Published in final edited form as:

Psychiatry Res. 2017 September ; 255: 52–58. doi:10.1016/j.psychres.2017.05.022.

Peripheral zinc and neopterin concentrations are associated with mood severity in bipolar disorder in a gender-specific manner

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Abstract

Bipolar disorder (BD) is a recurrent, episodic mood disorder for which there are no current diagnostic, prognostic or theranostic biomarkers. Two peripheral markers of the acute phase immune response, zinc and neopterin, are consistently associated with severity of depression in literature. Given gender differences in clinical presentation of BD and in inflammatory processes,

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we aimed to explore the interaction between gender and immune biomarkers to predict mood severity in BD. Participants with DSM IV BD I and II were recruited through the Pennsylvania Psychiatric Institute during an acute mood episode. Healthy controls (HC) were recruited through advertisements. Participants fasted for at least 6 hours when blood was drawn for biomarkers. We found that zinc concentrations were significantly lower in the BD group at baseline ($p<.05$), and there was also a significant interaction between gender and zinc ($p<.05$), associated with depression severity. Also, we found a significant interaction between gender and neopterin, associated with mania severity ($p<.05$). We found that mania severity was associated with neopterin in men, while depression severity was positively associated with zinc in women. Our report bears replication in larger samples and highlights the potential for differences in the underlying pathophysiology between men and women with BD.

Keywords

biological marker; zinc; inflammation; gender; bipolar depression

1. Introduction

Bipolar disorder (BD) is a recurrent, episodic mood disorder with an estimated lifetime prevalence of 3.9% in the U.S. (Kessler et al., 2005). Mood episodes may be experienced in BD as major depressive, manic, hypomanic and mixed episodes (American Psychiatric Association, 2013). BD type I (BD-I) is defined by the lifetime experience of at least one manic episode, and BD type II (BD-II) is defined by the lifetime experience of at least one hypomanic episode and at least one depressive episode (American Psychiatric Association, 2013). Though many pharmacotherapies exist for BD, individuals living with BD still suffer with mood symptoms approximately 50% of the time (Judd et al., 2002). While BD is equally prevalent in men and women, the clinical presentation and co-morbidities can differ. Women with BD have higher rates than men of BD-II, co-morbid anxiety disorders, post-traumatic stress disorder (PTSD) and bulimia (Baldassano et al., 2005, Saunders et al., 2012). The risk for migraine and the impact of co-morbid migraine on poor mood outcome is greater in women with BD (Altshuler et al., 2010; Saunders et al., 2014). Moreover, poor sleep quality affects women with BD more than men with BD by increasing frequency and severity of mood episodes (Gruber et al., 2009, 2011; Saunders et al., 2015). This suggests that gender is an important moderator of symptomatology in BD and may point to differing underlying pathophysiology in men and women with BD.

Zinc is an essential micronutrient and plays multiple roles in the brain, as a signaling element, as a co-factor in enzymatic reactions and as a modulator of the dopaminergic system (Frederickson et al., 2005). In human studies of major depressive disorder (MDD), peripheral zinc concentrations were shown to be significantly lower in groups of men and women with depression compared to healthy controls, and zinc concentration has been inversely correlated to severity of depression in men and women (McLoughlin and Hodge, 1990; Maes et al., 1994; Amani et al., 2010; Siwek et al., 2010). Also, studies in male rodents have shown that dietary zinc deficiency is causally related to depressive-like phenotypes, and zinc supplementation can reverse depressive-like behaviors (Szewczyk et

al., 2002, 2009; Nowak et al., 2003; Cie lik et al., 2007; Mlyniec and Nowak, 2012b). In this way, literature has supported peripheral zinc as having an important role as a biomarker for both men and women in MDD. However, to our knowledge, no studies have directly probed gender differences in the relationship between peripheral zinc and BD.

Zinc concentration in the periphery is reduced in the presence of pro-inflammatory cytokines (Liuzzi et al., 2006). While some inflammatory markers have been found to be associated with mood states in BD and in MDD, the role of inflammation as an inciting, moderating or mediating factor in the development or persistence of mood episodes is unclear. Neopterin is a circulating signaling marker of cellular inflammation produced by activated macrophages, and has been shown to have an association with depression severity (Maes et al., 1994). Also, neopterin negatively correlates with peripheral zinc in men and women with MDD (Maes et al., 1994). Moreover, while there are clear gender differences in autoimmune disease, and gender-based differences in inflammatory activation due to sex hormones (Fish et al., 2008), the role of gender differences in inflammation in mood disorders has not been explored fully.

To address the gaps in knowledge regarding circulating biomarkers of zinc and inflammatory status, we measured the peripheral zinc and neopterin concentrations in symptomatic men and women with BD, in depressed or mixed states, and compared them to healthy control participants. We also examined the relationship between mood severity, zinc, and neopterin as a function of gender in participants with BD.

2. Methods

2.1 Participants

Participants with DSM IV BD I and II (N=27, men=14, women=13; age range=19-55y) were recruited through the Pennsylvania Psychiatric Institute (PPI) in Harrisburg, PA. Healthy control participants (HC, N=31, men=13, women=18; age range=20-58y), with no personal or family history of mood disorders, were recruited through advertisements posted in the Penn State College of Medicine and Penn State Milton S. Hershey Medical Center. Exclusion criteria included inability to consent, pregnancy, intoxication with alcohol or substances of abuse, major endocrinological or rheumatological illness, and use of non-steroidal anti-inflammatory drugs (NSAIDs). The study was approved by the institutional review board (IRB 39364EP) at Penn State Hershey College of Medicine and complied with the Declaration of Helsinki. No research was conducted until consent was obtained from each participant. If a participant was found to be unable to demonstrate adequate insight into illness, they were considered unable to consent.

2.2 Rating scales

The Mini Neuropsychiatric Interview, a DSM-IV TR-based structured interview assessment, was performed at baseline to confirm diagnosis of BD (Sheehan et al., 1998). Interviews were conducted by physicians and trained research assistants. Demographic information was collected from the individual, and clinical information including current medication use, smoking status was collected via self-report. Depressive symptoms were rated with

Hamilton Depression Rating Scale 21 plus atypical items (HDRS-21 + AT: Hamilton, 1960). Manic symptoms were assessed with Young Mania Rating Scale (YMRS: Young et al., 1978). A combination of clinically significant manic and depressed symptoms defined a mixed-manic phenotype (MM). HDRS-21 + AT scores between 0 and 6 indicated no depression, scores between 7 and 17 indicated mild depression, scores between 18 and 24 indicated moderate depression, and scores over 24 indicated severe depression (Zimmerman et al., 2013). YMRS scores below 7 were considered not manic. Scores between 7 and 12 were mild, and above 12 were severe manic phenotypes (Young et al., 1978). Height and weight were measured, and body mass index (BMI) was calculated using the formula: weight (kg) divided by [height (m)] $\times$ [height (m)]. Biological samples were collected as described below.

During the study, participants received naturalistic treatment, and dietary intake was not controlled. After discharge from the hospital or partial hospital program, participants were followed each week by phone and assessed for clinical improvement. A return visit was scheduled with repeat measures of mood and a blood draw when the subject was asymptomatic, or after 3 months had elapsed (regardless of whether or not they had resolved symptoms). Due to irregular contact with some participants, the maximum number of days for follow-up was 187 (the median was 22 days and average was 52 days). Due to unstable housing situations, approximately 50% of the subjects were lost to follow-up (14 out of 27). At the return visit, height and weight were measured, medication use was recorded, and mood was assessed using the HDRS-21 + AT and YMRS.

2.3 Sample collection and biomarker analysis

Blood samples were drawn for serum in vacutainers in the morning between 7:15 and 10:30 AM for the BD group (average time was 8:24 AM), and between 8:00 AM and 2:00 PM for the HC group (average time was 9:19 AM). All participants had been fasting for at least 6 hours at the time of blood draw. After centrifugation for 10 min at 654.03 g, the serum was extracted and stored in plastic tubes at -80° C until used. For zinc analysis, serum samples were digested in nitric acid (1N) for at least 24 hours and Zn²⁺ concentration was assessed using flame atomic absorption spectrometry (AAS) as previously described (Dempsey, et al., 2012). Neopterin was measured by enzyme-linked immunosorbent assay (BRAHMS, Hennigsdorf, Germany) according to the manufacturer's instructions, with a detection limit of 2 nmol/L.

2.4 Statistical analysis

For comparison of zinc concentrations between Healthy Controls (HC) vs Bipolar Subjects (BD), and women vs. men groups, we used a two-way analysis of covariance (ANCOVA) with sex and diagnosis as predictor variables. Body Mass Index (BMI) was significantly different between the BD and HC groups ($t = 3.457$, $p = 0.001$) and was a covariate in the ANCOVA analysis. Multiple linear regression analyses were performed to analyze the predictive power of three main effects, zinc, neopterin and gender, on mood severity. For comparison of two time points, baseline and follow-up, zinc concentrations and mood scales, a paired t-test was used. Categorical variables between BD and HC groups were compared using a χ^2 test. All statistical analyses were performed using SPSS version 22,

IBM SPSS Statistics (IBM Corporation, Armonk, NY, USA) software. A significant effect was documented at $p<.05$.

3. Results

3.1 Demographic and clinical data

Table 1 describes the demographic, clinical and biological data from the sample. Thirty BD subjects were recruited, and 27 had samples available for this analysis (13 women and 14 men). The BD and HC groups did not differ in age, gender, race, or ethnicity. A lesser proportion of the BD group was married and employed. BMI was higher in the BD group than the HC group, and a greater proportion of the BD group smoked cigarettes. The BD group had 78% BD-I, and the treatments being taken at the time of the study are described in Table 1. On average, the BD group was experiencing severe depressive symptoms and moderate manic symptoms at the time of the study. At baseline, there were 8 depressed BD participants, 18 mixed-state BD participants and 1 manic BD participant.

3.2 Peripheral biomarkers in BD and HC

The unadjusted mean zinc concentration ($\pm$ SD) for BD was 94.2 ($\pm$ 15.6) μ g/dL, and in HC it was 106.3 ($\pm$ 17.9) μ g/dL. We found mean zinc to be significantly lower in the BD participants than the HC participants ($p=0.037$) (Table 1, Figure 2). The range of zinc concentrations was greater in the BD participants than the HC subjects (Figure 1). High outliers were defined as any value above the 75th percentile score plus 1.5*interquartile range (IQR). Low outliers were defined as any value below the 25th percentile minus 1.5*IQR. Three outliers were present in the BD participants and were removed because they were not representative of physiological concentrations of zinc. The bounds for acceptable serum zinc concentrations were made based on recommended clinical cutoffs (Hotz et al., 2003). The total number of BD participants after removal of outliers was 24 (11 women and 13 men). One subject was zinc-deficient. There was no statistically significant difference in mean zinc by gender (Figure 2).

The unadjusted mean neopterin concentrations ($\pm$ SD) were 6.2 ($\pm$ 2.5) nM in BD and 5.4 ($\pm$ 1.4) nM in HC. We found no significant difference in neopterin between HC and BD groups (Table 1). We found no significant correlation between neopterin and zinc in our population ($F(3, 20)=.655$, $p=.589$).

3.2 Differential association between zinc, neopterin and mood symptoms by gender

We then assessed for an association between peripheral zinc and neopterin concentrations, and mood symptoms by gender. A multiple linear regression was calculated to determine association between depression severity score and zinc by gender ($F(3, 20)= 2.336$, $p=.1$). The interaction of gender $\times$ zinc was significantly associated with depression severity scores (Figure 2, $t=2.41$, $p<.05$). As illustrated in Figure 3, zinc and depression severity scores were positively associated in women and negatively associated in men.

We then calculated a multiple linear regression to determine the association between mania severity score and neopterin by gender ($F(3,20)=4.583$, $p=.013$). There was a significant

interaction between gender and neopterin associated with mania severity ($t=-2.72$, $p<.05$). As seen in Figure 4, mania severity had a positive association with neopterin concentration in men, but not in women. A multiple linear regression was calculated to determine association between depression severity and neopterin by gender; no significant regression equation was found ($F(3, 20)=1.118$, $p=.365$). Also, a multiple linear regression was calculated to determine association between mania severity and zinc, and no significant equation was found ($F(3,20)=.372$, $p=.774$).

3.3 Follow up zinc and mood state analysis

Twelve BD participants completed the follow-up visit (4 women and 8 men). As seen in Figure 5, peripheral zinc increased between baseline and follow-up ($t=-2.64$, $p=0.02$). At the follow up time point, zinc concentration in the BD group increased to a level exceeding that of zinc in the HC group at baseline.

4. Discussion

Here we have shown that zinc concentrations were lower in a cohort of symptomatic participants with BD than HC, and that zinc increased at follow-up when the BD participants were asymptomatic. Moreover, we have shown for the first time a gender- specific relationship between zinc and depression severity, and neopterin and mania severity.

BD is diagnosed as a syndrome based on clinical symptoms. Evidence supports that there are multiple possible etiological causes for BD (Belmaker, 2004). The search for biomarkers in this field serves several purposes – to investigate etiological hypotheses or to develop as diagnostic, prognostic, or theranostic markers. While low-level inflammation has been associated with MDD and BD, inflammation is a consequence of the immune response that has evolved to protect the organism, and may have evolved sex-specific differences in this system due to differing reproductive needs (Raison and Miller, 2013), and energy demands. Inflammatory markers may not distinguish between diagnoses, but may be used prognostically to either predict an oncoming episode or to predict treatment response. In this study, we investigated associations between neopterin as an inflammatory marker and zinc as a constitutive co-factor in inflammatory response, and mood state in BD. We then asked if the relationship between neopterin, zinc, and mood state differed between men and women because mood phenotype in BD and inflammatory responses differ by gender.

Zinc has the potential to influence mood through its action as a neuromodulator in the brain. Zinc ion interacts with many receptors and transporters in the brain, including those for glutamate, serotonin and dopamine (Richfield et al., 1993; Wu et al., 1997; Schetz et al., 1997, 1999; Hubbard et al., 2000). Also, during periods of oxidative stress, labile zinc can accumulate and act as a potent neurotoxin and contribute to neuronal and glial death (Sensi et al., 2011). Post-mortem studies show increased markers of oxidative stress and inflammation in the brains of people with BD (Kim et al., 2010; Rao et al., 2010). Such observations have contributed to the hypothesis of neuroprogression as part of the underlying pathophysiology of BD, though a connection to zinc has not been made (Berk et al., 2011). There exists a paucity of literature examining how peripheral inflammation and zinc concentrations correspond to labile zinc in the brain, and in turn, how this associates

with mood. Pre-clinical models have begun to probe into these questions and more work in this area is greatly needed.

In the majority of studies examining zinc as marker of depressed mood state in men and women with MDD, lower peripheral zinc concentration has been reliably reproduced. However, the literature is fairly sparse with respect to zinc in symptomatic men and women with BD. Stanley and Wakwe (2002) reported that, in a group of in-and-out patient BD subjects being treated with antipsychotic medication, zinc was reduced in participants with BD compared to healthy controls. However, the authors did not include gender as a component of their analyses. Conversely, González-Estecha et al. (2011) found zinc to be increased in mania in a cohort of men and women with BD. We examined a group of men and women who were hospitalized for BD and many were experiencing both manic and depressive symptoms at the time of the study. We therefore examined mood symptoms quantitatively rather than categorically. We found significantly lower zinc concentrations in BD participants at baseline regardless of gender, and a significant increase in zinc at follow-up that was correlated with a decrease in mood symptoms. The changes in zinc that we observed fit within the context of the current literature.

It has yet to be fully elucidated why peripheral zinc decreases based on mood state in symptomatic BD. Although reduced zinc has been implicated in mood disorders, the underlying biological etiology and implication for the illness remains vague. While decades of literature show that dietary zinc deficiency hinders neurological development and can induce depression (Prasad, 1969), peripheral zinc is not necessarily altered in periods of dietary zinc deficiency, and does not reflect cellular zinc status, due to tight homeostatic control mechanisms (Maret and Sandstead, 2006). Therefore we cannot conclude that our BD cohort was zinc deficient based on this measure alone. However, there is evidence in literature to support other sources contributing to zinc diminishment in BD.

Another underlying factor to consider is inflammation. It is known that markers of inflammation such as pro-inflammatory cytokines are elevated in unipolar depression, bipolar depression and mania (Maes et al., 1994, 1995, 1997a, 1997b; Dickerson et al., 2007; Drexhage et al., 2010a; Rao et al., 2010) and inflammation may resolve in periods of euthymia (Brietzke et al., 2009). Pro-inflammatory cytokines, such as IL-1 β and IL-6, enable the removal of zinc from the periphery as part of the acute phase response (Liuzzi et al., 2005). Also, peripheral zinc levels are negatively correlated with increased concentration of neopterin, IL-6, and CD4/CD8 ratios in MDD (Maes et al., 1994, 1997a, 1997b, 1999). Further, studies looking at post mortem brain tissue (Gawryluk et al., 2011a, 2011b; Shelton et al., 2011) and CSF (Lindqvist et al., 2009; Martinez et al., 2012) have found that markers of inflammation are increased in the brain in MDD.

Although there is ample evidence in the literature to support an inverse relationship between inflammation and peripheral zinc, we did not observe a significant increase in neopterin – a marker of cellular immune system activation – in our men and women with BD. Our result seems to be consistent with prior literature. Hoekstra et al. (2006) measured neopterin in symptomatic and euthymic BD patients and found it to be decreased relative to healthy controls and MDD participants, irrespective of symptomatic status. Also, Reininghaus et al.

(2014) observed that peripheral neopterin was significantly lower in euthymic BD participants compared to healthy controls. A possible explanation for these observations centers on the role of the cytokine IFN- γ , which is required for neopterin release from monocytes/macrophages (Murr et al., 2002). IFN- γ release has been reported to be lower in BD (Barbosa et al., 2014). In this way, perhaps neopterin is not being stimulated for release in our BD group. In the current study we have shown that, while there were no differences in mean neopterin concentration between groups, neopterin was differentially associated with mania severity between genders. Although neopterin is positively associated with mania severity in men, the causal relationship remains an unknown, due to the possibility of increased cytokine production caused by enhanced psychomotor activities in manic states.

There are known gender disparities in immune activation, which may partly underlie the gender difference we observed in the association between neopterin and mania severity. In a rodent model of trauma hemorrhage and sepsis, it was found that females in proestrus have significantly higher survival rates than males (Choudhry et al., 2005). Male sex is an independent risk factor for severe infections in surgical patients (Offner et al., 1999), and women have better survival rates during sepsis (Schröder et al., 1998). This phenomenon may be related to the fact that the sex hormone 17- β estradiol (E2) inhibits excess inflammatory response. E2 mediates broad anti-inflammatory effects in the body (Fish et al., 2008) and can inhibit the production of pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α from monocytes and macrophages in vitro (Kramer et al, 2004). Also, ovarian fluctuations of E2 can influence pro-inflammatory cytokine concentration (Bouman et al, 2005). Additionally, there is some evidence to indicate that peripheral zinc fluctuates during the female menstrual cycle. One study found that zinc is highest during the menses and follicular phases of the menstrual cycle (Deuster et al., 1987). It should be noted that of the 11 women in the BD group, 4 women reported having regular menstrual periods, 6 women reported irregular periods, and 1 woman did not report on the frequency of her period.

In this way, it is possible that the lack of E2 in males may influence neopterin and mania severity, while the presence of E2 may influence zinc and depression severity in women. The effect of the ovulatory cycle on mood variability is not well characterized in women with BD (Sit et al., 2011). Some women with BD-I may experience perimenstrual mood worsening (Blehar et al., 1998), and oral contraceptives have been shown to relieve mood variability in women with BD who experience mood worsening around their menses (Rasgon et al., 2003). However, studies have failed to find a significant association between mood symptoms and menstrual phase in women with BD (Shivakumar et al., 2008; Sit et al., 2011). Future work should explore differences in biology and phenotype of BD between men and women.

Due to the small sample size, we were not able to control for medications in the BD participants, which is clearly a distinct difference from the HC population. Also, we found that more participants in the BD group use tobacco than in the HC group ($p<.0001$). However, statistical analysis revealed no significant differences in zinc concentrations between BD smokers and BD non-smokers ($p=0.20$). Another limitation of this study was the high dropout rate of the participants in the follow-up study. Some dropouts may have been due to transient housing situations and contact issues. Due to the number of dropouts, a

response bias may be present (i.e., only the subjects with resolved mood symptoms were motivated to continue their participation). As is common in BD, our BD participants were obese – the average BMI was 30.1 (± 5.8), and that obesity is associated with low-level, chronic inflammation (Gregor and Hotamisligil, 2011). Also, obesity is linked to reduced peripheral zinc (Tussing-Humphries and Nguyen, 2007). BMI was accounted for in our statistical modeling, and we found zinc to be increased at follow-up, while the average BMI remained unchanged. This indicates that obesity-related inflammation is unlikely to be the entire cause of the reduction in zinc. Another limitation of this study was the use of peripheral biomarkers, which do not necessarily reflect inflammation or zinc in the CNS. However, Leboyer et al., (2012) discussed BD within a whole-body framework, arguing that BD can be conceptualized as a multi-systemic inflammatory disease. The authors' argument lends credence to the value of peripheral biomarker analyses.

Here we have shown that men and women with BD differ in terms of how the concentration of peripheral biomarkers associates with depression and mania severity. Mania severity in men is associated with neopterin, whereas depression severity in women is associated with zinc. These results may indicate that identifying mood symptoms in men and women with BD requires the use of different biomarker measures. Future work should extend this study toward identifying biomarkers for mood state in BD that differ by gender, and elucidate the mechanism underlying these gender differences. Further, we recommend that any biomarker research in BD using men and women should include gender as a component in the analysis.

Acknowledgments

The authors thank the participants and families for generously being part of this project. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the Penn State Milton S. Hershey Medical Center and College of Medicine

Funding Sources: The project described was supported by the National Center for Advancing Translational Sciences, Grant KL2 TR000126. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Dr. Postolache's contribution was supported by a Distinguished Investigator Award (DIG-1-162-12) from the American Association for Suicide Prevention.

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Highlights

1. Peripheral zinc was reduced in symptomatic bipolar disorder compared to healthy controls
2. Women with bipolar disorder showed a positive correlation between zinc concentration and depression severity
3. Peripheral neopterin was positively correlated with mania severity in men with bipolar disorder
4. Zinc and neopterin concentrations were not correlated with one another in the overall bipolar group

Figure 1. Box and whisker plot for peripheral zinc in bipolar disorder (BD) and healthy control (HC) groups at baseline

The range of zinc concentrations was larger for the bipolar population (Range=129.25), compared to healthy controls (Range=63.5). Women with bipolar disorder had two outliers, and men had one. Middle bar in each box plot is the median value. Asterisks (*) represent outliers.

Figure 2. Two-way ANCOVA of peripheral zinc concentrations by diagnosis and gender
 A main effect showed that participants with bipolar disorder (BD) had significantly lower zinc concentrations on average ($p=.037$), as compared to healthy controls (HC). Bipolar disorder $N=24$ (men $N=13$ and women $N=11$) and healthy controls $N=31$ (men $N=13$ and women $N=18$). Data represents marginal means $\pm$ SE. Marginal means are means adjusted for the covariate BMI.

Figure 3. Peripheral zinc is associated with depression severity in women

There is a significant interaction between zinc and gender in prediction of depression severity (HDRS-21 +AT). Women have a positive correlation between zinc and depression severity (Pearson's $R=0.61$), and men have a negative correlation (Pearson's $R=-0.33$).

Figure 4. Neopterin predicts mania severity in men

There is a significant interaction between gender and neopterin in prediction of mania severity (YMRS). The correlation was stronger for men (Pearson's $R=.74$) than women (Pearson's $R=.38$).

Figure 5. Baseline and follow up values for participants with bipolar disorder

Zinc concentration significantly increased at follow up. N=12 (men N=4 and women N=8).

Data represented as mean $\pm$ SE. ***p<.001, **p<.01, *p<.05.

Demographic and clinical data of the participants with bipolar disorder (BD) and healthy controls (HC) at baseline

Data represented as Mean ($\pm$ SD) or N (%). P values represent comparisons between 'BD all' and 'HC all' groups. *Neopterin N values (BD=27 men=14, women=13; HC=31 men=13, women=18).

1. Demographics and clinical data						
	BD all (n=27)	BD women (n=13)	BD men (n=14)	HC all (n=31)	HC women (n=18)	HC men (n=13)
Age (y)	34.2 (±10.6)	33.3 (±9.9)	34.6 (±11.5)	31.3 (±10.2)	32.5 (±9.9)	29.4 (±10.8)
Sex (F)	13 (48.1%)			18 (58.1%)		
Race						
Caucasian	25 (93%)	12 (92.3%)	13 (92.9%)	26 (83.9%)	15 (83.3%)	11 (84.6%)
Black	1 (4%)	0	1 (7.1%)	1 (3.2%)	0	1 (7.7%)
Asian	0	0	0	4 (12.9%)	3 (16.7%)	1 (7.7%)
> than one	1 (3.7%)	1 (7.7%)	0	0		
Ethnicity						
Not Hispanic	26 (96.3%)	12 (92.3%)	14 (100%)	29 (93.5%)	18 (100%)	11 (84.6%)
Hispanic	1 (3.7%)	1 (7.7%)	0	2 (6.5%)	0	2 (15.4%)
Marital Status						
Married	6 (22.2%)	4 (30.8%)	2 (14.3%)	16 (51.6%)	9 (50%)	7 (53.8%)
Separated	1 (3.7%)	0	1 (7.1%)	1 (3.2%)	0	1 (7.7%)
Divorced	3 (11.1%)	1 (7.7%)	2 (14.3%)	0	0	0
Never married	17 (63.0%)	8 (61.5%)	9 (64.3%)	14 (45.2%)	9 (50%)	5 (38.5%)
Employment						
Employed	5 (18.5%)	1 (7.7%)	4 (28.6%)	17 (54.8%)	14 (77.8%)	3 (23.1%)
Unemployed	16 (59.3%)	10 (76.9%)	6 (42.9%)	2 (6.5%)	1 (5.6%)	1 (7.7%)
Disabled	4 (14.8%)	2 (15.4%)	2 (14.3%)	0	0	0
Student	1 (3.7%)	0	1 (7.1%)	11 (35.5%)	3 (16.7%)	8 (61.5%)
Retired	0	0	0	1 (3.5%)	0	1 (7.7%)
BMI	30.1 (±5.8)	30.5 (±5.8)	29.8 (±6)	25.2 (±5.0)	23.6 (±4.6)	27.5 (±4.9)
Current smoker	13 (48.1%)	5 (38.5%)	8 (57.1%)	1 (3.2%)	1 (5.6%)	0
BD type I	21 (77.8%)	12 (92.3%)	9 (64.3%)			
Mood stabilizer	21 (77.8%)	11 (84.6%)	11 (78.6%)	0	0	0
p						
						0.31
						0.3
						0.19
						0.18
						0.03
						<0.0001
						0.001
						<0.0001

1. Demographics and clinical data							
	BD all (n=27)	BD women (n=13)	BD men (n=14)	HC all (n=31)	HC women (n=18)	HC men (n=13)	p
Antipsychotics	15 (55.6%)	7 (53.8%)	8 (57.1%)	0	0	0	
Sedatives	17 (63.0%)	10 (76.9%)	6 (42.9%)	0	0	0	
Antidepressants	13 (48.1%)	8 (61.5%)	6 (42.9%)	0	0	0	
Stimulants	0	0	0	0	0	0	
HDRS 21+AT	34.4 (± 14.5)	35.5 (± 15.4)	32.6 (± 14.2)	0.4 (± 0.6)	1.5 (± 0.6)	1.7 (± 1.2)	
YMRS	13.4 (± 10.8)	12.6 (± 9.1)	14.1 (± 12.5)	0	0	0	
*Neopterin (nmol/L)	6.2 (± 2.5)	6.1 (± 1.7)	6.2 (± 3.2)	5.4 (± 1.4)	5.4 (± 1.5)	5.5 (± 1.3)	.2
Zinc ($\mu\text{g/dL}$)	94.2 (± 15.6)	90.9 (± 17.6)	97.0 (± 13.8)	106.3 (± 17.9)	109.9 (± 17.8)	101.2 (± 17.6)	.037