies. Most studies had a cross sectional design and were influenced by risk of bias mainly due to small sample size, lack of data on mood state at the time of the CSF puncture and not considering potential confounders including age, gender, diagnoses, BMI, life style factors such as smoking, and psychotropic medication.

Conclusion: Specific monoamine CSF biomarkers may be related to the pathophysiology of BD. Future studies must aim at increasing the level of evidence by validating the positive findings in prospective studies with stringent methodology.

Keywords: Cerebrospinal fluid, bipolar disorder, biomarker, systematic review.

INTRODUCTION

Since 1957 when Arvid Carlsson demonstrated that dopamine was a neurotransmitter in the brain (1,2) levels of neurotransmitter precursor and metabolites have been measured in cerebrospinal fluid (CSF) to access central neurochemical function. The pathophysiological processes of several psychiatric disorders may be detectable in CSF. Biomarkers in psychiatric disorders may assist with diagnosis, prediction of disease course, or identification of response outcome to treatments. CSF biomarkers have been proposed in many studies but no CSF biomarkers are integrated into routine clinical practice. Although CSF biomarkers have been investigated in mania and bipolar disorder for more than half century, surprisingly, no exhaustive systematic review has ever been published on CSF biomarkers in BD.

Objectives

We aimed to systematically review studies of CSF biomarkers in patients with bipolar disorder (BD) versus healthy control individuals (HC). Further, we investigated the effect of age, gender, clinical state, medication, technical characteristics of tests, fasting state and, cognitive function if applicable. Finally, risk of bias was systematically assessed.

METHODS

Protocol

A protocol describing methods for the review was prepared and approved by all authors prior to the study. The review is reported according to the PRISMA Statement (3).

Eligibility criteria

Eligible for review were original studies published in English reporting on levels of biological CSF markers in patients ≥ 18 years with diagnosis of BD compared to HC. Studies were excluded if: 1) the groups of patients with BD or the HC group comprised of less than ten 10 individuals, 2) biomarkers were assessed post-mortem, 3) patients had mixed diagnoses and data regarding patients with BD could not be extracted separately, or 4) the smaller study, when more than one publication reported results regarding identical parameters from the same study population.

Search

Studies were identified by conducting a literature search in MEDLINE and PubMed (January 1950 to August 2017) and EMBASE (1974 – August 2017) limits; English language and human, using the following search terms both as keywords and as text words: Cerebrospinal fluid AND bipolar disorder. In addition reference lists of relevant studies were searched by hand.

Study selection and data collection process

Study titles and abstracts identified by the initial search were screened by UK. Subsequent retrieval of full text articles or other additional information, assessment for eligibility and data extraction was performed independently by two researchers; UK and AHS. Disagreements were resolved by discussion with LVK.

The association between cognitive function in BD and various CSF markers has been sporadically investigated (4-7), but these data were not included in this review.

Data items

A data sheet was constructed and the following data was extracted: Study identification, age, gender, duration of illness, BD subtype, symptom severity, duration of current affective state, medication use, smoking, alcohol use, BMI, exercise or physical activity, biomarker concentration in CSF, measurement method, blinding of analysts, time of day and fasting state at lumbar puncture. In comparisons between BD patients and HC, baseline data for BD patients were used from longitudinal studies.

Risk of bias in individual studies

Tools for assessing quality in observational epidemiological studies has been given less attention compared to tools assessing quality in clinical trials (8). We evaluated five domains as put forward by Sanderson et al. (8): 1) Methods for selecting study participants by appropriate source population and inclusion or exclusion criteria, 2) Methods for measuring exposure and outcome variables by appropriate measurements for both exposure(s) and/or outcome(s), 3) Design-specific source of bias (excluding confounding) by appropriate methods outlined to deal with any design-specific issues such as recall bias, interviewer bias, biased loss to follow up or blinding, 4) Methods to control

confounding by appropriate design and/or analytical methods, 5) Statistical methods (excluding confounding) by appropriate use of statistics for primary analysis of effect.

RESULTS

Study selection

Figure 1 presents an overview of the study selection. The electronic database search in PubMed identified 407 titles. Reviews, meta-analyses, editorials or letters were removed after screening of titles and abstracts (n=41). Full text assessments of the remaining 366 papers lead to the exclusion of 332 papers. An additional search in EMBASE supplemented by hand searches (n=3) (9-11) yielded no further titles to be included. In summary, 34 studies published from 1968-2017 were included in the qualitative synthesis.

Cerebrospinal fluid biomarkers

A total of 117 unique biomarkers were investigated in the included studies, see Table 1. The biomarkers could be categorized into six groups: Monoamine biomarkers (5,12-18), inflammatory biomarkers (19-25), hormone biomarkers (13,26-31), neuropeptide biomarkers (4,13-15,18,19,24,29,32-41), metabolomics markers (42), and other biomarkers (29,43).

Overall, statistically significant differences (P<0.05) between BD and HC were found for 40 biomarkers and of these eleven biomarkers were evaluated in more than one study. The results were replicated regarding increased homovanillic acid (HVA) (5,12,17,18) and increased 5-hydroxy-indoleacetic acid (5-HIAA) (12,18), and both increased and decreased levels were found between BC and HC regarding, 3-methoxy-4-hydroxy-phenylglycol (MHPG) (12,18) and neural cell adhesion molecule (N-CAM) (19,25). No statistically significant differences were found between BD and HC regarding the remaining 77 biomarkers (Table 1).

Monoamines

Seven monoamine biomarkers were investigated in a total of eight studies including a total of 249 patients with BD and 315 HC (5,12-18) (participants overlap in Sellgren (5) et al and Pålsson et al. (18)). Increased levels were replicated regarding 5-HIAA (12,18) and HVA (5,12,17,18). These studies were characterized by high numbers of participants (17,18) and subgroup analyses revealed

higher concentrations of the biomarker among patients of female gender with mania (12) and a history of psychosis (5,18).

Divergent results were found regarding MHPG, since an older study found increased MHPG (12), whereas a recent large study found decreased levels of MHPG (18).

No statistically significant differences between the BD and HC groups were found in four studies regarding 5-HIAA (13-15,17) and in three studies regarding HVA and MHPG (13-15). In a recent study, kynurenic acid (KYNA) was increased in a BD subgroup with a history of psychosis (5), but the finding has not yet been replicated.

Overall, data were conflicting due to smaller studies with no clear information regarding age and gender distributions in the samples (13-15). One study (17) had a HC group significantly younger than the BD group.

Inflammation

A total of twelve CSF inflammatory biomarkers were investigated in seven studies including a total of 237 patients with BD and 268 HC (19-25). Among inflammatory biomarkers only N-CAM was investigated more than once. Thus, N-CAM levels were increased in a small older study with uneven gender distribution (19) and decreased in a large, recent, age and gender-matched study (25). Highly statistically significant differences were found, but not replicated regarding interleukin (IL)1β, IL6 (21), IL8 (22), monocytes chemoattractant protein 1 (23) and, chittinase-3-like protein 1 (23).

No differences between BD and HC were found regarding levels of gamma-globulin (20), variable alternative sliced exon immune-reactive protein (N-CAM VASE) (24), IgG (19), soluble cluster of differentiation 14 (23), and tissue inhibitor of metallo-protease-1 and 2 (23).

Hormones

A total of 14 hormone biomarkers were investigated in seven studies including a total of 113 patients with BD and 124 HC (13,26-31). Statistically significant differences between BD and HC were found in three smaller studies regarding cortisol (26), melatonin (28), pregnenolone (31), however none of the results were replicated.

None of the remaining biomarkers differentiated the BD from the HC groups: Adreno-corticotrophin (ACTH) (14), alfa-melanocytes stimulating hormone (14), atrial natriuretic factor (14), calcitonin (14), corticotrophin releasing factor (CRF) (14), growth hormone (27), norepinephrine (14) progesterone (31), thyrotropin-releasing hormone (30), tyrosine (13) and vasopressin (14).

Neuropeptides

The results regarding a line of 41 neuropeptide biomarkers were reported in 25 studies including a total of 340 patients with BD and 408 HC (4,13-15,18,19,24,29,32-41).Within the group of neuropeptides statistically significant differences between BD and HC were shown regarding cholecystokinin (CCK) and somatostatin. Thus, CCK was investigated in two older and small studies; one study showed decreased levels of CCK (39) and the other study with no information on age and gender distributions, showed no statistically significant differences between the BD and HC groups (38). Somatostatin was investigated in three smaller, older studies with no information on age and gender. Decreased levels of somatostatin in BD were found in one study (40) and no statistically significant differences between BD and HC were found in two other studies (14,38). Amyloidβ-42 (Aβ-42) was decreased in a small study of late-life BD versus HC (4). Furthermore, in a large study on younger BD and HC (age range 27-50) no statistically significant differences were found regarding Aβ-42 (32). A replication of no statistically significant differences between BD and HC was found regarding β-endorphin (14,34), GABA (13-15), and total CSF protein (19,24). Recent studies have suggested differences between BD and HC regarding amyloid precursor protein α (32), Aβ42/Aβ40 ratio (32), Aβ42/Aβ38 ratio (32), Aβ42/T-tau (4), Aβ 40/P-tau protein (P-tau) ratio (4), glutamine (41), neurofilament light chain (NF-L) (35), secretogranin-II (SgII) (33), and CSF/serum albumin ratio (37). The results remain to be replicated.

Metabolomics

A recent study of a panel of metabolomics biomarkers in 54 BD males versus 40 HC males (42) found thirteen statistically significantly altered biomarkers: Uric acid, fructose 6-phosphate, ribose 5-phosphate, CoA, 2-oxoisovaleric acid, lactic acid, pyruvic acid, citric acid, isocitric acid, *cis*-aconitic acid, urea, alanine, and tryptophan. After multivariate logistic regression with adjustments for BMI only CSF isocitric acid levels were statistically significantly higher in BD versus HC.

Other

A highly statistically significant difference between ten patients with BD and ten HC was found for sorbitol, but not for glucose (43). The results have not yet been replicated. Results regarding magnesium did not differentiate between 130 patients with BD and 59 HC.

Risk of bias

The following study characteristics were identified to have an effect on the results in one or more studies: 1) study design, 2) sample size of study participants, 3) diagnosis, 4) symptoms, 5) inclusion and exclusion criteria, 6) age, 7) gender, 8) height and weight, 9) medication, 10) smoking, and 11) ethnicity/genetic, 12) statistics, and regarding the biomarkers 13) pre-analytical factors, 14) methods for biomarker analyses.

1) Study design.

The patients were selected from both inpatient (29,30,36,38) and outpatient wards (36). A possible effect of hospitalization was rejected by Koslow et al. (12). The included studies were all cross sectional case-control studies. Some authors included follow-up data of subsets of the BD participants in order to reveal effects of medication (17,27,29-31). Berrettini et al. made an attempt to assess the stability of GHRH over time by repeating CSF GHRH in 11 of 37 HC after a time span of 3 weeks to two years and found a statistically significant correlation between the first and the second lumbar puncture (27). No other studies reported longitudinal follow-up of the HC group. Thus, no evidence regarding stability of the biomarkers was given among HC or BD in repeated measures in a larger sample.

2) Sample size.

The size of the study samples ranged from 10 to139 patients with bipolar disorder and 10 to113 healthy control individuals. A majority of the studies were small (<30 BD), though contrasted by the larger cohorts from the St Göran Bipolar Project including 139 patients with BD and 113 HC (5,18,21-23,32,35,41,42), the studies by George et al. including 76 patients with BD and 59 HC (29,31), and further the recent study by Hidese et al. including 57 patients with BD and 111 HC (25). Small studies increase the risk of both type 1 and 2 errors. Lack of power may specifically have contributed to no statistically significant differences found in the studies of HVA (13-15), dihydroxy-phenyl-acetic acid (DOPAC) (14) and dopamine sulfate (DPS) (14).

3) Diagnosis.

In case control studies it is obviously important that the segregation of the groups is strict in order to avoid systematic errors. Diagnosis of bipolar disorder was thorough across the studies: DSM III (19,24,30), DSM IV (4,5,15,18,21-25,28,30,32,33,35,37,41,42), specified by Research Diagnostic Criteria (44) (13,16,26,29-31,34,36,38,40,43). Besides information on BD, demographical information, other clinical parameters as duration of illness, duration of current affective state, smoking have been reported in newer studies and may influence findings.

The healthy control groups were often not described in ways that permit its replication. A line of authors reported that HC were retrieved by newspaper advertisement (12,15,25,29,31), among colleges at hospitals (5,17,20,21), or via national registers (5,18,21-23,32,35,41,42). The selection of healthy control individuals for studies of BD is important, since BD often presents with minor psychiatric disorders prior to the onset of the first hypomania or mania. Thus, a healthy control group that includes participants with past minor depressive episodes, isolated episodes of panic disorder, eating disorders, or obsessive compulsive disorder that had remitted spontaneously or with psychotherapy counseling (32) may be problematic and lead to overlooking CSF markers as the HC group may present with deviations in CSF markers similar to those in BD groups.

4) Mood episodes, symptoms and subtypes of BD.

BD patients presented with all types of mood episodes in the included studies. Thus, data could be extracted from the papers regarding patients grouped as mania (12,13,16,17,20,26,34,38,40) or as bipolar depressed (15,39,40). Regarding MHPG Koslow et al. found statistically significant differences between patients with mania and HC, but they found no changes between BD as a group and HC (12). One could suggest that CSF biomarkers differ during mania and depression, but data did not support this. A line of studies investigated patients with either BD type I or type II (5,19,21-24,28,29,31-33,35,37,41,42) and different results for the two subtypes were found regarding CSF Neural cell adhesion molecule (N-CAM) levels (19) and secretogranin-II (33). A number of studies did not specify the subtype of BD (14,27,28,30,36,43), and the St. Göran cohort included a small number of patients with other affective diagnoses including cyclothymia and schizo-affective disorder (5).

When patients are examined in the euthymic state, CSF markers may reflect trait markers (45,46), however the definition of euthymia differs across studies. The St. Göran cohort included patients

with BD in a euthymic state defined as a scores below 14 on both Montgomery-Åsberg Depression Rating Scale and Young Mania Rating Scale (33) at the date of spinal tap. Berrettini et al. included patients that were euthymic by history and clinical observation for a minimum of four weeks prior to study (36). Mann et al recruited a group of patients with BD being currently euthymic during the previous month, as assessed by a maximum score of 7 in the 21-item Hamilton Rating Scale for Depression (HAMD), and a maximum score of 4 in the Young Mania Rating Scale (15).

Regarding monoamines, subgroup analyses of clinical features of the BD revealed that the severity of the disorder (or a factor related to severity) may be important to consider, as the most extreme biomarker levels were found among participants with BD type I (5,12). The effect of specific symptoms was explored by Berettini et al, who found no differences between small subgroups with (n=6) and without (n=20) a history of suicidality in relation to CSF DOPAC, DPS, HVA, MHPG, ACTH, α-melanocyt stimulating hormone, atrial natriuretic factor, calcitonin, CRF, norepinephrine, vasopressin, β-endorphine, β-lipoprotein, calmodulin, GABA, n-terminal fragment of propiomelatonocortin, and neurotensin (14). Furthermore, psychotic features differentiated participants from those with no psychotic features in various CSF markers including HVA (5) and KYNA (18). An effect of diagnostic subtype was shown for SG-II (33), thus higher levels were found regarding BD type I compared with to BD type II. George et al. found no correlation between magnesium levels and severity of depression or mania, on the day of the lumbar puncture (29). In a longitudinal study of nine patients Rubinow et al. showed a statistically significantly lower CSF somatostatin level (P< 0.02) during depressed states compared to those in manic or improved states (40). Finally, the sAPP-α and β concentrations were negatively associated with co-morbid anxiety (32). In conclusion symptoms may affect a CSF biomarker.

5) Inclusion and exclusion criteria.

Recent studies clearly reported criteria regarding BD participants, whereas older studies were not that clear, which complicates replication of the results.

6) Age.

Most studies attempted age- and gender matching between BD and HC. However, as can be seen from Table 1, it was not always possible to extract the precise data. Participants´ ages ranged from below 20 years (17) to 81 years (4). Examples of effects of age were seen, e.g., a statistically significant effect of postmenopausal status in women was shown on CSF MHPG, whereas no effect

of age was found in men (12). Furthermore, CSF magnesium did not change as a function of age (29). The Aβ42/Aβ38 was negatively associated with age as found by Jakobsson et al. (32). Thus, age may affect a CSF biomarker.

7) Gender.

Participants were of both genders in all but two papers that included men only (21,42). In a line of studies no precise information on gender could be extracted from the papers (5,12-15,17,19,20,28,30,35,36,38-41). George et al. found that CSF pregnenolone was non-significantly lower in all women. No differences were found in CSF progesterone or neuropeptide diazepam binding inhibitor (DBI) (31). Koslow et al. found decreased HVA in five females with mania compared to 32 female HC (12). George et al reported levels of CSF magnesium were significantly higher in men than in women (p < 0.05) (29). Frye et al. (30) found a gender difference (female lower), P<0.05) regarding CSF thyrotropin-releasing hormone (TRH). The sAPP-α and β concentrations were positively associated with male gender in BD (32). Thus, gender may affect a CSF biomarker.

8) Height and weight.

The sAPP-α and β concentrations were negatively associated with BMI in BD (32) and BD tended to have higher BMI than HC (32). Berretini et al. found a statistically significant effect of bodyweight regarding CSF GHRF (27). Palsson et al. found statistically significant effects of height and BMI on CSF glutamate markers (41). Thus, height and weight may affect a CSF biomarker.

9) Medication.

In a total of 15 studies the patients with BD were drug free at the time of the lumbar puncture (12-16,24,26,27,29,31,34,36,38-40) and statistically significant differences were found regarding cortisol (26), pregnonolone (31) and, somatostatin (40). In the remaining 19 studies the patients received medication at the time of the lumbar puncture (4,5,17-23,25,28,30,32,33,35,37,41-43).

Regarding *lithium* Berrettini et al. found that lithium treatment was associated with increased CSF 5-HIAA (P=0.05) (47) and no association was seen with GABA (48). Results from the St Gøran study showed that in patients with BD CSF IL8 (22), glutamine and D-serine levels were positively associated with lithium treatment (41). Berrettini et al. found no effect of lithium on GHRF levels in 13 patients with BD who provided both a CSF sample on lithium, and a second CSF sample, after a

minimum of two weeks off lithium (27). Further, no statistically significant differences were found in CSF serum/ albumin ratio (37) or CSF magnesium concentrations (29) regarding lithium among patients with BD.

Regarding *antipsychotics* Zetterberg et al. found statistically significant differences regarding CSF/serum albumin ratio between BD on antipsychotics compared to BD on other treatments (37). Isgren et al. reported that increased CSF IL8 in BD was positively associated with antipsychotic treatment (22).

As for *anticonvultants* Palsson et al. found that CSF glutamine and D-serine levels were positively associated with valproate and furthermore, CSF L-serine was associated with lamotrigine (41). Frye el al. (30) obtained a second lumbar puncture after six weeks of a blinded study with carbamazepine (n=15 BD patients), lamotrigine (n=10 BD patients), and no significant changes were found on TRH. There were no statistically significant differences in CSF/serum albumin ratio regarding anticonvulsants (37). George et al. found no association with carbamazepine (n = 32 BD patients) and CSF magnesium concentrations (29).

Regarding other types of medication, Sjöström et al. (17) did a second lumbar puncture (LP) 7-10 days after the first LP to test the effect of probenecid and methylperidol versus treatment as usual in an experimental trial. In HC, 5-HIAA increased by 60% (P<0.01) and HVA by 200% (P<0.02) after probenecid, and a further effect was found regarding 5-HIAA, but not regarding HVA by the addition of methylperidol. The increases after probenecid were lower in the BD group, 20% regarding HVA and 73% regarding 5-HIAA, Frye el al. (30) found no change in CSF TRH obtained after six weeks on nimodipine (n=16), gabapentin (n=10), venlafaxine (n=13), or bupropion (n=13). There were no statistically significant differences in CSF/serum albumin ratio regarding anxiolytics, and antidepressants (37). The sAPP-α and β concentrations were negatively associated with the use of benzodiazepines and positively associated with the use of mirtazapine (32). Regenold et al. found no association with medication on sorbitol (43).

In order to combine data regarding medicated patients Hidese et al. converted daily doses of antipsychotics to chlorpromazine-equivalent doses and those of antidepressants were converted to imipramine-equivalent doses according to a published guideline for Japanese (25,49). Hidese et al. found no statistically significant differences in N-CAM between drug free and medicated patients with BD (25).

Furthermore, the studies included in this review did not allow an analysis of potential confounding by indication. Patients with BD type I may more often be treated with lithium, divalproate and antipsychotics whereas lamotrigine and antidepressants will be used more extensively in patients with BD type II (50). Poltorak et al. reported that three samples were available from a single patient before and after electroconvulsive therapy (ECT). The CSF concentrations of total N-CAM were decreased by 40% after a course of 16 bilateral treatments (19). In conclusion, ECT and medication may influence levels of a CSF biomarker.

10) Smoking.

Smoking is often more common in patients groups than among HC (e.g. Jakobsson et al. (33)) and smoking status has previously been associated with CSF biomarker levels of amino acids in CSF (51). However, Pålsson et al. found that adding smoking as a co-variate did not explain observed differences between BD and HC for glutamate markers (41). Thus, smoking may affect a CSF biomarker.

11) Ethnicity/genetics.

Data in this review derived from studies conducted in USA (National Institute of Health hospitals) (12-16,19,24,26,27,29-31,34,36,38,40,43), Brazil (4), Japan (25), Belgium (39), Germany (28) and Sweden (5,17,18,20-23,32,33,35,37,41,42). Regenold et al. found that concentrations of sorbitol did not differ significantly when all subject were grouped by race, i.e. African-American versus white (43). However, it is not clear how ethnicity may influence results as no clear pattern appears across these study groups. Further, potential effects of some genetic variations have been investigated. A statistically significant association was found between the risk allele in rs1006737 SNP and a decreased CSF P tau/T tau ratio in BD, thus linking variation in the *CACNA1C*, encoding the alpha 1C subunit of the L-type voltage-gated calcium channel (52). To elucidate the genetic variability underlying individual levels of CSF KYNA in BD, Sellgren et al. conducted a genome-wide association study against CSF KYNA and found one SNP (rs 10158645 at 1p21.39) that reached genome-wide statistical significance (5). Due to heritability of BD a family history of BD and schizophrenia was used in a line of studies, e.g. (41).

12) Statistics.

Three projects reported extensively on different markers obtained in the same participants described in different papers: Berrettini et al. studies (14,27,36), National Institute of Mental Health - Clinical Research Branch studies (12,19,24,40,53), and St. Göran Bipolar Project (5,18,21-23,32,35,41,42). Thus, there is an increased risk of chance findings due to multiple testings (i.e., a type 1 error). Thus, Palsson et al. found that the mean concentration of glutamine (adjusted for age, sex, BMI and height) was significantly higher in BD than in HC (P=0.0026). However, this difference did not survive correcting for multiple testing (18). Highly statistically significant findings (P<0.001) were found in other studies regarding increased HVA (5), 5-HIAA (18), IL-1β (21), IL-8 (22), Aβ-42/T-tau ratio (4), NF-L (35), isocitric acid (42), and decreased somatostatin (40), decreased IL-6, (21), melatonin (28) suggesting that these were not chance findings. However, highly statistically significant findings regarding MHPG were pointing in different directions. Thus, levels of MHPG in BD versus HC were increased in one study (12) and decreased (18) in another.

13) Pre-analytical sampling and storage of CSF.

Most studies report that the biomarkers were collected in the morning under standardized conditions, such as fasting, lateral decubitus or sitting position, storage of CSF at minus 70-80 degrees and authors provided a precise description of the methods used to handle the CSF. Regarding CSF GHRF Berretini et al. (27) found no evidence of a rostro-caudal gradient as proposed by Gjerris et al. (54). Few studies gave information of the type of containers used for sampling and storage, e.g. polypropylene tubes (4,14,42) or low protein absorption tubes (25), types of needles (25), and whether blood contaminated CSF samples were included (17,18,43). Authors reported blinding of readers of the cerebrospinal fluid marker and the diagnosis of the participants in five studies, only (12,13,29,34,37). In most studies it was unclear if the CSF was collected at the same time the diagnosis was given. Bipolar patients may have rapid changes from euthymia to depression or hypomania or mania, thus information regarding the timespan between assessment of the diagnosis and the collection of CSF is important as CSF markers may vary with affective states. Furthermore, it is unclear in most studies whether data collection was planned prospectively or retrospectively. Finally, no authors gave information on the frequency of side effects following lumbar puncture in the research setting. A precise description of the methods is important when attempts are made to replicate findings.

14) Analytics.

Multiple different methods have been used to analyze biomarkers in the included studies of this review: Protein clusters (55), metabolomics (42), radio-immuno assays (26,27,30,31,33,34,36,39,40), radio receptor assays (RIA) (34), enzyme-linked immunosorbent assays (23,25,28,35), various immune assays (4,5,21,22,32,37,38), high performance liquid chromatography (HPLC) (5,16,31,41), gas chromatographic (GC) mass spectrometric (12,43), Western blots (19). As mentioned previously, increased concentrations of HVA was found in BD compared with HC in three studies. The results were in concert even though they used different methods: Sjøstrøm et al. used a fluorometric method (17), Koslow et al. used a modification of the GC - mass spectrometric procedures by Fri et al and Swahn et al. (12), and Pålsson et Sellgren et al. used HPLC with electrochemical detection (5,18). Berrettini et al. and Mann et al. also used HPLC, but their results regarding HVA did not separate BD from HC (14,15).

Increased concentrations of 5-HIAA were found between BD and HC in two studies that used different analytical methods, thus Koslow et al. used a modification of the GC - mass spectrometric procedures by Fri et al and Swahn et al. (12), and Pålsson et al. used HPLC with electrochemical detection (18). Berrettini et al. (14) and Mann et al. (15)also used HPLC, and their results regarding HIAA, did not separate BD from HC (14).

MHPG results where not in concert eventhough HPLC was used by four groups (12-15). Divergent statistically significant results were provided regarding Neural cell adhesion molecule (N-CAM), which was analysed with the use of Western blots by Poltorak et al. (19), and with an ELISA technique by Hidese et al. (25).

Aβ42, P-tau and T-tau protein (Innobia Alz/Bio3 kits) (4,32), somatostatin (RIA) (14,38,40), were analyzed by similar techniques, but the results were divergent.

No statistically significant differences were found regarding GABA in three studies using different techniques including Ion-exchange flurometric measurements (13), HPLC (14), and GC- mass spectrometric (15). Furthermore, β-endorphines were analyzed with RIA in two studies (14,34), and both studies found no statistically significant differences between BD and HC.

CSF markers in relation to blood-based markers

Lumbar puncture is time consuming and the participants may suffer side effects (e.g. headache). If CSF markers correlate with blood markers it would be an obvious clinical advantage to use blood markers. Data is limited in the included studies, though Jakobsson et al. found no correlation between blood high-sensitivity C-reactive protein and CSF inflammatory markers and stresses the importance of complementing blood analyses with CSF analyses to elucidate brain-specific inflammatory mechanisms (23). Bumb et al. found decreased melatonin in CSF in BD but not in serum (28). For proteins that are highly expressed in extracerebral tissues little correlation of their blood concentration with CSF can be expected. However, some brain-derived proteins, *e.g.*, tau and NFL, can now be measured in blood using ultrasensitive technologies (ref: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4941042/). Plasma/serum and CSF concentrations of NFL correlate (ref: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/26870824/; https://www.ncbi.nlm.nih.gov/pubmed/27071153) and plasma/serum NFL would be highly interesting to examine in the context of BD and medications.

Comparisons to other diagnostic groups

A line of the included studies examined biomarkers across diagnostic groups: Schizophrenia (13,15,16,20,24-26,34,38,39), ADHD (41), major depression (25,28,30,31,38-40,43), confusion (20), neurosis (20), alcoholism (20), psychopathy (20), anorexia nervosa (26,38), mild cognitive impairment/ dementia (4) and Parkinson (39).

DISCUSSION

This review aimed at providing an exhaustive review of the exciting literature regarding cerebrospinal biomarkers in patients with BD versus HC. A total of 34 case-control studies investigated 117 unique biomarkers that could be divided into the following groups: Monoamines, hormones, inflammation, neuropeptides, metabolomics and others. A statistically significant difference between biomarker concentrations in BD and HC were found regarding 40 biomarkers. Increased levels of the monoamines HVA and 5-HIAA were replicated across studies.

A large proportion of the statistically significant differences in CSF biomarkers between BD and HC derived from 19 studies where the patients received medication for BD whereas only three biomarkers showed statistically significant differences between drug free BD and HC. Medication

may influence levels of the biomarker in CSF and it may be a risk of bias along with age, gender, smoking, height, weight, symptoms and diagnoses (BDI/BDII). Further, the stability of biomarkers in BD and HC has not received much attention yet and variation i.e. by season, new episodes and symptom levels are possible risk of bias that could be investigated in longitudinal studies.

When biomarker levels are different between patients with a specific disorder and healthy control individuals in a cross sectional case-control study it is unknown whether the identified biomarker is causing the condition or is a result of the condition, or both. Is the biomarker related to the mood disorder itself or is it a compensatory response to maintain homeostasis with potential therapeutic benefits? These questions can be addressed in longitudinal study designs.

Conclusion

In summary, although cerebrospinal biomarkers in BD versus HC have been investigated during six decades the level of evidence is surprisingly low. The highest level of evidence was reached for the monoamines HVA and 5-HIAA, since data were replicated in different cohorts. Thus, an imbalance of monoamines may relate to the pathology of BD. A total of 77 of the studied CSF biomarkers did not differentiate between BD and HC. Most studies were influenced by risk of bias mainly due to small sample size, lack of data on mood state at the time of lumbar puncture and not considering potential confounders including age, gender, BMI, life style factors such as smoking, and psychotrophic medication.

The available evidence derives largely from case control studies and only some studies supplemented data by follow-up data of subsets of the BD participants that (4,12,15,17,20,27,29-31,34,40,43) revealed effects of medication and electro convulsive therapy. However, at the moment several groups are investigating different cohorts so future larger longitudinal studies with strict methodology will increase the level of evidence towards revealing the pathology of bipolar disorder that may likely implicate multiple biomarkers.

Funding

European Research Councils, Swedish State Support for Clinical Research (ALFGBG),

Frimurarestiftelsen and the Knut and Alice Wallenberg Foundation.

Conflict of interests

Henrik Zetterberg has served at advisory boards of Eli Lilly, Roche Diagnostics, has received travel support from TEVA, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg.

Figure 1: PRISMA Flow Diagram
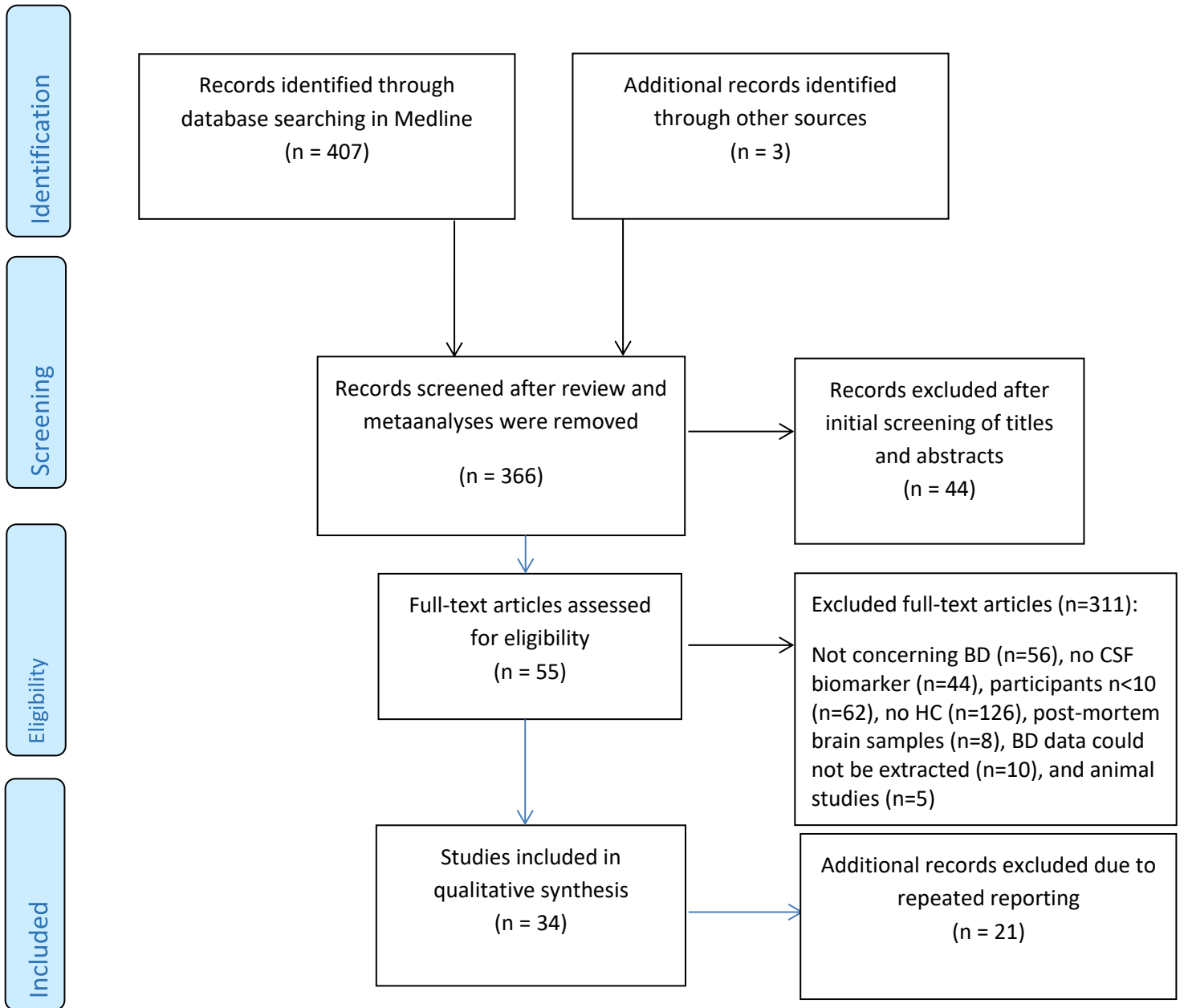
MONOAMINES	Study	Number	Age[a]	Sex (m/f)	Biomarker levels[a]	P value
Dihydroxy-phenyl-acetic acid (DOPAC) pmol/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 2.81±0.91 BD, su: 1.80±0.74 HC: 2.77±1.26	NS
Dopamine sulfate (DPS) pmol/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD,su: 6 HC: 30	NA	NA	BD, nsu: 4.2±2.0 BD, su: 2.4±0.9 HC: 3.4±2.0	NS
Homovanillic acid (HVA) pmol/ml	Sjøstrøm et al. 1972 (17)	Mania: 47 HC: 54	Mania: 21-70[c] HC: < 20 til 30[c]	Mania: 28/19 HC: 35/19	BD: 59±6 (SEM) HC: 34±3 (SEM)	**P< 0.01**
	Koslow et al. 1983 (12)	BD: 38 Mania: 14 HC: 61	BD: 43.6±14.4 HC: Age matched	BD: 23/11 Mania: 9/5 HC: 30/32	BD, males: 182.0±60.5 BD, females: 203.0±69.2 Mania, males: 240.0±88.5 Mania, females:324.0±128.0 HC, males: 220.0±68.2 HC, females: 240.0±81.8	BD/HC: NS Mania female/HC: **P<0.02**
	Sellgren et al. 2015 (5) and Pålsson 2017 (18)	BD: 103 HC: 113	BD: 40±13 HC: 38±13	BD: 43/60 HC: 52/61	BD: 264±112 HC: 206±70	**P< 0.001** Higher HVA was associated with a history of psychosis
ng/ml	Gerner et al. 1984 (13)	Mania: 13 HC: 37	Mania: 34 HC: 31	Mania: 10/4 HC: 18/20	Mania: 38.0±5.0 HC:28.6±2.5	NS
	Berrettini et al. 1986 (14)	BD nsu: 20 BD su: 6 HC: 30	NA	NA	BD, nsu: 204±87 BD, su: 176±94 HC: 176±57	NS
	Mann et al. 2014 (15)	BD: 37 HC: 38	BD: NA HC: 34.8±13.3	BD: NA HC: 22/16	NA	NS
5-Hydroxy-indole-acetic acid (5-HIAA) pmol/ml	Sjøstrøm et al. 1972 (17)	Mania: 47 HC: 54	Mania: 21-70[c] HC: < 20 til 30[c]	Mania: 28/19 HC: 35/19	BD: 34±2 (SEM) HC: 29±1 (SEM)	NS
	Koslow et al.	BD: 45	BD: 43.6±14.4	BD: 23/12	BD males: 107.0±34.7	Mania/HC:

	1983 (12)	Mania: 14 HC: 58	HC: Age matched	Mania: 9/5 HC: 29/29	BD females: 122.0±31.4 Mania, males: 118.0±43.6 Mania, females: 161.0±41.2 HC, males: 108.0±22.5 HC, females 114.3±37.1	**P<0.02** Mania, females/HC: P<0.01 Mania, males/HC: NS
ng/ml	Gerner et al. 1984 (13)	Mania: 13 HC: 37	Mania: 34 HC: 31	Mania: NA HC: NA	Mania: 22.8±2.9 HC: 22.2±1.8	NS
	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 98±31 BD, su: 105±49 HC: 72.3±21.3	NS
	Mann et al. 2014 (15)	BD: 37 HC: 38	BD: NA HC: 34.8±13.3	BD: NA HC: 22/16	BD: NA HC: NA	NS
	Pålsson 2017 (18)	BD: 103 HC: 113	BD: 40±13 HC: 38±13	BD: 43/60 HC: 52/61	BD: 116±42 HC: 98±31	**P< 0.001**
Indole-3-acetic Acid (IAA) ng/ml	Anderson et al. 1984 (16)	Mania: 10 HC: 36	Mania: 30.7±9.7 HC: 31.1±11.3	Mania: 7/3 HC: 7/19	Mania: 4.32±0.63 HC: 4.39±0.37	NS
Kynurenic acid (KYNA) nM	Sellgren et al. 2015 (5)	BD, no psychosis: 40 BD, psychosis: 36 HC: 46	NA	NA	BD no psychosis: 1.72± 0.12[d] BD psychosis: 2.08±0.18[d] HC: 1.6±0.10[d]	BD no psychosis/ HC: NS BD psychosis/ HC: **P<0.05**
3-Methoxy-4-hydroxy-phenylglycol (MHPG) pmol/ml	Berrettini et al. 1986 (14)	BD nsu: 20 BD su: 6 HC: 30	NA	NA	BD nsu: 51.9±27.0 BD su: 42.7±6.1 HC: 44.7±7.6	NS
	Koslow et al. 1983 (12)	BD: 38 Mania: 14 HC: 61	BD: 43.6±14.4 HC: Age matched	BD: 23/11 Manic: 9/5 HC: 30/31	BD: 46.2±11.2 Mania: 59.9±19.6 HC: 43.3±8.4	Mania/HC: **P<0.0001** BD/HC: NS
	Gerner et al. 1984 (13)	Mania: 14 HC: 34	Mania: 34 HC: 31	Mania: 10/4 HC: NA	Mania: 45.9±2.1 HC: 42.0±2.1	NS
	Mann et al. 2014 (15)	BD: 37 HC: 38	BD: NA HC: 34.8±13.3	BD: NA HC: 22/16	NA	NS
	Pålsson 2017 (18)	BD: 103 HC: 113	BD: 40±13 HC: 38±13	BD: 43/60 HC: 52/61	BD: 38±8 HC: 42±7	**P< 0.001**

HC: Healthy control, Nsu: No suicidality, Su: Suicidality, NS: Non statistically significant, NA: Not applicable, Hosp: Hospitalized, Not-hosp: Not hospitalized

a-: Median ± SD, b: Median (interquartile range), c: Range, d: Standard error of the mean

INFLAMMATION	Study	Number	Age[a]	Sex (m/f)	Biomarker levels[b]	P value
Interleukin-1β (IL-1β) pg/mL	Søderlund et al. 2011 (21)	BD I: 15 BD II: 15 HC: 30	BD: 43,2±13,5 HC: 25.4±7.2	BD: 30/0 HC: 30/0	BD: 4,2±0,5[d] HC: 0,8±0,04[d]	**P<0.001**
Interleukin 6 (IL-6) pg/ml	Søderlund et al. 2011 (21)	BD I: 15 BD II: 15 HC: 30	BD: 43,2±13,5 HC: 25.4±7.2	BD: 30/0 HC: 30/0	BD: 1,5±0.2[d] HC: 2.6±0.2[d]	**P<0.001**
Interleukin 8 (IL-8) pg/mL	Isgren et al. 2015 (22)	BD I: 65 BD II: 46 BD other: 10 HC: 71	BD: 36.0 (28.0-50.0)[b] HC: 32.0 (27.0-43.0)[b]	BD: 47/74 HC: 26/45	BD: 33.1 (27.2-41.4) HC: 27.9 (24.4-35.5)	**P<0.001**
Gamma-globulin	Dencker et al. 1968 (20)	Mania: 11 HC: 20	Mania: 35-44[e] HC: 27	Mania: NA HC:12/8	Electrophoresis Apar gel: Mania: 5/11 HC: 0/20 Immunoelectrophoresis: Mania: 2/11 HC: 0/20	NA
Variable alternative sliced exon immune-reactive protein (N-CAM VASE)	Vawter et al. 2000 (24)	BD I: 7 BD II: 9 HC: 37	BD I: 43.1±5.0[d] BD II: 33.4±3.0[d] HC: 33.4±1.9[d]	BD I: 3/4 BD II: 6/3 HC: 24/13	No difference between BD/HC	NS
Neural cell Adhesion molecule (N-CAM) ng/ml	Poltorak el al. 1996 (19)	BD I: 16 BD II: 12 HC: 13	BD I: 39.40±10.11 BD II: 35.55±10.92 HC: 30.85±9.07	BD I: NA BD II: NA HC: 10/3	BD I: 175±25 BD II: 150±30 HC: 125±15	BDI/HC: **P<0.05** BDII/HC: NS
	Hidese et al. 2017 (25)	BD: 57 HC: 111	BD: 43.1±11.6 HC: 42.5±15.4	BD: 30/27 HC: 64/47	BD: 215±82.9 HC: 247.2±78.5	**P=0.039**

Biomarker	Reference	Sample size	Age	Sex	Value	P-value
Monocyte Chemoattractant protein 1 (MCP-1) pg/ml	Jakobsson et al. 2015 (23)	BD I: 62 BD II: 43 BD NOS: 20 HC: 71	BD: 36 (28-50)[b] HC: 34 (27-46)[b]	BD: 50/75 HC: NA	BD: 493 (417-602) HC: 440 (377-521)	**P=0.004**
Chitinase-3-like protein 1 (YKL-40) ng/ml	Jakobsson et al. 2015 (23)	BD I: 62 BD II: 43 BD NOS: 20 HC: 87	BD: 36 (28-50) HC: 34 (27-46)	BD: 50/75 HC: 39/48	BD: 80.0 (55.9-107.7) HC: 440 (377-521)	**P=0.014**
IgG	Poltorak el al. 1996 (19)	BD I: 16 BD II: 12 HC: 13	BD I: 39.40±10.11 BD II: 35.55±10.92 HC: 30.85±9.07	BD I: NA BD II: NA HC: 10/3	NA	P > 0.9
Soluble cluster of differentiation 14 (sCD14) ng/ml	Jakobsson et al. 2015 (23)	BD I: 62 BD II: 43 BD NOS: 20 HC: 87	BD: 36 (28-50) HC: 34 (27-46)	BD: 50/75 HC: 39/48	BD: 49.5 (33.5-69.6) HC: 43.3 (29.0-55.4)	P=0.19
Tissue inhibitor of metallo-Proteinase-1 (TIMP-1) ng/ml	Jakobsson et al. 2015 (23)	BD I: 62 BD II: 43 BD NOS: 20 HC: 87	BD: 36 (28-50)[b] HC: 34 (27-46)[b]	BD: 50/75 HC: 39/48	BD: 33.9 (27.8-39.7) HC: 32.0 (28.4-36.8)	P=0.19
Tissue inhibitors of metallo-proteinase-2 (TIMP-2) ng/ml	Jakobsson et al. 2015 (23)	BD I: 62 BD II: 43 BD NOS: 20 HC: 87	BD: 36 (28-50)[b] HC: 34 (27-46)[b]	BD: 50/75 HC: 39/48	BD: 65.6 (56.1-76.0) HC: 60.9 (51.5-74.3)	P=0.13

HC: Healthy control, BD: Bipolar disorder patients, Nsu: No suicidality, Su: Suicidality, NS: Non significant, NA: Not applicable.

[a]: Median ± SD, [b]: Median (interquartile range), [c]: Range, [d]: Standard error of the mean.

HORMONES	Study	Number	Age[a]	Sex (m/f)	Biomarker levels[a]	P value
Adreno-Corticotropin (ACTH) pg/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 20.7±5.7 BD, su: 24.3±5.8 HC: 22.8±5.8	NS
Alfa- melanocyte Stimulating hormone (α-MSH) pg/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 22.2±1.9 BD, su: 21.5±4.7 HC: 22.1±2.6	NS
Atrial natriuretic factor (ANF) pg/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 15.4±5.7 BD, su: 22.0±3.9 HC: 15.1±2.9	NS
Calcitonin pg/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 77.3±17.2 BD, su: 79.1±14.2 HC: 77.6±17.2	NS
Corticotropin releasing factor (CRF) pg/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 30.2±11.3 BD, su: 28.2±21.3 HC: 33.0±11.9	NS
Cortisol ng/ml	Gerner et al. 1983 (26)	Mania: 10 HC: 22	NA	NA	Mania: 8.5±0.6[d] HC: 6.62±0.42	Mania/HC: **P<0.05**
Growth hormone releasing factor (GHRF) pg/ml	Berrettini et al. 1987 (27)	BD: 34 HC: 30	BD: 36±10 HC: 32±13	BD: 10/14 HC: 20/17	BD, no Li+: 23.12±7.8 BD, Li+: 23.6±6.9 HC: 23.4±7.2	NS
Melatonin pg/ml	Bumb et al. 2016 (28)	BD: 24 HC: 13	NA	NA	BD: 8.5±2.9 HC: 10.6±7.5	**P<0.001**
Norepinephrine (NE) pmol/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 0.52±0.29 BD, su: 0.46±0.23 HC: 0.40±0.19	NS
Pregnenolone ng/ml	George et al. 1994 (31)	BD I: 11 BD II: 11	BD I: 38.9±9.9 BD II: 43.4±8.9	BD I: 4/7 BD II: 5/6	BD I: 0.16 BD II: 0.27	**P<0.01**

		HC: 10	HC: 25.3±4.8	HC: 5/5	HC: 0.35	
Progesterone ng/ml	George et al. 1994 (31)	BD I: 11 BD II: 11 HC: 10	BD I: 38.9±9.9 BD II: 43.4±8.9 HC: 25.3±4.8	BD I: 4/7 BD II: 5/6 HC: 5/5	BD I: NA BD II: NA HC: NA	NS
Thyrotropin-releasing hormone (TRH) pg/ml	Frye et al. 1999 (30)	BD: 28 HC: 34	BD: NA HC: 32.5±10	BD: 11/17 HC: 22/12	BD: 3.70 HC: 3.61	NS
Tyrosine ng/ml	Gerner et al. 1984 (13)	Mania: 13 HC: 37	Mania: 34 HC: 31	NA	Mania: 1678±104 HC: 1830±90	NS
Vasopressin pg/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, nu: 6 HC: 30	NA	NA	BD, nsu: 4.5±0.9 BD, su: 5.0±1.2 HC: 4.0±1.0	NS

HC: Healthy control, BD: Bipolar disorder, Nsu: No suicidality, Su: Suicidality, NS: Non significant, NA: Not applicable.

[a]: Median ± SD, [d]: Standard error

Biomarker	Study	Number	Age [b]	Sex (m/f)	Biomarker levels[a]	P value
NEUROPEPTIDES						
Amyloid βI-42 (AβI-42) pg/ml	Jakobsson et al. 2013 (32)	BD: 139 HC: 71	BD: 36 (28-50) HC: 32 (27-43)	BD: 55/84 HC: 26/45	BD: 257±58 HC: 255±54	P=0.453
Amyloidβ 38 (Aβ-38) pg/ml	Jakobsson et al. 2013 (32)	BD: 139 HC: 71	BD: 36 (28-50) HC: 32 (27-43)	BD: 55/84 HC: 26/45	BD: 1203±488 HC: 1254±463	P=0.557
Amyloidβ 40 (Aβ-40) pg/ml	Jakobsson et al. 2013 (32)	BD: 139 HC: 71	BD: 36 (28-50) HC: 32 (27-43)	BD: 55/84 HC: 26/45	BD: 7848±2301 HC: 8280±2712	P=0.402
Amyloidβ 42 (Aβ-42) pg/ml	Jakobsson et al. 2013 (32)	BD: 139 HC: 71	BD: 36 (28-50) HC: 32 (27-43)	BD: 55/84 HC: 26/45	BD: 935±373 HC: 920±336	P=0.607
	Forlenza et al. 2016 (4)	BD: 16 HC: 25	BD: 70.5±4.9[a] HC: 72.0±4.4[a]	BD: 4/12 HC: 5/20	BD: 384.7±141.3 HC: 464.4±154.1	**P=0.007**
Amyloid Precursor Protein-α (APP-α) ng/ml	Jakobsson et al. 2013 (32)	BD: 139 HC: 71	BD: 36 (28-50) HC: 32 (27-43)	BD: 55/84 HC: 26/45	BD: 732±323 HC: 864±279	**P=0.004**
Amyloid Precursor Proteinβ (APP-β) ng/ml	Jakobsson et al. 2013 (32)	BD: 139 HC: 71	BD: 36 (28-50) HC: 32 (27-43)	BD: 55/84 HC: 26/45	BD: 308±170 HC: 356±152	P=0.056
Amyloidβ 42/ Amyloidβ 40 (Aβ-42/ Aβ-40)	Jakobsson et al. 2013 (32)	BD: 139 HC: 71	BD: 36 (28-50) HC: 32 (27-43)	BD: 55/84 HC: 26/45	BD: 0.117±0.020 HC: 0.111±0.017	**P=0.029**
Amyloidβ 42/ Amyloidβ 38 (Aβ-42/ Aβ-38)	Jakobsson et al. 2013 (32)	BD: 139 HC: 71	BD: 36 (28-50) HC: 32 (27-43)	BD: 55/84 HC: 26/45	BD: 0.789±0.109 HC: 0.741±0.097	**P=0.002**
Amyloidβ 42/ T-tau pg/ml	Forlenza et al. 2016 (4)	BD: 16 HC: 25	BD: 70.5±4.9[a] HC: 72.0±4.4[a]	BD: 4/12 HC: 5/20	BD: 14.0±7.7 HC: 5.5±3.1	**P<0.0001**
Amyloidβ 42/ P-tau pg/ml	Forlenza et al. 2016 (4)	BD: 16 HC: 25	BD: 70.5±4.9[a] HC: 72.0±4.4[a]	BD: 4/12 HC: 5/20	BD: 35.9±25.2 HC: 39.5±15.4	**P=0.002**
Bombesin fmol/ml	Gerner et al. 1982 (38)	Mania: 10 HC: 29	NA	NA	Mania: 32 HC: 35	NS
Cholecystokinin (CCK) fmol/ml	Gerner et al. 1982 (38)	Mania: 10 HC: 29	NA	NA	Mania: 9.5±1.5 HC: 10±1.5	NS

pmol/l	Verbanck et al. 1984 (39)	BD depr.: 12 HC: 51	BD: NA HC: 52	BD: NA HC: 29/22	BD: 2.8±0.6 HC: 5.4±0.8	**P<0.05**
Cromogranin II (GgB) nmol/l	Jakobsson et al. 2013 (33)	BD I: 76 BD II: 50 HC: 71	BD: 34 (28-50) HC: 32 (27-43)	BD: 49/77 HC: 26/45	BD I: 19 BD II: 20 HC: 20	BDI/HC: P=0.07 BDII/ HC: P=0.95
Diazepam binding inhibitor	George et al. 1994 (31)	BD I: 11 BD II: 11 HC: 10	BD I: 38.9±9.9[a] BD II: 43.4±8.9[a] HC: 25.3±4.8[a]	BD I: 4/7 BD II: 5/6 HC: 5/5	BD I: NA BD II: NA HC: NA	NS
B-endorphin (BE) pmol/l	Naber et al. 1981 (34)	Mania: 12 HC: 33	Mania: 34±13[a] HC: 31±13[a]	Mania: 3/9 HC: 21/12	Mania: 58±27 HC: 59±39	NS
	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu 37.0±5.8 BD, su: 41.3±12.6 HC: 40.2±6.9	NS
Beta-lipoprotein (B-LPH) pg/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 82.9±23.9 BD, su: 61.8±8.3 HC: 73.1±20.1	NS
Calmodulin pg/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 28.4±20.4 BD, su: 21.7±18.6 HC: 29.5±15.9	NS
Gamma amino butyric acid (GABA) pmol/ml	Gerner et al. 1984 (13)	Mania: 12 HC: 36	Mania: 34[a] HC: 31[a]	NA	Mania: 171±12.4 HC: 190±5.2	NS
	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 135±23 BD, su: 113±46 HC: 127±44	NS
	Mann et al. 2014 (15)	BD: 37 HC: 38	BD: NA HC: 34.8±13.3[a]	BD: NA HC: 22/16	BD: 18.7±12.3 HC: 17.4±7.6	P>0.05
Glutamate µM	Palsson et al. 2015 (41)	BD: 132 HC: 87	BD all: 26 (28-48) HC: 35 (27-45)	NA	BD: 0.75±0.38 HC: 0.68±0.19	P=0.15
Glutamine µM	Palsson et al. 2015 (41)	BD: 132 HC: 87	BD all: 26 (28-48) HC: 35 (27-45)	NA	BD: 516±82.5 HC: 499±65.6	**P<0.026**
Glycine µM	Palsson et al. 2015 (41)	BD: 132 HC: 87	BD all: 26 (28-48) HC: 35 (27-45)	NA	BD: 8.2±4.4 HC: 7.6±3.5	P=0.36
Heart-type fatty	Jakobsson et al.	BD: 133	BD: 35 (28-50)	BD: 52/81	BD: 453±17	P=0.11

acid binding protein (H-FABP) pg/ml	2014 (35)	HC: 86	HC: 35 (28-46)	HC: 39/47	HC: 409±21	
Myelin basic protein (MBP) pg/ml	Jakobsson et al. 2014 (35)	BD: 133 HC: 86	BD: 35 (28-50) HC: 35 (28-46)	BD: 52/81 HC: 39/47	BD: 553±15 HC: 508±19	P=0.068
Neurofilament light chain (NF-L) pg/ml	Jakobsson et al. 2014 (35)	BD: 133 HC: 71	BD: 35 (28-50) HC: NA	BD: 52/81 HC: NA	BD: 480±25 HC: 359±34	**P=0.001**
Neuropeptid Y (NPY) pg/ml	Berrettini et al. 1986 (14)	BD, ns: 20 BD, s: 6 HC: 30	NA	NA	BD, ns: 101±24 BD, s: 96±36 HC: 103±21	NS
N-terminal fragment of proopio-melatonocortin (N-POMC) pg/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 372±169 BD, su: 561±266 HC: 436±184	NS
Neurotensin pg/ml	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 65.0±5.6 BD, su: 65.8±11.9 HC: 65.2±6.8	NS
Opioid activity activity pmol/ml	Naber et al. 1981 (34)	Mania: 13 HC: 41	Mania: 34±13[a] HC: 31±13[a]	Mania: 3/10 HC: 27/14	Mania: 4±4 HC: 4±4	NS
Secretogranin-II (SgII) nmol/l	Jakobsson et al. 2013 (33)	BD I: 76 BD II: 50 HC: 71	BD: 34 (28-50) HC: 32 (27-43)	BD: 49/77 HC: 26/45	BD I: 1.8 BD II: 1.9 HC: 1.9	BDI/ HC: **P=0.031** BDII/ HC: P=0.57
S100B pg/ml	Jakobsson et al. 2014 (35)	BD: 133 HC: 86	BD: 35 (28-50) HC: 35 (28-46)	BD: 52/81 HC: 39/47	BD: 873±19 HC: 850±23	P=0.452
D-serine µM	Palsson et al. 2015 (41)	BD: 132 HC: 87	BD all: 26 (28-48) HC: 35 (27-45)	NA	BD: 1.84±0.42 HC: 1.77±0.38	P=0.42
L-serine µM	Palsson et al. 2015 (41)	BD: 132 HC: 87	BD all: 26 (28-48) HC: 35 (27-45)	NA	BD: 24.6±0.38 HC: 24.6±5.2	P=0.81
Somatostatin pg/ml	Rubinow et al. 1983 (40)	BD, depr.: 18 HC: 39	NA	NA	BD, depr.: 39 HC: 62.8±6.38	**P<0.001**

fmol/ml	Gerner et al. 1982 (38)	Mania: 10 HC: 29	NA	NA	Mania: 17±3 HC: 15±1.5	NS
	Berrettini et al. 1986 (14)	BD, nsu: 20 BD, su: 6 HC: 30	NA	NA	BD, nsu: 33.7±14.8 BD, su: 26.3±19.3 HC: 32.5±15.8	NS
Substance P pg/ml	Berrettini et al. 1985 (36)	BD: 24 HC: 21	NA	NA	BD: 13.47±4.99 HC: 17.12±5.56	NS
Total-tau protein (T-tau) pg/ml	Jakobsson et al. 2013 (32)	BD: 139 HC: 71	BD: 36 (28-50) HC: 32 (27-43)	BD: 55/84 HC: 26/45	BD: 35±14[d] HC: 36±14[d]	P=0.453
	Forlenza et al. 2016 (4)	BD: 16 HC: 25	BD: 70.5±4.9[a] HC: 72.0±4.4[a]	BD: 4/12 HC: 5/20	BD: 90.4±67.2 HC: 83.3±51.5	**P=0.002**
Phosphorylated tau protein (P-tau) pg/ml	Jakobsson et al. 2013 (32)	BD: 139 HC: 71	BD: 36 (28-50) HC: 32 (27-43)	BD: 55/84 HC: 26/45	BD: 27±7 HC: 28±7	P=0.371
	Forlenza et al. 2016 (4)	BD: 16 HC: 25	BD: 70.5±4.9[a] HC: 72.0±4.4[a]	BD: 4/12 HC: 5/20	BD: 35.9±25.2 HC: 39.5±15.4	**P=0.002**
Tryptophan ng/ml	Gerner et al. 1984 (13)	Mania: 13 HC: 37	Mania: 34[a] HC: 31[a]	NA	Mania: 364±17.2 HC: 392±14.5	NS
Vasoactive intestinal peptide (VIP) pg/ml	Berrettini et al. 1986 (14)	BD -SA: 20 BD +SA: 6 HC: 30	NA	NA	BD, nsu: 15.2±5.7 BD, su: 17.6±7.3 HC: 18.0±7.4	NS
Albumin	Poltorak et al. 1996 (19)	BD I: 16 BD II: 12 HC: 13	BD I: 39.40±10.11[a] BD II: 35.55±10.92[a] HC: 30.85±9.07[a]	BD I: NA BD II: NA HC: 10/3	NA	P<0.2
CSF/serum albumin ratio	Zetterberg et al. 2014 (37)	BD: 134 HC: 86	BD: 36 (28-50) HC: 34 (28-46)	BD: 54/80 HC: 38/48	BD, no antipsychotics: 5.4±0.2 BD, antipsychotics: 7.5±0.37 HC: 4.97±0.22	**P<0.004**
Protein (total) mg/dL	Vawter et al. 2000 (24)	BD I: 7 BD II: 9 HC: 37	BD I: 43.1±5.0[d] BD II: 33.4±3.0[d] HC: 33.4±1.9[d]	BD I: 3/4 BD II: 6/3 HC: 24/13	BD I: 29.5±4.2 BD II: 32.0±8.8 HC: 25.2±8.7	P>0.095
	Poltorak el al.	BD I: 16	BD I: 39.40±10.11[a]	BD I: NA	NA	P>0.9

| | 1996 (19) | BD II: 12 | BD II: 35.55±10.92[a] | BD II: NA |
| | | HC: 13 | HC: 30.85±9.07[a] | HC: 10/3 |

HC: Healthy control, Nsu: No suicidality, Su: Suicidality, NS: Non significant, NA: Not applicable.

[a]: Median ± SD, [b]: Median (interquartile range), [d]: Standard error of the mean

OTHER Biomarkers	Study	Number	Age[a]	Sex (m/f)	Biomarker levels[a]	P value
Glucose	Regenold et al. 2000 (43)	BD: 10 HC: 10	BD: 38.7±12.4 HC: 41.1±8.2	BD: 4/6 HC: 6/4	BD: 60.0±7.6 HC: 58.9±4.2	NS
Sorbitol µmoles/l	Regenold et al. 2000 (43)	BD: 10 HC: 10	BD: 38.7±12.4 HC: 41.1±8.2	BD: 4/6 HC: 6/4	BD: 22.9±4.6 HC: 15.6±1.9	**P=0.0002**
Magnesium	George et al. 1994 (29)	BD I: 76 BD II: 54 HC: 59	BD I: 41.4±13.8 BD II: 40±11.9 HC: 30.5±12.5	BD I: 40/36 BD II: 33/21 HC: 22/37	BD I: 1.12±0.01 BD II: 1.12±0.11 HC: 1.13±0.07	NS

HC: Healthy control, Nsu: No suicidality, Su: Suicidality, NS: Non significant, NA: Not applicable, [a]: Median ± SD

Biomarker	Study	Number	Age [b]	Sex (m/f)	Biomarker levels[a]	P value
METABOLOMICS						
cyclic AMP (cAMP) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 39	BD: 41 (32-52) HC: 36 (30-47))	All males	BD: 0.03±8.13E-03 HC: 0.03±7.23E-03	P=0.533
cyclic GMP (cGMP) μM	Yoshimi et al. 2016 (42)	BD: 44 HC: 34	NA	All males	BD: 7.54E-03±3.35E-03 HC:7.15E-03±2.99E-3	P=0.594
Xanthine μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 2.1±0.6 HC: 2.0±0.4	P=0.377
ADP-ribose μM	Yoshimi et al. 2016 (42)	BD: 11 HC: 10	NA	All males	BD: 4.81E-03±8.27E-04 HC: 4.41E-03±3.09E-04	P=0.154
Uric acid μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 29±11 HC: 23±8.9	**P=0.008**
Nicotinamide adenine dinucleaotide phosphate (oxidized form) (NADP+)	Yoshimi et al. 2016 (42)	BD: 14 HC: 11	NA	All males	BD: 0.02±2.24E-03 HC: 0.02±3.33E-03	P=0.978
Fructose 6-phosphate μM	Yoshimi et al. 2016 (42)	BD: 37 HC: 28	NA	All males	BD: 0.1±0.02 HC: 0.1±0.03	**P=0.049**
Acetyl CoA μM	Yoshimi et al. 2016 (42)	BD: 13 HC: 15	NA	All males	BD: 0.01±2.07E-03 HC: 0.01±3.14E-03	P=0.996
Ribose 5-phosphate μM	Yoshimi et al. 2016 (42)	BD: 23 HC: 11	NA	All males	BD: 0.04±0.02 HC: 0.03±07.95E-03	**P=0.013**
Glycerol 3-phosphate μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 3.8±1.2 HC: 3.74±1.1	P=0.619

Phosphocreatine µM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 1±0.4 HC: 0.9±0.3	P=0.135
Xanthosine monophosphate (XMP) µM	Yoshimi et al. 2016 (42)	BD: 11 HC: 10	NA	All males	BD: 0.03±2.78E-03 HC: 0.02±1.38E-03	P=0.210
Adenylosuccinic acid µM	Yoshimi et al. 2016 (42)	BD: 15 HC: 11	NA	All males	BD: 0.03±2.85E-03 HC: 0.03±2.32E-03	P=0.927
2-Oxoisovaleric acid µM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 3.9±0.6 HC: 3.6±0.5	**P=0.021**
Lactic acid µM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 1.601±247 HC: 1.480±171	**P=0.006**
Glycolic acid µM	Yoshimi et al. 2016 (42)	BD: 52 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 8.4±2.2 HC: 8.1±2.8	P=0.467
Pyruvic acid µM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 21±11 HC: 15±6.9	**P=0.002**
Succinic acid µM	Yoshimi et al. 2016 (42)	BD: 53 HC: 38	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 4.0±1.3 HC: 3.6±1.4	P=0.255
Citric acid µM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 227±54 HC: 180±35	**P<0.0001**
Isocitric acid µM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 4.8±1.1 HC: 3.4±0.9	**P<0.0001**
cis-Aconitic acid µM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 1.7±0.5 HC: 1.2±0.4	**P<0.0001**
Urea µM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 4392±968 HC: 5035±999	**P=0.002**
Glycine (Gly) µM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 4.9±2.9 HC: 4.4±1.7	P=0.323
Alanin (Ala) µM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 37±10 HC: 32±9.8	**P=0.033**

γ-Aminobutyric acid (GABA) μM	Yoshimi et al. 2016 (42)	BD: 13 HC: 13	NA	All males	BD: 0.5±0.09 HC: 0.5±0.2	P=0.357
Serine (Ser) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 30±6.9 HC: 31±4.6	P=0.663
Creatinine μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 67±11 HC: 66±12	P=0.590
Valine (Val) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 23±7.5 HC: 22±7.7	P=0.698
Threonine (Thr) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 32±7.9 HC: 32±7.6	P=0.998
Hydroxyproline μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 2.0±0.4 HC: 1.9±0.3	P=0.086
Creatine μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 58±8.2 HC: 57±8.1	P=0.567
Leucine (Leu) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 17±4.6 HC: 16±3.9	P=0.267
Isoleucine (Ile) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 5.3±2.1 HC: 4.6±1.5	P=0.098
Asparagine (Asn) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 7.0±1.1 HC: 6.9±1.3	P=0.555
Ornithine μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 5.6±1.9 HC: 5.2±1.0	P=0.173
Hypoxanthine μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 3.1±0.6 HC: 2.9±0.5	P=0.146
Glutamine (Gln) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 711±66 HC: 692±67	P=0.171
Lysine (Lys) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 36±7.0 HC: 36±6.6	P=0.774
Methionine (Met) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 4.0±1.0 HC: 4.0±1.0	P=0.698

Histidine (His) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 12±1.5 HC: 12±1.5	P=0.494
Phenylalanine (Phe) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 10.0±1.7 HC: 9.6±1.5	P=0.165
Arginine (Arg) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 20±3.3 HC: 20±3.2	P=0.455
Citrulline μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 2.3±0.5 HC: 2.2±.0.4	P=0.150
Tyrosine (Tyr) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 11±2.4 HC: 9.7±2.3	P=0.084
Tryptophan (Trp) μM	Yoshimi et al. 2016 (42)	BD: 54 HC: 40	BD: 41 (32-52) HC: 36 (30-47)	All males	BD: 2.0±0.3 HC: 1.8±0.3	**P=0.035**

[a]: Median ± SD, [b]: Median (interquartile range)

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