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Research paper

Increased prevalence of metabolic syndrome in patients with bipolar disorder compared to a selected control group-a Northern Netherlands LifeLines population cohort study

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ABSTRACT

Objectives: Metabolic syndrome (MetS) is highly prevalent among patients with bipolar disorder (BD). The aims of this cross-sectional study were to determine the prevalence of MetS in Dutch BD subjects and compare it with a control group, to examine the association of demographic and clinical characteristics with MetS in BD, and to determine the extent to which metabolic dysregulation is treated in those patients.

Methods: 493 Dutch adult patients (≥ 18 years) with BD receiving psychotropic drugs and 493 matched control subjects were compared using data from the biobank Lifelines. We determined MetS according to the National Cholesterol Education Program Adult Treatment Panel III-Adapted (NCEP ATP III-A) criteria. The difference in the prevalence of MetS and the associations with characteristics were analyzed with logistic regression.

Results: BD subjects (30.6%) showed a significantly higher prevalence of MetS compared to the control group (14.2%) ($p < .001$, OR:2.67, 95% CI:1.94-3.66). Univariate analysis showed that smoking, body mass index (BMI) and antidepressant drug use were associated with MetS. Multivariate analysis showed that smoking (OR:2.01) was independently associated with MetS in BD. For hypertension, hyperglycemia and lipid disorder pharmacological treatment was provided to respectively 69.5%, 24% and 18.4% of the BD subjects in our sample.

Limitations: Duration of illness of BD subjects was unknown.

Conclusions: This study demonstrated a higher prevalence of MetS in Dutch BD subjects compared to persons without BD. In addition, a remarkable undertreatment of some of the components of MetS was found.

1. Introduction

Bipolar disorder (BD) is a chronic and severe mental disorder with high psychiatric and medical burden (Zigmond et al., 2015). This major affective disorder is characterized by unusual mood fluctuations ranging from hypomania and/or mania to depression (American Psychiatric Association, 2013). Life expectancy is shortened in BD patients by 12-20 years in men and by 11-17 years in women compared to the general population (Laursen et al., 2013). The origin of this reduction in life expectancy is besides an increased prevalence of suicide, mainly due to the significant influence of somatic comorbidity.

The most prevalent somatic condition in BD is cardiovascular disease (CVD), while other frequently occurring somatic conditions are auto-immune disorders, obesity and diabetes (SayuriYamagata et al., 2017). The cluster of risk factors for CVD and type 2 diabetes mellitus (T2DM), consist the so-called metabolic syndrome (MetS), as defined by the

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National Cholesterol Education Program Adult Treatment Panel III-Adapted (NCEP ATP III-A) (Alberti et al., 2009). Previous studies suggest that there is an increased prevalence of MetS in patients with BD compared to the general population (Fagiolini et al., 2008; McElroy and Keck, 2014; Sicras et al., 2008; Vancampfort et al., 2013). A meta-analysis from 2013 describes an overall prevalence of 37.3% MetS in BD patients, with a significantly higher prevalence of MetS in patients treated with antipsychotics (Vancampfort et al., 2013).

Apart from the somatic burden itself, it seems that MetS is also associated with the exaggeration of psychiatric symptomatology of patients. Patients with an accumulation of three or more somatic conditions show more frequent suicidal behavior, rapid cycling, anxiety disorders and are treated more often with anxiolytics and mood stabilizers in comparison to patients without somatic comorbidity (Forty et al., 2014). What is more, patients with MetS are more likely to report a history of suicide attempts compared to those without MetS (Fagiolini et al., 2005). Finally, it appears that the time to depressive recurrence in BD patients with obesity is shorter compared to non-obese controls (Fagiolini et al., 2003).

On global scale there are great differences described in prevalence of MetS in BD patients, with a spread of more than 30%.[9] A little is known about the prevalence of MetS in the Netherlands. Merely a couple of studies described a varying prevalence, ranging from 28.4 to 53%, of MetS in Dutch BD patients (De Jong et al., 2018; Konz et al., 2014; Silarova et al., 2015; Simoons et al., 2019). Although the literature shows a strongly increased prevalence of MetS in BD, both globally and nationally, there is a lack of compliance with screening protocols for MetS (Mitchell et al., 2012; Simoons et al., 2018). For example, in a Dutch cohort study of 324 patients, including 198 patients (61.1%) using psychotropic drugs, 186 patients (57.4%) were not routinely screened (Simoons et al., 2018).

Summarized, previous studies describe an increased prevalence of MetS in BD patients, resulting in a higher rate of somatic comorbidity and mortality, with a lack of compliance to screening protocols for MetS. Moreover, there is a deficiency in studies focusing on the prevalence of MetS in Dutch BD patients on a societal scale. Therefore, the aims of this cross-sectional large scale cohort study were to determine the prevalence of MetS in Dutch subjects with BD in comparison with a selected control group, to examine the influence of demographic and clinical characteristics on MetS in BD, and to analyze the pharmacological treatment of metabolic dysregulation.

2. Materials and methods

2.1. Study design

This cross-sectional study was carried out by the Department of Psychiatry, part of the University Medical Center Groningen (UMCG). This study was performed by medical data utilization from the Lifelines biobank (www.lifelines.nl). Lifelines is a cohort study that has been collecting data from residents of the three northern provinces of the Netherlands (Groningen, Drenthe and Friesland) since 2006. The LifeLines Cohort Study is conducted according to the principles of the Declaration of Helsinki and in accordance with research code of the UMCG. The LifeLines study is approved by the medical ethical committee of the University Medical Center Groningen, The Netherlands. All participants signed an informed consent prior to participation.

2.2. Participants

The dataset supplied by Lifelines provides data of 152.141 participants, including 494 participants with bipolar disorder, who were identified by self-report based on clinical diagnosis by a psychiatrist, within a group of patients in with a history depressive episodes as defined by the Mini International Neuropsychiatric Interview (MINI, Sheehan et al., 1998). Bipolar subtype information was unavailable. In this study we will only focus on the data of baseline assessment (2008-2013). The following inclusion criteria were maintained for the BD group:

(1) Age $\geq$ 18 years.
(2) Met criteria for bipolar I disorder, bipolar II disorder, cyclothymic disorder, other specified bipolar disorder or unspecified bipolar disorder, diagnosed by a psychiatrist.
(3) Lifelines possesses screening data of all five parameters (blood pressure, triglycerides, high-density lipoprotein (HDL) cholesterol, fasting glucose and abdominal circumference), so MetS could be determined.

Composition of the control group: In order to facilitate a clinically relevant comparison, the selected control group includes Lifelines participants without psychiatric disorders (dementia, depression, social phobia, agoraphobia, panic disorder, anxiety disorder, bipolar disorder, schizophrenia, eating disorder, OCD and ADHD) that is comparable in socio-educational level. To compile this control group, a similar sample to the BD group has been searched based on gender, age, education level and smoking behavior. We explored these four characteristics for all BD subjects, to make matches on these characteristics with the selected participants without psychiatric disorders. Data of the smoking behavior were missing for 23 BD subjects and data of educational level were missing for two BD subjects. For these in total 25 BD subjects, a control patient was included in which the same characteristic (smoking behavior or educational level) was missing, while the other three characteristics were corresponding. For six BD subjects, a perfect match could not be found based on the four characteristics. Therefore, there is an additional smoking participant in the control group, an additional non-smoking participant in the control group and there are four participants with a different level of education compared to the BD group. Age and gender are identical in both groups.

2.3. Study variables

The study variables include metabolic syndrome and its associated criteria, demographic- and clinical characteristics, psychotropic drug treatment (antipsychotics, mood stabilizers, antidepressants, benzodiazepines/hypnotics/sedatives and psychostimulants) and drug treatment for metabolic dysregulation. A short explanation of the study variables is displayed below:

2.3.1. Metabolic syndrome

In this study, the definition according to the NCEP ATP III-A was followed Third Report of the National Cholesterol Education Program (NCEP) (2002). According to these criteria, the diagnosis of MetS is made at the presence of three or more abnormalities in the following five characteristics:

(1) Abdominal obesity, defined as a waist circumference $\geq$ 102 cm (40 inch) in men and $\geq$ 88 cm (35 inch) in women.
(2) Serum triglycerides $\geq$ 150 mg/dL or drug treatment for elevated triglycerides.
(3) Serum HDL cholesterol $<$40 mg/dL in men and $<$50 mg/dL in women or drug treatment for low HDL cholesterol.
(4) Blood pressure $\geq$ 130/85 mmHg or drug treatment for elevated blood pressure.
(5) Fasting plasma glucose $\geq$ 100 mg/dL or drug treatment for elevated blood glucose.

The measurements for the MetS criteria were performed at various locations of Lifelines scattered over the north of the Netherlands. Blood pressure was measured ten times, with the average of measurements nine and ten as the final value. The waist circumference was measured midway the superior border of the iliac crest and the inferior border of

the ribs.

2.3.2. Demographic and clinical characteristics

Lifelines collected various demographic and clinical data from participants by the use of questionnaires. In this study, the following demographic and clinic characteristics were examined: age, gender, employment status, educational level, marital status, body mass index (BMI), smoking status, the use of psychotropic drugs and the use of drugs to treat metabolic disruption. For the characteristic smoking, we defined smoking as the current consumption of tobacco or the use of tobacco in the last month. Psychotropic drugs included all officially registered drugs, provided with an anatomic therapeutic chemic (ATC) code, prescribed for psychiatric disorders.

2.4. Statistical analysis

The data collected in this study were processed using descriptive and inferential statistics. All statistical analyses were performed using IBM SPSS (version 25, Chicago USA). To determine whether there was a significant difference in prevalence of MetS (including the associated five components) between BD subjects and control subjects, the chi-squared test was used. The effect size for the various categorical variables of MetS was expressed in odds ratio (OR). To investigate the influence of different independent variables on the dichotomous dependent variable (MetS) for both BD subjects and control subjects, logistic regression analysis was performed. For univariate analysis an independent *t* test was performed for continuous variables and a Chi-square test for categorical variables. Multivariate logistic regression analysis (backward stepwise method) was performed to determine which variables had an independent significant influence on the dependent variable. Outcomes with a P value of ≤ 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

The results of this study were obtained from a study population of BD subjects (n=493) with an average age of 46.7 years (SD=10.8 years) and a control group (n=493) with an average age of 46.7 years (SD=10.8). The ages of the patients of both groups are between 19 and 83 years. Table 1 shows the demographic and clinical patient characteristics.

Table 1
Demographic and clinical characteristics of both BD patients (N=493) and control patients (N=493).

Characteristic	BD group	Control group
Age		
mean (SD)	46,7 (10,8)	46,7 (10,8)
minimum	19	19
maximum	83	83
Gender, n (%)		
male	193 (39,1)	193 (39,1)
female	300 (60,9)	300 (60,9)
Education level, n (%)		
no education	8 (1,6)	7 (1,4)
elementary school[a]	25 (5,1)	27 (5,5)
lower vocational education [b]	86 (17,4)	85 (17,2)
lower (theoretical) secondary education[c]	59 (12)	59 (12)
secondary vocational education, work-study route[d]	132 (26,8)	133 (27)
upper secondary education[e]	53 (10,8)	52 (10,5)
upper vocational education[f]	94 (19,1)	95 (19,3)
university	22 (4,5)	21 (4,3)
other	12 (2,4)	12 (2,4)
unknown	2 (0,4)	2 (0,4)
Smoking status, n (%)		
smoker	182 (36,9)	183 (37,1)
non-smoker	288 (58,4)	289 (58,6)
unknown	23 (4,7)	21 (4,3)
Marital status, n (%)		
married or registered partnership	181 (36,7)	234 (47,5)
living with partners	35 (7,1)	43 (8,7)
single	65 (13,2)	25 (5,1)
widow or widower	7 (1,4)	4 (0,8)
divorced	37 (7,5)	14 (2,8)
other	6 (1,2)	6 (1,2)
serious relation, not cohabiting (LAT relation)	21 (4,3)	5 (1,0)
unknown	141 (28,6)	162 (32,9)
Employment status, n (%)		
paid work	236 (47,8)	404 (81,9)
retired	20 (4,1)	21 (4,3)
unemployed or looking for work	28 (5,7)	8 (1,6)
unfit for work	131 (26,6)	6 (1,2)
life on welfare	1 (0,2)	0 (0,0)
fulltime housewife/house husband	31 (6,3)	32 (6,5)
student	2 (0,4)	0 (0,0)
national assistance benefit	9 (1,8)	2 (0,4)
unknown	35 (7,1)	20 (4,1)
BMI		
Mean (SD)	27,3 (5,1)	26,4 (4,3)
minimum	17,0	17,7
maximum	48,7	45,7

Abbreviations: BD, bipolar disorder; SD, standard deviation; LAT, living apart together; BMI, body mass index.

3.2. Prevalence of MetS in BD subjects compared to control subjects

The prevalence of MetS was significantly increased in BD subjects (30.6%) compared to the control group (14.2%) ($p < 0.001$), with an OR of 2.67 (CI:1.94–3.66). Table 2 describes the comparison in the prevalence of MetS and associated parameters between BD subjects and the control group. This overview shows that central obesity, hyperglycemia or the use of medication against hyperglycemia, low HDL cholesterol or the use of medication against low HDL cholesterol and hypertriglyceridemia or the use of medication against hypertriglyceridemia occur significantly more in BD subjects compared to the control subjects ($p < 0.001$). The only parameter without a significant difference between BD subjects (26.0%) and the control group (25.6%) was hypertension or the use of antihypertensive drugs.

3.3. Psychotropic drug use in BD subjects

An overview of the use of psychotropic drugs by BD subjects and the corresponding average BMI per type of psychotropic drugs is shown in Table 3. The different types of psychotropic drugs are subdivided into the subgroups: antipsychotics, mood stabilizers, antidepressants, benzodiazepines/hypnotics/sedatives and psychostimulants. Within each subgroup some patients use more than one specific drug. Antipsychotics are subdivided into first generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). 135 BD subjects were not using any psychotropic drugs. These 135 patients also have the lowest average BMI compared to all patients using any type of psychotropic drugs.

3.4. The prevalence of pharmacological treatment for metabolic dysregulation

For the pharmacological treatment of metabolic dysregulation in BD subjects and control subjects we analyzed the prevalence of hypertension, hyperglycemia and lipid disorders (defined as: low HDL cholesterol and/or hypertriglyceridemia). Fig. 1 provides an overview of the prevalence of pharmacological treatment for these metabolic dysregulations in BD subjects and control subjects diagnosed with MetS. We observed that 69.5% of the BD subjects and 50.0% of the control subjects received pharmacological treatment for hypertension. For hyperglycemia and lipid disorder the pharmacological treatment was, respectively, 24.0 and 18.4% in BD subjects and 6.0 and 11.9% in control subjects.

Table 2
Prevalence of MetS and its criteria in BD patients (*N*=493) and the control group (*N*=493).

Variable	BD group n (%)	Control group n (%)	*P*[a]	OR (95% CI)
MetS	151 (30.6)	70 (14.2)	<.001	2.67 (1.94 – 3.66)
Central obesity	252 (51.1)	185 (37.5)	<.001	1.74 (1.35 – 2.24)
Hypertension or medication for hypertension	128 (26.0)	126 (25.6)	0.884	NS
Hyperglycemia or medication for hyperglycemia[b]	111 (22.5)	53 (10.8)	<.001	2.41 (1.69 – 3.44)
Low HDL cholesterol or medication for low HDL cholesterol	217 (44.0)	92 (18.7)	<.001	3.43 (2.57 – 4.57)
Hypertriglyceridemia or medication for hypertriglyceridemia	174 (35.3)	99 (20.1)	<.001	2.17 (1.63 – 2.89)

abbreviations: BD, bipolar disorder; MetS, metabolic syndrome; CI, confidence interval; OR, odds ratio; NS, not significant; HDL cholesterol, high-density lipoprotein cholesterol.

[a] difference between BD group and control group (X^2 test).

[b] non-fasting serum glucose was determined in seven BD patients and three control patients.

Table 3
Psychotropic drug treatment in BD patients and the mean BMI per subtype psychotropic drug.

Psychotropic drug type	BD patients n	BMI mean, (SD)
Antipsychotics [a]	130	28.0 (5.8)
FGAs	15	29.3 (7.7)
SGAs	118	27.8 (5.7)
Aripiprazole	9	30.9 (8.5)
Clozapine	5	28.4 (6.7)
Olanzapine	31	28.0 (6.0)
Quetiapine	65	27.2 (5.1)
Quetiapine ≤100mg	32	27.2 (4.9)
Quetiapine >100mg	25	26.8 (5.1)
Risperidone	15	29.4 (5.5)
Mood stabilizers [b]	180	28.6 (5.6)
Anticonvulsants	61	27.1 (4.4)
Carbamazapine	10	27.9 (4.5)
Lamotrigine	17	27.4 (4.5)
Valproic acid	38	28.7 (4.0)
Lithium	133	28.2 (5.0)
Antidepressants [c]	168	27.0 (4.5)
Benzodiazepines/hypnotics/sedatives [d]	113	28.4 (5.5)
Psychostimulants [e]	11	26.4 (4.5)
No psychotropic drug treatment	135	26.2 (4.5)

abbreviations: BD, bipolar disorder; BMI, body mass index; FGAs, first generation antipsychotics; SGAs, second generation antipsychotics.

[a] 22 patients used a combinations of antipsychotics. The dosage of quetiapine is missing for 8 patients.

[b] 20 patients used a combinations of mood stabilizers.

[c] 21 patients used a combination of antidepressants.

[d] 25 patients used a combination of benzodiazepines.

[e] One patient used a combination of psychostimulants.

3.5. Demographic and clinical factors associated with MetS in BD subjects and control subjects

Univariate analysis showed that MetS was significantly more prevalent in BD subjects with a higher age (t_{491}=3.81, p=0.00, d= 0.37), a higher BMI (t_{491}=5.41, p=0.00, d= 0.52), who were smoking (X^2_1=6.04, p=0.01, OR=1.64) and who received antidepressants drug treatment (X^2_1=5.66, p=0.02, OR=1.64). Additionally, MetS was more prevalent in BD subjects with secondary or tertiary education/intermediate vocational education (X^2_1=6.40, p=0.01, OR=1.92) as highest education level compared to BD subjects who received higher vocational education/university. For the control subjects, univariate analysis showed a higher prevalence of MetS for patients with a higher age (t_{491}=3.86, p=0.00, d= 0.48), who were male (X^2_1=7.64, p=0.01, OR=2.05), without paid work (X^2_1=3.44, p=0.02, OR=2.09) and a higher BMI (t_{491}=9.06, p=0.00, d=1.11). The control subjects with primary education (X^2_1=10.88, p=0.00,OR=4.72) as highest education level showed a higher prevalence of MetS compared to control subjects who received higher vocational education/university.

After correction for confounders the multivariate analysis showed that mean age (p=0.01, OR=1.03) and smoking status (p=0.00, OR=2.01) were significantly associated with MetS in BD subjects. For control subjects the multivariate analysis showed that mean age (p=0.00, OR=1.04) and mean BMI (p=0.00, OR=1.27) were significantly associated with MetS. A significant interaction was observed of BMI with BD in MetS (p=0.008). This interaction was not observed in age and smoking status. An overview of the univariate- and multivariate analysis of the demographic and clinical factors is provided in Table 4.

4. Discussion

To our knowledge this cross-sectional study is the first study in a relatively large population sample (N=493) researching the prevalence of MetS in Dutch BD subjects and comparing it with a selected control group. The primary outcome of this study is an increased prevalence of MetS in BD subjects (30.6%) compared to the selected control group (14.2%). Univariate analysis showed that smoking, higher age, higher BMI and antidepressant drug use were associated with MetS. Multivariate analysis showed that smoking (OR:2.01) and higher age (OR:1.03) were independently associated with MetS in BD. For hypertension, hyperglycemia and lipid disorders pharmacological treatment was provided to respectively 69.5, 24 and 18.4% of the BD subjects in our sample, which underlines the previously documented lack of monitoring and pharmacological treatment of metabolic dysregulation in BD subjects.

Compared to the previous published studies in the Netherlands by De Jong et al. (2018) and Simoons et al. (2019) with a prevalence of respectively 42.6 and 53.0% MetS in BD subjects, the prevalence we found is considerably lower. This could possibly be explained by the difference in age between our study population and the participants in the previous studies. The mean age of our study population was 46.7 years, while the mean age of the previous Dutch studies were respectively 52.5 years and 50 years. Additionally, in these studies only outpatients with BD were observed, while in our study the data obtained through Lifelines contained a study population with inpatients, clinical patients and patients without any medical healthcare contacts on regular basis. These differences might contribute to a different outcome in prevalence of MetS in our study compared to the previous Dutch studies. Another Dutch study by Silarova et al. (2015) with a larger sample-size (241 BD subjects) shows a prevalence of 28.4% MetS in BD subjects, which corresponds better with our findings. Moreover, Silarova et al. (2015) compared the prevalence in BD subjects with non-psychiatric controls, displaying a prevalence of 16.5% MetS in these non-psychiatric controls. Once more, this finding is in line with the prevalence of 14.2% MetS in our control group.

However, a comparison of our findings with a meta-analysis by Vancampfort et al. (2013) which displays the prevalence of MetS on globally scale, shows a more corresponding result. This meta-analysis (81 articles, *n*=6983) demonstrates a global prevalence of 37.3% and a European prevalence of 32.4% of MetS in BD subjects. This meta-analysis refers to a study by Tillin et al. (*n*=2346), which shows a prevalence of 18.4% MetS in healthy European males and 14.4% in healthy European females (Tillin et al., 2005). These findings are in line with our observed prevalence of MetS in the control group.

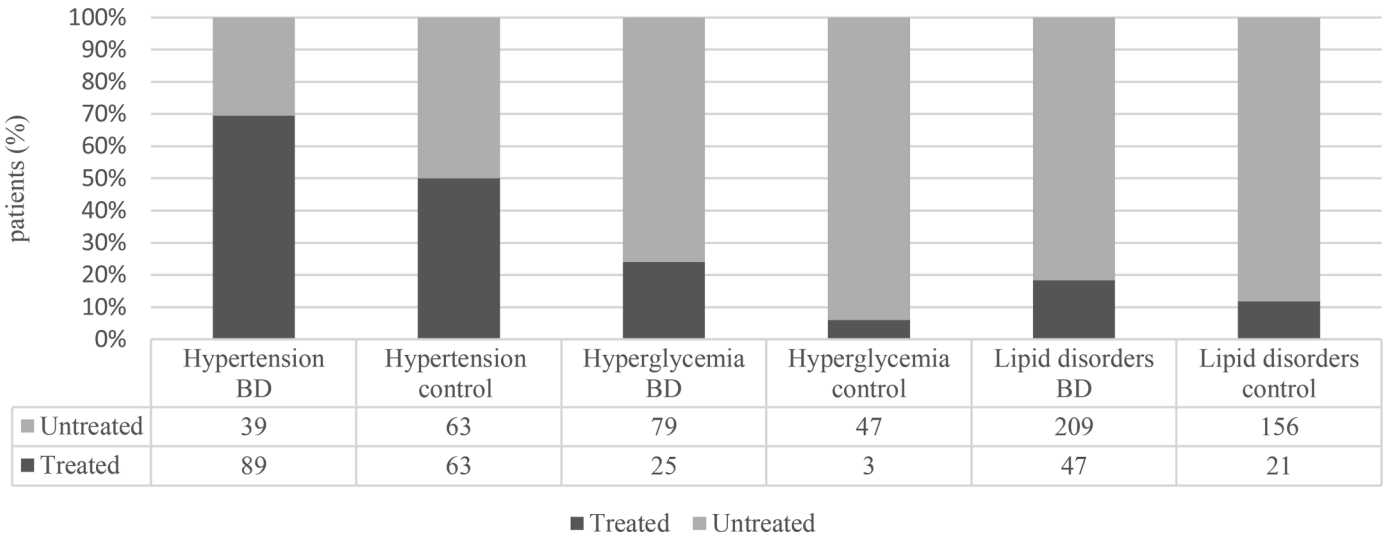

Fig. 1. Prevalence of pharmacological treatment for hypertension, hyperglycemia and lipid disorders in absolute numbers for BD- and control patients. abbreviations: BD, bipolar disorder.

Table 4
Associations of demografic and clinical charesteristics with MetS in both BD patients (*N*=493) and control patients (*N*=493).

Characteristic	BD patients		P[a]	OR (95% CI)		Control patients		P[a]	OR (95% CI)	
	MetS (N=151)	**No MetS (N=342)**		**Univariate analysis**	**Multivariate analysis**	**MetS (N=70)**	**No MetS (N=423)**		**Univariate analysis**	**Multivariate analysis**
Sex, n (%)			0.53					0.01		
Male	56 (37.1)	137 (40.1)		0.88 (0.59-1.31		38 (54.3)	155 (36.6)		2.05 (1.23-3.42)	
Female	95 (62.9)	205 (59.9)		1 (reference)		32 (45.7)	268 (63.4)		1 (reference)	
Age, mean (SD), years	49.5 (11.1)	45,5 (10.4)	<.001	1.04 (1.02-1.05)	1.03 (1.01-1.06)	51.2 (11.4)	46.0 (10.5)	<.001	1.05 (1.02-1.07)	1.04 (1.01-1.09)
Level of education, n (%)[b]			0.04					<.001		
≤ Primary education	10 (6.9)	23 (6.9)	0.25	1.67 (0.70-3.97)		12 (17.9)	22 (5.3)	<.001	4.72 (1.88-11.90)	
Secondary or tertiary education/ intermediate vocational education	110 (76.4)	220 (65.7)	0.01	1.92 (1.16-3.17)		43 (64.2)	286 (69.4)	0.44	0.28 (0.13-0.60)	
Higher vocational education/university	24 (16.7)	92 (27.4)		1 (reference)		12 (17.9)	104 (25.3)		1 (reference)	
Marital status, n (%)[c]			0.35					0.64		
Married	57 (43.5)	124 (53.2)		0.81 (0.52-1.26)		27 (67.5)	207 (71.1)		0.84 (0.42-1.71)	
Unmarried	74 (56.5)	109 (46.8)		1 (reference)		13 (32.5)	84 (28.9)		1 (reference)	
Employment status, n (%)[d]			0.06					0.02		
Paid work	60 (44.8)	176 (54.3)		1 (reference)		51 (76.1)	353 (86.9)		1 (reference)	
Unpaid work/ not employed	74 (55.2)	148 (45.7)		1.47 (0.98-2.00)		16 (23.9)	53 (13.1)		2.09 (1.11-3.93)	
Smoking status, n (%)[e]			.004					0.79		
Smoker	69 (46.9)	113 (35.0)		1.64 (1.11-2.44)	2.01 (1.26-3.49)	25 (37.3)	158 (39.0)		0.93 (0.55-1.59)	
Non-smoker	78 (53.1)	210 (65.0)		1 (reference)	1 (reference)	42 (62.7)	247 (61.0)		1 (reference)	
BMI, mean (SD) (kg/m^2)	29,2 (5,1)	26,6 (4,9)	<.001	1.11 (1.06-1.15)		30.4 (4.5)	25.7 (3.9)	<.001	1.26 (1.18-1.34)	1.27 (1.16-1.39)
Psychotropic drugs, n (%)										
Antipsychotics	31 (20,5)	99 (28,9)	0.05	0.63 (0.40-1.00)						
Antidepressants	63 (41,7)	105 (30,7)	0.02	1.62 (1.09-2.40)						
Mood stabilizers	51 (33,8)	129 (37,7)	0.40	0.84 (0.56-1.26)						

abbreviations: BD, bipolar disorder; MetS, metabolic syndrome; CI, confidence interval; OR, odds ratio; NS, not significant; BMI, body mass index; . [a] Chi-square test for continuous variables, independent *t* test for continuous variables. [b] 14 missing casus in BD, 14 missing casus in controls. [c] 129 missing casus in BD, 162 missing casus in controls. [d] 35 missing casus in BD, 20 missing casus in controls. [e] 23 missing casus in BD, 21 missing casus in controls.

We observed a significantly higher risk of MetS in BD subjects compared to the control group, with an OR of 2.67 (CI:1.94–3.66). This risk is relatively high compared to the findings of the global meta-analysis of Vancampfort et al. (2013) displaying a OR of 1.98 (CI:1.74–2.25) and the most comparable Dutch study by Silarova et al. (2015) showing a OR of 1.79 (CI:1.20-2.67). Additionally, we found a higher risk for BD subjects in developing four of the five characteristics of MetS. Solely the risk for hypertension was not significantly increased for BD subjects compared to the control group. In our study, abdominal obesity was the most prevalent increased variable in BD subjects (51.1%), which is in line with the findings of the previous Dutch studies (De Jong et al., 2018; Silarova et al., 2015; Simoons et al., 2019). Moreover, the findings of Vancampfort et al. (2013) show a corresponding prevalence of abdominal obesity (48.7%) on global scale. Furthermore, the rates for low HDL cholesterol (42.1%) and hypertriglyceridemia (39.3%) were also comparable to our findings of respectively 44.0 and 35.3%. Divergent to our findings are the observed rates of hypertension (47.1%) and hyperglycemia (11.4%) in Vancampfort et al. (2013) which are respectively higher and lower compared to our findings. This could possibly be explained by the influence of the enormous demographic spread of the included studies in the meta-analysis.

Contrary to our expectations there was no association between the use of antipsychotics and the presence of MetS in BD subjects, while Vancampfort et al. (2013) concluded that BD subjects using antipsychotics were at greater risk to develop MetS in comparison with antipsychotic free BD subjects. In spite of the fact that the use of antipsychotics in our sample of BD subjects is quite low (23.8%) compared to the Dutch study by De Jong et al. (2018) they also did not observe any significant associations between psychotropic drug use and MetS in Dutch BD subjects. A possible explanation for the fact that we did not find any associations between antipsychotic use and MetS in BD subjects could be that a relative small fraction of the prescribed antipsychotics in our study were at high risk for metabolic dysregulation. The antipsychotics that are mainly well known for their metabolic side effects are clozapine (n=5) and olanzapine (n=31). In our study, only 30.5% of patients were treated with these antipsychotics. On the contrary, quetiapine is described as an antipsychotic drug with a moderate risk on metabolic adverse effects. In our study, 55.1% of the patients using antipsychotics were treated with quetiapine, while more than half of them received a low dosage ($\leq$ 100mg) (Musil et al., 2015). Interestingly, the mean BMI of patients treated with clozapine and olanzapine is higher than those treated with quetiapine, though definite conclusions cannot be made due to the limited number of patients in those groups. This finding supports the previously mentioned possible explanation for us not finding an association between antipsychotic drug use and MetS, considering an increased BMI is one of the most prevalent adverse effects of antipsychotics and will possibly play a major role in the onset of MetS (Correll et al., 2008; Musil et al., 2015; Newcomer, 2005). Surprisingly, we did find a significant association in univariate analysis between antidepressant drug use and MetS (p=0.02, OR=1.64). Several studies describe weight gain and its metabolic consequences and MetS as adverse effects of some antidepressants (Li et al., 2020; Gramaglia et al., 2018; McIntyre et al., 2010; Serretti and Mandelli, 2010).

This study indicates a significant association between age (p=0.01, OR=1.03), smoking (p=0.00, OR=2.01) and MetS in multivariate analysis. The higher prevalence of MetS in older BD subjects has been also previously described in several studies, since higher age is a risk factor for CVD (Kumar et al., 2017; Park et al., 2003). Interestingly, there is a significant association between smoking and MetS in BD subjects, while in the control group this association is not present, even though the number of smokers is approximately the same in both groups. In particular, there is a two-fold increase in the risk of developing MetS for smoking BD subjects compared to non-smoking BD subjects. Since we did not quantify the smoking behavior, we are not able to speculate about possible clarifications for this noteworthy association between smoking and MetS in the BD group in the absence of an association in the control group.

Strikingly, despite the increased prevalence of MetS in BD subjects, the individual components of MetS were found substantially undertreated. More specifically, hypertension appears to be relatively well diagnosed and treated in BD subjects. On the other hand, hyperglycemia and lipid disorders, is treated in only 24.0% and 18.4% of patients, respectively. It is worth mentioning that metabolic dysregulation in the control group is also substantially undertreated. At this point it is worth mentioning that there is a discrepancy between the MetS criteria according to the NCEP ATP III-A and the present diagnosis criteria in Dutch healthcare. Particularly, the NCEP ATP III-A implements lower cut-off values for hypertension, hyperglycemia and lipid disorders compared to the Dutch treatment standards. It is likely that this results in a seemingly higher rate of undertreatment in both BD subjects and control subjects. Nevertheless, considering the increased morbidity and mortality caused by metabolic dysregulation in BD, the observed percentages of pharmacological treatment for this metabolic dysregulation are extraordinary low. Especially in the psychiatric patient population, with a large proportion of psychotropic drug use, the essential importance of adequate screening and treatment for metabolic dysregulation must not be underestimated.

The design of the current study is subject to limitations that could be addressed in future research. First, the duration of illness of BD subjects was unknown, therefore this variable could not be included in the logistic regression analysis. Second, the number of patients in each setting -outpatient and inpatient- is unclear. This information would facilitate judgements on the maintenance of screening protocols and the eventual treatment for metabolic dysregulation. Third, in ten patients (seven BD subjects, three control subjects) non-fasting blood samples were taken, while the criteria by the NCEP ATP III-A describe to determine MetS, and especially hyperglycemia, with fasting blood samples. To prevent exclusion of these ten patients, all non-fasting glucose samples indicating hyperglycemia were disregarded. In these patients MetS was diagnosed at the presence of three or more deviant parameters out of the residual four characteristics. To our knowledge, the analysis of non-fasting blood samples to determine the lipid profile was not prohibited, because there are only minimal changes in levels of lipids in response to normal food intake, which is clinically unimportant (Langsted et al., 2008). Moreover, according to the NCEP ATP III-A criteria, it is not mandatory to analyze fasting blood samples to diagnose lipid disorders. Fourth, there are several other factors that can possibly influence the development of MetS. For example, we did not explore physical activity, nutrition, sleeping behavior and other lifestyle factors, which is limiting our insight into the associated factors causing an increased prevalence of MetS in BD. Fifth, in addition to age and gender, we matched our control group by social-educational factors (education level and smoking behavior) to provide a comparison that is clinically more relevant. Since smoking behavior has a complex relation with MetS, there may be a risk of overmatching bias. However, because prevalence of MetS in the current analysis is comparable (or slightly lower) with other studies that have investigated the prevalence of metabolic syndrome in the Dutch population, overmatching does not seem to have had a significant influence (Silarova et al., 2015; Slagter et al., 2017; Wolffenbuttel et al., 2017). Finally, this study is only representative for the study population of the northern regions of the Netherlands, because it was carried out by the use of data of inhabitants of this specific region of the Netherlands. There are also several strengths of our study. First, to our knowledge, this study was based on the largest study population (N=493) performed in the Netherlands researching the prevalence of MetS in BD subjects. Second, a strength of this study is the creation of its own control group out of 152.141 participants, selecting on age, gender, education level and smoking behavior, resulting in two equivalent groups on these four variables. Third, our sample consists a large group (N=135) of medication free BD subjects, whereas most previous studies do not have a substantial group

of BD subjects not using any psychotropic drugs.

In conclusion, we demonstrate a high prevalence of MetS in Dutch BD subjects compared to a selected control group. Univariate analysis showed a significant association between antidepressant drug use and MetS. Most remarkable is the significant association between smoking and MetS in multivariate analysis for BD subjects, while this association was not present in the control group. In spite of the increased prevalence of MetS in BD subjects, our results show a considerable undertreatment of metabolic dysregulation, which underlines the essence of routinely screening and eventual complementary pharmacological treatment for metabolic dysregulation. Future research on larger scale should focus on the role of smoking and antidepressant drug use in the prevalence of Mets in BD.

CRediT authorship contribution statement

M.P. Schuster: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft. **J. Borkent:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **M. Chrispijn:** Conceptualization, Investigation, Supervision, Visualization, Writing – original draft. **M. Ioannou:** Validation, Visualization, Writing – review & editing. **B. Doornbos:** Conceptualization, Methodology, Validation, Visualization, Writing – original draft. **H. Burger:** Conceptualization, Methodology, Visualization, Writing – original draft. **B.C.M. Haarman:** Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declarations of Competing Interest

None of authors have any financial and personal relationships with other people or organizations to report that could inappropriately influence (bias) this work.

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