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Metabolic syndrome in patients with bipolar disorder: Comparison with major depressive disorder and non-psychiatric controls ☆

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ABSTRACT

Objective: We aimed to investigate the prevalence of the metabolic syndrome (MetS) and its individual components in subjects with bipolar disorder (BD) compared to those with major depressive disorder (MDD) and non-psychiatric controls.
Methods: We examined 2431 participants (mean age 44.3 ± 13.0, 66.1% female), of whom 241 had BD; 1648 had MDD; and 542 were non-psychiatric controls. The MetS was ascertained according to NCEP ATP III criteria. Multivariable analyses were adjusted for age, sex, ethnicity, level of education, smoking status and severity of depressive symptoms, and in the case of BD subjects, also for psychotropic medication use.
Results: Subjects with BD had a significantly higher prevalence of MetS when compared to subjects with MDD and non-psychiatric controls (28.4% vs. 20.2% and 16.5%, respectively, $p < 0.001$), also when adjusted for sociodemographic and lifestyle factors (OR 1.52, 95% CI: 1.09–2.12, $p = 0.02$ compared to MDD; OR 1.79, 95% CI: 1.20–2.67, $p = 0.005$ compared to non-psychiatric controls). The differences between BD subjects with controls could partly be ascribed to a higher mean waist circumference (91.0 cm vs. 88.8, respectively, $p = 0.03$). In stratified analysis, the differences in the prevalence of MetS between patients with BD and MDD were found in symptomatic but not in asymptomatic cases.
Conclusion: This study confirms a higher prevalence of MetS in patients with BD compared to both MDD patients and controls. Specifically at risk are patients with a higher depression score and abdominal obesity.

Introduction

Bipolar disorder (BD) is one of the world's 25 most disabling conditions with a prevalence of approximately 1–5% in the general population [1,2]. BD is a chronic illness associated with substantial morbidity, disability, and mortality with the most prevalent medical illnesses being cardiovascular disease, diabetes mellitus, obesity and thyroid disease [3]. The high prevalence of these medical conditions may be due to an increased prevalence of metabolic risk factors in patients with BD, such as abdominal obesity, increased triglycerides, decreased high-density lipoprotein (HDL), and hypertension [4]. Findings from a previous review [5] and meta-analysis [6] indicated that patients with BD are at high risk for metabolic syndrome (MetS).

The MetS represents a cluster of cardiovascular and metabolic abnormalities including abdominal obesity, hypertension, dyslipidemia and insulin resistance [7]. Screening for MetS may be of importance to help decrease the risk of cardiovascular disease and diabetes mellitus type 2 in individuals with BD [3]. Recent reviews concluded that MetS is highly prevalent among patients with BD, with prevalence ranging from 17–53% and a prevalence proportion ratio of 1.6 when compared with the general population [5,8]. Additionally, co-occurring MetS in BD population is associated with a more severe clinical presentation of BD, suicidality, and decreased functional recovery [9–11]. Several mechanisms have been hypothesized to explain the association between MetS and BD. These include side effects of psychotropic medications, adoption of unhealthy lifestyles, neuroendocrine and immuno-inflammatory

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abnormalities, as well as a shared genetic vulnerability [5]. Many of the studies reporting on the prevalence of MetS in BD used either non-psychiatric controls [12,13] or subjects with schizophrenia as comparison groups [14–16] and the burden of evidence varies considerably by geographic area [5].

Therefore, our first aim was to investigate the prevalence of MetS in subjects with BD compared to those with major depressive disorder (MDD) and a non-psychiatric control group in the Netherlands. Second, this study aimed to elucidate which of the individual MetS components were most strongly associated with BD. Third, more detailed analyses were performed to explore whether sociodemographic factors, smoking status, and psychotropic medication [17,18] contributed to individual MetS components in BD.

Methods

Sample and procedure

Subjects selected for these analyses participated in the 2-year follow-up (data collection from September 2006 to February 2009) assessment of the Netherlands Study of Depression and Anxiety (NESDA); and in the 2-year follow-up (data collection from December 2009 to January 2011) assessment of the Bipolar Stress Study. NESDA is an ongoing longitudinal cohort study including 2981 persons aged 18 to 65 years, designed to examine the long-term course and consequences of depressive and anxiety disorders. Subjects in the NESDA study were selected to represent of range of depressive and anxiety symptoms and included subjects without a history of depressive or anxiety disorders ('non-psychiatric controls'). Subjects with a primary psychiatric diagnosis other than depression and anxiety (e.g. psychotic disorder, obsessive compulsive disorder, or severe addiction disorder) were not invited to participate in NESDA. All subjects ($N = 2596$, 87.1%) in the 2-year follow-up assessment were recruited from the community or from primary or specialized mental health care settings in 3 Dutch regions (i.e., Amsterdam, Groningen, Leiden). The 2-year follow-up assessment consisted of a face-to-face interview, written questionnaires, and biological measurements. For the purpose of this study, the data from the 2-year follow-up were selected as this was the time point at which BD was first diagnosed in the NESDA study. The study design is described elsewhere in more detail [19,20]. The study protocol was approved by the Ethical Review Board of each participating center, and all patients signed informed consent.

The Bipolar Stress Study is a 2-year longitudinal cohort study, designed to identify risk factors that have an impact on the clinical course and the treatment of outpatients with BD. Subjects in the Bipolar Stress Study were outpatients with BD type 1, BD type 2, and BD Not Otherwise Specified (NOS). All 122 subjects were recruited from the outpatient Clinic for Mood Disorders in The Hague, The Netherlands. The 2-year follow-up assessment consisted of a face-to-face interview, written questionnaires, and biological measures. For the purpose of this study, the data from the 2-year follow-up were selected as this was the time point at which MetS components were measured in the Bipolar Stress Study. The study design is described elsewhere in more detail [21]. The study was approved by the local Medical Ethics Committee, and all patients signed informed consent.

In the 2-year follow-up assessment of the NESDA study, data were collected among 2596 subjects (response rate was 87.1%) [19] diagnosed with anxiety disorder, depressive disorders, BD, or no history of a psychiatric disorder (control). We excluded 276 subjects diagnosed only with a lifetime anxiety disorder and 5 subjects diagnosed only with lifetime dysthymia. This resulted in a sample of 2315 (89.2%) subjects. This sample was enriched with 122 BD patients from the Bipolar Stress Study. From the latter group, 6 patients were excluded aged >65 years (as the age range within the NESDA study was 18–65 years). Thus 2431 subjects (BD = 241; MDD = 1648; controls = 542) were included in the analyses (Fig. 1).

In the present study, there were missing data for some variables as follows: MetS 9.9%; waist circumference 5.6%; triglyceride level 12.5%; HDL-cholesterol 12.3%; systolic and diastolic blood pressure 5.6%; and glucose level 11.7%.

BD subjects from the NESDA study did not differ from BD subjects in the Bipolar Stress Study in gender ($p = 0.41$), ethnicity ($p = 0.93$), smoking status ($p = 0.51$), and use of tricyclic antidepressants (TCA, $p = 0.70$) or other antidepressants ($p = 0.92$), but they were younger ($p = 0.01$), used more often selective serotonin re-uptake inhibitors (SSRI, $p = 0.01$), used less antipsychotic, antiepileptic and lithium medication (all $p < 0.001$), and had a higher severity of depressive symptoms ($p < 0.001$).

Measures

Bipolar and major depressive disorder

In the NESDA study, MDD or BD were diagnosed according to the fourth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) criteria using the Composite International Diagnostic Interview [22].

In the Bipolar Stress Study, BD was diagnosed according to the DSM-IV Text Revision (DSM-IV-TR) criteria using the Dutch version of the MINI International Neuropsychiatric Interview Plus (version 5.00-R; MINI-PLUS) [23].

The metabolic syndrome

MetS was defined according to the National Cholesterol Education Program—Adult Treatment Panel III [24] definition. It requires the presence of three or more of the following five criteria: 1) abdominal obesity, i.e., waist circumference ≥102 cm in men and ≥88 cm in women; 2) hypertriglyceridemia, i.e., elevated triglyceride level ≥1.70 mmol/L; 3) low high-density lipoprotein (HDL) cholesterol, i.e. HDL < 1.03 mmol/L in men and < 1.30 mmol/L in women; 4) hypertension, i.e., elevated blood pressure ≥130/85 mmHg or use of antihypertensive medication, indicating that those patients using antihypertensive medication, irrespective of their blood pressure, were still considered as fulfilling this criterion for hypertension; and 5) hyperglycemia, i.e., elevated fasting glucose level ≥6.1 mmol/L or anti-diabetic medication. Additionally, in line with previous research [25], the number of MetS components was used as an indicator of severity of metabolic abnormalities. Furthermore, in addition to the MetS, associations with individual metabolic components as continuous variables were examined to investigate consistency across components. In line with previous research [26], in the analyses of individual continuous metabolic components, if the participant had a glucose level of <7 mmol/L [126 mg/dL] and used antidiabetic medication, the participant's glucose level was coded as 7 mmol/L [126 mg/dL]. If the participant used antihypertensive medication, an additional 10 mmHg was added to the systolic blood pressure and an additional 5 mmHg to the diastolic blood pressure [27]. Waist circumference was measured with a measuring tape to the nearest 0.1 cm midway between the lower rib margin and the iliac crest, upon light clothing. In the NESDA study, levels of HDL-cholesterol and triglycerides were determined using enzymatic colorimetric assay; the levels of glucose were determined using hexokinase method. The lipids were sampled using a heparine tube whereas the glucose were sampled using a sodium fluoride tube and kept on ice. In the Bipolar Stress Study, a Modular P800, E170 analyzer and corresponding reagents (Roche Diagnostics, Almere, The Netherlands) were used to determine blood plasma levels of glucose, triglycerides, and HDL-cholesterol. Glucose was measured spectrophotometrically with an enzymatic hexokinase method. Triglyceride levels were measured with an enzymatic colorimetric method. HDL-cholesterol levels were quantified using an enzymatic colorimetric test after complexation of the chylomicrons. Between day coefficients of variation were 0.9–1.0% for glucose, 1.0% for triglycerides and 2.1–3.0% for HDL cholesterol. In the NESDA study, blood pressure was defined as the average of

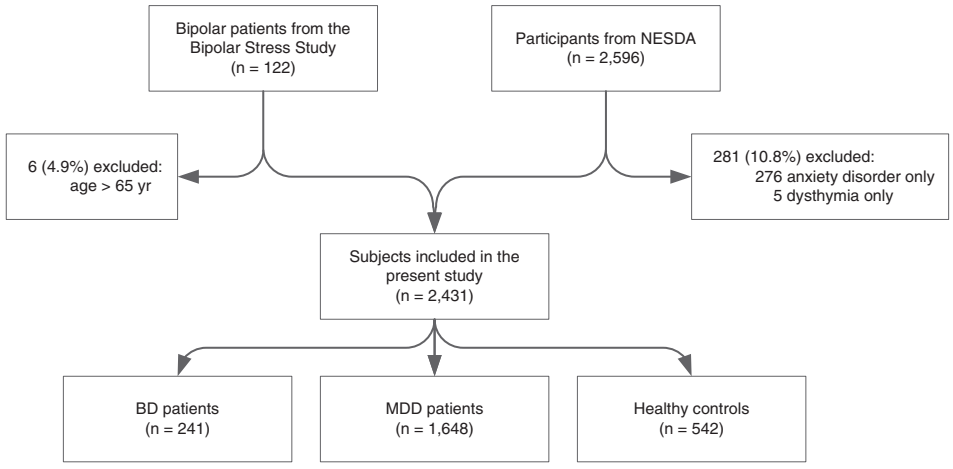

Fig. 1. Flow-chart diagram of the participants. N = Number, BD = bipolar disorder, MDD = major depressive disorder, NESDA = the Netherlands Study of Depression and Anxiety.

two successive Omron M4 IntelliSense (HEM-725A; Omron Healthcare, Inc., Bannockburn, IL, USA) blood pressure monitor readings on the right arm, with the respondent in supine position. In the Bipolar Stress Study, blood pressure was accordingly measured only once on the right arm using Omron M6 IntelliSense (Omron Healthcare, Inc., Bannockburn, IL, USA).

Covariates

Sociodemographic characteristics included age, sex, ethnicity (non-North-European descent/North-European descent), and level of education (basic—less than 9 years of schooling; intermediate—less than 15 years of schooling; high—more than 15 years of schooling). Smoking status was used as a binary variable (non-smoker/smoker).

A previous study indicated that MetS abnormalities were mainly linked to the severity of symptoms, suggesting state associations and less clear trait associations [25]. Therefore, analyses were adjusted for the severity of the depressive symptoms in the case of BD and MDD patients. The severity of depressive symptoms was measured using a shortened version (QIDS-sr16) of the Inventory of Depressive Symptomatology (IDS-SR). IDS-SR is a self-administered questionnaire designed to assess the severity of depressive symptoms [28,29]. It assesses all DSM-IV criterion symptom domains for major depressive disorder plus commonly associated symptoms (e.g. anxiety, irritability) and symptoms relevant to melancholic and atypical features. The questionnaire consists of 30 items, each with four answering options (coded 0 through 3). The questionnaire uses a 7-day timeframe for assessing symptom severity. The QIDS-sr16 is a shortened version of the IDS-SR that includes only the 9 criterion symptom domains of MDD, using 16 items of the IDS-SR. Scores on the QIDS-sr16 range from 0 to 27.

Antidepressant (ATC code N06Ax), lithium (ATC code N05AN), and antipsychotic medication (ATC code N05Ax) use within the past month were coded according to the Anatomical Therapeutic Chemical (ATC) Classification System (http://www.whocc.no/). Antidepressant use was subdivided into SSRI (ATC code N06AB), TCA (ATC code N06AA), and other antidepressants (mainly serotonergic and noradrenergic-working antidepressants; N06AF and N06Ax).

In the present study, the proportions of missing data for some variables were as follows: smoking status 0.9%; the severity of depressive symptoms 3.5%, SSRI 0.2%; TCA 0.2%; and other antidepressants 0.1%.

Statistical analyses

Non-normally distributed variables (i.e., number of MetS components, HDL-cholesterol, triglyceride, glucose) were naturally log-transformed. Sociodemographic and clinical characteristics of BD, MDD, or non-psychiatric control groups were compared using χ^2 tests for categorical variables and analysis of variance (ANOVA) for continuous variables. For the presence of MetS, two comparisons were made using multivariate logistic regression analyses: first the BD group was compared with the MDD group, and second the BD group was compared with the non-psychiatric control group, adjusted for age, sex, ethnicity, level of education, and smoking status in Model 1. In Model 2, the severity of the depressive symptoms was added as a covariate to those of Model 1. For the total number of MetS components and for each MetS component we used ANOVA and analysis of covariance (ANCOVA). Two post-hoc (LSD) comparisons were made: first the BD group was compared with the MDD group, and second the BD group was compared with the non-psychiatric control group. In ANCOVA, adjustments were done for age, sex, ethnicity, level of education, and smoking status (in Model 1), and in Model 2, the severity of depressive symptoms was added to those of Model 1. Next, focusing on the 241 BD patients, we explored which variables contributed to the presence of MetS, to the total number of MetS components, or to the individual components of MetS using multivariate regression analyses. These variables included age, sex, ethnicity, level of education, smoking status, severity of depressive symptoms, and use of lithium, antipsychotic medication, SSRIs, TCAs, and other antidepressants yielding standardized beta-coefficients or odds ratios (ORs) with their 95% confidence intervals (CI), for continuous and dichotomous (i.e. presence of MetS) variables, respectively. All analyses were performed using the statistical software IBM SPSS 20.0 for Windows (IBM company, Chicago, Illinois, USA). Statistical significance was inferred at $p < 0.05$.

Results

Characteristics of the sample

The sociodemographic status, smoking status, and clinical characteristics of the participants are shown in Table 1 according to their DSM-IV diagnosis and in Table 2 according to the severity of depressive symptoms. The mean age of the total sample was 44.3 years (*SD* 13.0), where 66.1% of the sample was female and 95.6% of the sample was of North-European descent.

Differences in MetS characteristics according to the presence of BD

Table 3 compares the MetS characteristics of BD patients with those of MDD patients, and non-psychiatric controls. Patients with BD had a significantly higher prevalence of MetS compared to patients with MDD and non-psychiatric controls (28.4% vs. 20.2% and 16.5%, respectively, $p < 0.001$). These differences remained statistically significant after multivariable adjustment (OR 1.52, 95% CI: 1.09–2.12, $p = 0.02$ when compared to MDD; OR 1.79, 95% CI: 1.20–2.67, $p = 0.005$ when compared to non-psychiatric control

Table 1
Characteristics of the total sample and subsamples according to the type of DSM-IV diagnoses

	Total sample	BD	MDD	Non-psychiatric controls	*p*-value
No. of participants	2431 (100%)	241 (9.9%)	1648 (67.8%)	542 (22.3%)	
Age					0.01
Mean (±SD)	44.33 (±12.96)	46.45 (±11.60)	44.34 (±12.54)	43.37 (±14.61)	
Range	19–68	20–67	19–68	20–67	
Sex					<0.001
Males	823 (33.9%)	98 (40.7%)	512 (31.1%)	213 (39.3%)	
Females	1608 (66.1%)	143 (59.3%)	1136 (68.9%)	329 (60.7%)	
Ethnicity					0.06
Non-North-European ancestry	106 (4.4%)	6 (2.5%)	83 (5.0%)	17 (3.1%)	
North-European ancestry	2325 (95.6%)	235 (97.5%)	1565 (95.0%)	525 (96.9%)	
Level of education					<0.001
Basic	158 (6.5%)	37 (15.4%)	103 (6.2%)	18 (3.3%)	
Intermediate	1289 (53.0%)	106 (44.2%)	932 (56.6%)	251 (46.3%)	
High	983 (40.4%)	97 (40.4%)	613 (37.2%)	273 (50.4%)	
Smoking status					<0.001
Non-smoker	1637 (67.3%)	139 (59.4%)	1062 (65.0%)	436 (80.6%)	
Smoker	773 (31.8%)	95 (40.6%)	573 (35.0%)	105 (19.4%)	
Psychotropic medication use					
SSRI	347 (14.3%)	43 (18.0%)	301 (18.3%)	3 (0.6%)	<0.001
TCA	71 (2.9%)	14 (5.8%)	56 (3.4%)	1 (0.2%)	<0.001
Other AD	155 (6.4%)	37 (15.4%)	116 (7.0%)	2 (0.4%)	<0.001
Antipsychotic medication	89 (3.7%)	61 (25.4%)	28 (1.7%)	0 (0.0%)	<0.001
Lithium	102 (4.2%)	97 (40.2%)	5 (0.3%)	0 (0.0%)	<0.001
Antiepileptic medication	68 (2.8%)	35 (14.5%)	29 (1.8%)	4 (0.7%)	<0.001
The severity of depressive symptoms (QIDS)					<0.001
Mean (±SD)	6.30 (±4.78)	8.54 (±5.49)	7.19 (±4.78)	2.68 (±2.39)	
Range	0–24	0–24	0–23	0–14	

Abbreviations: BD, bipolar disorder; MDD, major depressive disorder; SD, standard deviation.
NOTE: the significant differences in the psychotropic medication use between BD and MDD were as follows: SSRI and TCA: $p > 0.05$; Other AD, antipsychotic medication, lithium, antiepileptic medication: $p < 0.001$.

subjects). After adjusting for covariates, there were no significant differences in the number of MetS components between BD and MDD or non-psychiatric control subjects. Regarding individual MetS components, statistically significant differences between subjects with BD and non-psychiatric controls were found in multivariable models for waist circumference (higher mean levels in BD than non-psychiatric controls; 91.0 cm vs. 88.8 cm, respectively; $p = 0.03$) and systolic blood pressure (lower mean levels in BD than non-psychiatric controls; 132.7 mmHg vs. 135.6 mmHg, respectively; $p = 0.03$).

Next we conducted a stratified analysis according to the severity of depressive symptoms. There were 779 patients (35.7% of patients with BD and 42.1% of patients with MDD) with a QIDS-sr_{16} score less than 5 (i.e., no symptoms) and 1037 patients (59.8% of patients

Table 2
Characteristics of the participants according to the severity od depressive symptoms

	BD			MDD		
	Symptomatic patients	Non-symptomatic patients	Differences btw. groups	Symptomatic patients	Non-symptomatic patients	Differences btw. groups
No. of participants	144	86		893	693	
Age			p = 0.87			p = 0.24
Mean (±SD)	46.45 (±11.50)	46.72 (±11.87)		44.89 (±12.48)	44.10 (±12.67)	
Range	20–67	23–67		19–66	20–68	
Gender			p = 0.045			p = 0.13
Males	51 (35.4%)	42 (48.8%)		288 (32.3%)	199 (28.7%)	
Females	93 (64.6%)	44 (51.2%)		605 (67.7%)	494 (71.3%)	
Ethnicity						
Non-North-European ancestry	4 (2.8%)	1 (1.2%)	p = 0.42	52 (5.8%)	22 (3.2%)	p = 0.01
North-European ancestry	140 (97.2%)	85 (98.8%)		841 (94.2%)	671 (96.8%)	
Level of education			p = 0.09			p < 0.001
Basic	21 (14.6%)	15 (17.6%)		64 (7.2%)	30 (4.3%)	
Intermediate	72 (50.0%)	30 (35.3%)		547 (61.3%)	348 (50.2%)	
High	51 (35.4%)	40 (47.1%)		282 (31.6%)	315 (45.5%)	
Smoking status			p = 0.25			p = 0.21
Non-smoker	82 (57.3%)	54 (65.1%)		567 (63.9%)	462 (66.9%)	
Smoker	61 (42.7%)	29 (34.9%)		321 (36.1%)	229 (33.1%)	
Psychotropic medication use						
SSRI	28 (19.7%)	14 (16.3%)	p = 0.52	182 (20.5%)	101 (14.6%)	p = 0.002
TCA	7 (4.9%)	7 (8.1%)	p = 0.33	40 (4.5%)	14 (2.0%)	p = 0.01
Other AD	24 (16.9%)	10 (11.6%)	p = 0.28	66 (7.4%)	39 (5.6%)	p = 0.15
Antipsychotic medication users	32 (22.4%)	24 (27.9%)	p = 0.35	22 (2.5%)	5 (0.7%)	p = 0.01
Lithium users	42 (29.2%)	49 (57.0%)	p < 0.001	4 (0.4%)	1 (0.1%)	p = 0.39
Antiepileptic medication users	15 (10.4%)	18 (20.9%)	p = 0.03	21 (2.4%)	8 (1.2%)	p = 0.03
The severity of depressive symptoms (QIDS)			p < 0.001			p < 0.001
Mean (±SD)	11.83 (±4.21)	3.04 (±1.52)		10.49 (±3.74)	3.15 (±1.32)	
Range	6–24	0–5		6–23	1–5	

Abbreviations: BD, bipolar disorder; MDD, major depressive disorder; SD, standard deviation.
Note: patients—with a QIDS-sr16 score ≥ 6 (mild to severe symptoms); Non-symptomatic patients—with a QIDS-sr16 less than 5 (no symptoms).

Table 3
Prevalence of the metabolic syndrome, number of metabolic syndrome components and mean metabolic syndrome components according DSM-IV diagnosis

	BD	MDD	*p*-value for BD vs. MDD	Controls	*p*-value for BD vs. Controls
No. of participants	229	1464		498	
Metabolic syndrome	**65 (28.4%)**	**296 (20.2%)**	**0.004**	**82 (16.5%)**	<**0.001**
No. of MetS components					
Crude	1.65 (0.09)	1.39 (0.03)	0.004	1.30 (0.05)	0.001
Adjusted[a]	1.53 (0.08)	1.39 (0.03)	0.09	1.37 (0.05)	0.08
Adjusted[b]	1.48 (0.08)	1.38 (0.03)	0.24		
Waist circumference					
Crude	92.2 (0.03)	90.1 (0.01)	0.03	88.8 (0.02)	0.002
Adjusted[a]	91.0 (0.84)	90.3 (0.32)	0.43	**88.8 (0.57)**	**0.03**
Adjusted[b]	90.4 (0.86)	90.2 (0.33)	0.78		
Triglyceride level					
Crude	1.46 (0.03)	1.37 (0.01)	0.22	1.30 (0.02)	0.06
Adjusted[a]	1.38 (0.07)	1.37 (0.03)	0.91	1.33 (0.05)	0.59
Adjusted[b]	1.36 (0.07)	1.37 (0.03)	0.84		
HDL-cholesterol					
Crude	1.47 (0.03)	1.55 (0.01)	0.02	1.54 (0.02)	0.04
Adjusted[a]	1.50 (0.03)	1.54 (0.01)	0.12	1.55 (0.02)	0.08
Adjusted[b]	1.50 (0.03)	1.54 (0.01)	0.12		
Systolic blood pressure					
Crude	134.9 (1.23)	133.0 (0.48)	0.16	135.4 (0.89)	0.08
Adjusted[a]	132.7 (1.09)	133.3 (0.42)	0.59	**135.6 (0.74)**	**0.03**
Adjusted[b]	132.6 (1.12)	133.3 (0.43)	0.55		
Diastolic blood pressure					
Crude	81.1 (0.74)	79.8 (0.28)	0.11	79.3 (0.52)	0.04
Adjusted[a]	80.0 (0.67)	79.9 (0.26)	0.84	79.5 (0.45)	0.49
Adjusted[b]	79.8 (0.67)	79.9 (0.26)	0.95		
Glucose level					
Crude	5.31 (0.11)	5.36 (0.03)	0.02	5.31 (0.05)	0.009
Adjusted[a]	5.46 (0.07)	5.36 (0.03)	0.17	5.34 (0.05)	0.15
Adjusted[b]	5.46 (0.07)	5.36 (0.05)	0.23		

Data are mean values (standard errors) assessed by one-way ANOVA and univariate ANCOVA.
BD, bipolar disorder; MDD, major depressive disorder; MetS, metabolic syndrome.
Note: the severity of depressive symptoms was added to the Models only in groups with BD and MDD.
Bold values indicate significance at < 0.05.
[a] Adjusted for age, sex, ethnicity, level of education, and smoking status.
[b] Adjusted for age, sex, ethnicity, level of education, smoking status and the severity of depressive symptoms.

with BD and 54.2% of patients with MDD) with a QIDS-sr_{16} score ≥6 (i.e., mild to severe symptoms). In logistic regression analyses, we found that the difference between the groups with BD and MDD was more pronounced in symptomatic (depressed) than non-symptomatic patients, with adjusted odds ratios of 1.71 (95% CI: 1.12–2.61; $p = 0.01$) vs. 1.03 (95% CI: 0.56–1.90; $p = 0.92$), respectively. This indicates that BD patients were at a higher risk of developing MetS compared to MDD patients when they were symptomatic but not when they were non-symptomatic.

Determinants of the MetS (components) in patients with BD

Table 4 shows the potential independent correlates of MetS (components) in the 241 BD patients. Advanced age and male sex were the most important risk factors for MetS (components) in BD. These were significant predictors of a higher number of MetS components, larger waist circumference, higher triglyceride level, higher systolic and diastolic blood pressure, higher glucose level and lower HDL-cholesterol in BD patients (Table 4). Sensitivity analyses have shown that the type of BD (BD type I and BD type II) was not a significant predictor of MetS and its components. Lastly, only age (per 10 years, OR 1.5, 95% CI: 1.18–1.81, $p = 0.002$) and basic or intermediate education (OR 2.69, 95% CI: 1.31–5.52, $p = 0.01$) were significantly associated with higher odds for developing MetS in BD patients (Table 4).

Discussion

This study supports evidence that individuals with BD have a higher prevalence of MetS than those with MDD and non-psychiatric controls. This could partly be ascribed to a higher prevalence of abdominal obesity in individuals with BD compared to individuals with no history of psychiatric disorders. Advanced age and male sex were the most important risk factors for MetS in BD, but psychotropic use did not contribute to the presence of MetS.

Our finding that BD patients have a higher prevalence of MetS than MDD patients and non-psychiatric controls is consistent with previous findings in other BD populations. The odds ratio of 1.8 was similar to the prevalence proportion ratios of approximately 1.6 when compared to the general population (as summarized in a previous review by Murray et al. [8]). The prevalence rate of MetS in our BD group was 28.4%, which was comparable to the mean prevalence of 29.9% using the definition of ATP-III from 18 studies, as summarized in a meta-analysis [6]. The MetS prevalence of 16.5% in controls was also comparable to the estimated 14% prevalence of MetS in two Dutch population-based studies [30]. Our stratified analyses suggested that the differences were mediated in part by the severity of depressive symptoms, which is in line with the analysis of Van Reedt Dortland et al. [25]. That study concluded that the prevalence of MetS was not higher in subjects with MDD when compared to controls, but subjects with more severe depressive symptoms had higher odds of the presence of MetS. Thus current disease severity may be a stronger risk factor than diagnostic DSM-IV categories with respect to the risk of MetS.

Possible aetiological explanations for the higher risk of MetS in BD may be disturbances in the hypothalamic–pituitary–adrenal (HPA) axis, low-grade chronic inflammation, the sympathetic nervous system

Table 4
Potential determinants of the metabolic syndrome (components) in 241 patients with Bipolar Disorder

	MetS (yes/no) Odds ratio (95% CI)	No. of MetS components β-coefficient (p-value)	Waist circumference β-coefficient (p-value)	Triglyceride level β-coefficient (p-value)
Age (per 10 years)	**1.49 (1.18–1.81)****	**0.30 (<0.001)**	**0.19 (<0.001)**	**0.17 (0.01)**
Female sex	0.54 (0.28–1.05)	**−0.26 (<0.001)**	**−0.44 (<0.001)**	**−0.16 (0.03)**
Non-North-European ancestry	0.22 (0.02–3.25)	0.10 (0.11)	0.05 (0.44)	−0.01 (0.83)
Basic or intermediate education	**2.69 (1.31–5.52)****	**0.17 (0.01)**	0.07 (0.24)	0.09 (0.17)
Smoker	1.35 (0.70–2.63)	0.05 (0.46)	−0.03 (0.60)	**0.13 (0.05)**
Lithium use	0.99 (0.48–2.06)	0.08 (0.24)	−0.05 (0.44)	0.03 (0.71)
Antipsychotic use	0.93 (0.42–2.08)	0.08 (0.21)	0.04 (0.52)	0.01 (0.94)
SSRI use	1.36 (0.61–3.03)	0.03 (0.63)	−0.01 (0.84)	0.07 (0.30)
TCA use	0.82 (0.19–3.45)	0.02 (0.74)	−0.03 (0.69)	0.13 (0.07)
Other AD use	1.24 (0.52–2.95)	−0.03 (0.68)	−0.02 (0.72)	0.02 (0.74)
The severity of depressive symptoms	1.02 (0.96–1.09)	0.03 (0.63)	−0.02 (0.73)	**0.16 (0.02)**

	HDL-cholesterol β-coefficient (p-value)	Systolic blood pressure β-coefficient (p-value)	Diastolic blood pressure β-coefficient (p-value)	Glucose level β-coefficient (p-value)
Age (per 10 years)	0.08 (0.22)	**0.36 (<0.001)**	**0.30 (<0.001)**	**0.33 (<0.001)**
Female sex	**0.36 (<0.001)**	**−0.36 (<0.001)**	**−0.26 (<0.001)**	**−0.17 (0.01)**
Non-North-European ancestry	−0.07 (0.32)	−0.02 (0.78)	−0.06 (0.35)	**0.15 (0.03)**
Basic or intermediate education	−0.09 (0.18)	**0.14 (0.02)**	0.05 (0.42)	0.02 (0.82)
Smoker	−0.08 (0.26)	−0.02 (0.68)	0.01 (0.92)	**0.13 (0.05)**
Lithium use	−0.02 (0.75)	0.07 (0.29)	−0.09 (0.21)	−0.02 (0.77)
Antipsychotic use	−0.03 (0.64)	−0.01 (0.84)	0.08 (0.21)	0.07 (0.33)
SSRI use	0.02 (0.80)	0.05 (0.39)	0.01 (0.97)	−0.04 (0.56)
TCA use	0.03 (0.65)	−0.01 (0.95)	0.01 (0.88)	−0.05 (0.49)
Other AD use	−0.07 (0.29)	−0.08 (0.16)	0.15 (0.02)	−0.07 (0.29)
The severity of depressive symptoms	−0.01 (0.84)	0.01 (0.88)	0.04 (0.58)	0.01 (0.85)

Note: There were missing for some variables as follows: the number of MetS components 5.0%; waist circumference 4.1%; triglyceride level 6.6%; HDL-cholesterol 6.6%; systolic and diastolic blood pressure 3.0%; glucose level 6.6%; smoking status 3.0%; the severity of depressive symptoms 4.5%; SSRI 0.8%; TCA 0.4%; and other antidepressants 0.4%.
Bold values indicate significance at $p < 0.05$.
** $p < 0.01$

[31], and adverse lifestyle factors. First, to be more specific, HPA axis dysfunction is a well-recognized characteristic in patients with BD [32], which might explain the association between BD and MetS. Although difficult to determine with current methods of measurement using serum or saliva, systemic cortisol action may be elevated due to disturbed negative feedback at the hypothalamic or pituitary level in both BD and MDD patients. One of the most typical cortisol effects is redistribution of adipose tissue with fat accumulation in the abdominal region. In the long run this could lead to abdominal obesity. Genetically-determined disturbances of glucocorticoid sensitivity may increase the risk of both BD and MDD [33]. Interestingly, parallel to hypercortisolism due to endogenous or exogenous Cushing's syndrome, increased sensitivity to glucocorticoids has also been associated with features of the MetS [34].

Second, the higher risk of cardiac disease, diabetes, and metabolic abnormalities in BD subjects may be explained by an increased low-grade inflammatory state [30]. High levels of proinflammatory cytokines and acute-phase reactants were associated with MetS as well as with BD and MDD [31,35]. Recent studies have found that BD is associated with increased expression of pro-inflammatory markers including acute-phase proteins, like C-reactive protein, and cytokines, like interleukin-6 and interferon-γ, which may contribute to the presence of the abovementioned disorders [31]. Abdominal fat tissue is known to be metabolically highly active, with consequences for inflammatory status [36].

Third, the metabolic abnormalities in BD may be explained by a stimulated sympathetic nervous system, which has been found in individuals with BD [31]. In response to dietary intake, insulin-mediated glucose uptake in the central nervous system regulates sympathetic nervous system activity. Insulin-mediated sympathetic stimulation may subsequently contribute to hypertension [37].

Fourth, adverse lifestyle factors, such as smoking, alcohol intake, poor-quality diets (energy-dense diets that are nutrient-poor), and lack of exercise, are highly prevalent in BD patients and may explain the higher prevalence of metabolic abnormalities among those with BD [5,31]. Available data regarding the association between smoking and MetS are inconsistent, but a recent meta-analysis by Sun, Liu and Ning [38] based on data from prospective studies concluded that active smoking is associated with the development of MetS. The risk of alcohol abuse is higher in BD patients [39], which increases the risk of pancreatitis and consequently diabetes [9]. Additionally, physical inactivity and poor dietary habits have been reported in BD and are associated with weight gain and obesity [31].

We found that abdominal obesity was the MetS component most strongly associated with BD diagnosis, while systolic blood pressure was lower when compared to controls. The majority of previous studies among patients with BD also indicate that abdominal obesity is the key metabolic abnormality present among 18%–61% BD patients [40,41]. Generally, NCEP ATPIII emphasized the importance of abdominal obesity as the driving force of MetS [5,23], which may subsequently increase the risk for cardiovascular disease and type 2 diabetes in people with BD [31].

Lastly, in the present study, psychotropic use was not a significant predictor of MetS or its individual components in BD. Previous studies have reported that the use of lithium, valproic acid, and atypical antipsychotics (e.g. olanzapine, clozapine) contributed to obesity and MetS in the BD group, mainly due to the effects on appetite and glucose and lipid metabolism [5,42]. Similarly, a recent meta-analysis [6] indicated that patients taking antipsychotics might be at greater risk for MetS compared to those who were not using such medication. On the contrary, other studies [16,43], similar to our study, have not found such an association. This might be due to the naturalistic design: obese patients or those with other cardiometabolic risk factors may be less likely to be prescribed psychotropic medication that exacerbates the general metabolic condition, resulting in some confounding by treatment indication. However, it is also possible that glucose and lipid metabolism disturbances were already present in many BD patients before starting to use psychotropic medications [5], and recent evidence showed that BD was often associated with weight gain, independent of psychotropic treatment [44]. As most of our bipolar patients were not drug-naive, future studies should also include drug-naive bipolar patients.

Strengths and limitations

Our study has several strengths. First, this study was based on a large multi-center sample, with a significant group of patients with BD ($n = 241$). Second, the sample included in this study covered a wide-range of demographic characteristics among adult patients with BD and MDD (e.g., both genders and broad ranges of age and severity of depressive symptoms). Third, this study used both individuals with MDD and no history of psychiatric disorders as groups of comparison whereas most of previous studies focusing on the prevalence of MetS in BD used either non-psychiatric controls or subjects with schizophrenia.

There are also certain limitations of this study that should be considered. First, our cross-sectional design did not allow us to make causal inferences on whether psychopathology precedes metabolic abnormalities or vice versa. Next, we were unable to control for lifestyle indicators such as dietary intake, alcohol use, and physical activity. Third, the smoking status in the Bipolar Stress Study was measured only at the baseline and thus provided only a proxy indicator of smoking habits at the two-year mark. Fourth, the methods of assessment of MetS components differed somewhat between BD patients in NESDA and the Bipolar Stress Study. However, mean values of MetS components were similar for NESDA and the Bipolar Stress Study, except for HDL-cholesterol levels ($p = 0.03$). Fifth, manic symptoms were not assessed. Sixth, the prescription rates of psychotropic medication in this study reflect that we also included non-symptomatic participants with lifetime diagnoses of bipolar and depressive disorders. Moreover, some participants might have substantial benefit of other (psycho) therapeutic interventions to remain stable and this may influence the need of medication. Next, the concept of MetS has been criticized by the American Diabetes Association [45], which led us to analyze a dichotomous MetS indicator in addition to the individual components and the number of MetS components. This allowed us to confirm that some components (abdominal obesity) were more associated with BD than other components. Nevertheless, the WHO report [46], the American Heart Association, and the National Heart Lung and Blood Institute concluded that MetS is a concept with clinical relevance [6]. Eight, the original ATP III criteria [24] were used instead of the adjusted ATP III criteria [47,48], as information regarding nicotinic acid and derivatives of lovastatin and nicotinic acid was missing in the Bipolar Stress study.

Implications

We found that subjects with BD compared to those with MDD or no history of a psychiatric disorder had a higher prevalence of MetS, with the strongest contribution of abdominal obesity specifically in patients with symptomatic depression. The relatively high prevalence of MetS in the BD population therefore requires attention from both clinicians and researchers. Clinically, it might be relevant to apply individualized treatment for BD patients that also includes assessment of metabolic risk factors, psychoeducation, weight loss intervention [49], and improvement of health-related behaviors [5,50]. Additional research is needed to further examine the exact pathogenesis of MetS in BD and (severe) MDD patients. For instance, in addition to adverse lifestyle factors and medication, other potential commonly-shared aetiological pathways leading to both psychiatric disease and MetS (e.g. hyperactivity of the HPA axis and low-grade inflammation) should be further explored.

Competing interests statement

The authors have no competing interests to report.

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