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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