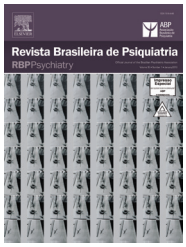
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REVIEW ARTICLE

Bipolar disorder and metabolic syndrome: a systematic review

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Abstract
Objective: Summarize data on metabolic syndrome (MS) in bipolar disorder (BD). *Methods*: A systematic review of the literature was conducted using the Medline, Embase and PsycInfo databases, using the keywords "metabolic syndrome", "insulin resistance" and "metabolic X syndrome" and cross-referencing them with "bipolar disorder" or "mania". The following types of publications were candidates for review: (i) clinical trials, (ii) studies involving patients diagnosed with bipolar disorder or (iii) data about metabolic syndrome. A 5-point quality scale was used to assess the methodological weight of the studies. *Results*: Thirty-nine articles were selected. None of studies reached the maximum quality score of 5 points. The prevalence of MS was significantly higher in BD individuals when compared to a control group. The analysis of MS subcomponents showed that abdominal obesity was heterogeneous. Individuals with BD had significantly higher rates of hypertriglyceridemia than healthy controls. When compared to the general population, there were no significant differences in the prevalence of low HDL-c in individuals with BD. Data on hypertension were also inconclusive. Rates of hyperglycemia were significantly greater in patients with BD compared to the general population. *Conclusions*: The overall results point to the presence of an association between BD and MS, as well as between their subcomponents.

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Introduction

Bipolar disorder (BD) is a chronic disease characterized by extreme changes in mood polarity. Onset typically occurs between adolescence and early adulthood. BD is associated with impairments in social and neuropsychological development, resulting in a high level of overall impairment. BD is the sixth leading cause of disability in the world and has a global prevalence estimated at .8%.[1]

In addition to the psychiatric symptoms associated with BD, there is also evidence suggesting that BD patients are at increased risk for clinical diseases in comparison to healthy controls. A sedentary lifestyle, smoking, and an unhealthy diet are prejudicial factors, as are metabolic disorders and neurological/cardiovascular diseases.[2] As a result, patients with BD have a life expectancy that is reduced by 25 to 30 years.[3]

Among the clinical diseases that are comorbid with BD, there is evidence of a high rate of metabolic syndrome (MS) in bipolar patients. MS is collection of metabolic risk factors with an unknown etiologic basis and pathophysiological mechanisms that increases the chances of developing cardiovascular disease and type 2 diabetes.[3] The prevalence of MS in the world population ranges from 6.0% to 70.3%, depending on variables such as diagnosis criteria, comorbidities, ethnic group and sex.[4]

In bipolar patients, MS comorbidity is associated with a more complex disease, a less favorable response to treatment, and adverse courses and outcomes, such as an increased risk for depressive symptoms and episodes, including the risk of suicide.[5,6]

Thus, the aim of this study is to summarize data on metabolic syndrome in patients with BD.

Methods

To identify studies that are relevant to the current study, a systematic review was conducted with the Medline, Embase and PsycInfo databases, using the keywords "metabolic syndrome", "insulin resistance" and "metabolic X syndrome", and cross-referencing them with "bipolar disorder" or "mania". The search was conducted during May of 2012 and was limited to human studies published in English. Duplicated articles were excluded. The remaining paper titles and abstracts were used to determine whether the reference might be pertinent to the review. The following types of publications were candidates for review: (i) clinical trials, (ii) studies involving patients diagnosed with bipolar disorder, or (iii) data about metabolic syndrome.

To assess the methodological weight of the studies, a 5-point quality scale was used that included the following items: a sample with at least 100 BD patients, a standardized BD diagnostic measure, use of the NCEP National Cholesterol Education Program (NCEP) or the International Diabetes Federation (IDF) criteria for MS, and a central aim of evaluating MS in BD patients or of comparing BD patients to controls or data from the general population. This quality score was based on a similar scoring method that used for two other published review articles relevant to the current study.[7,8]

Results

Search results

The literature search conducted using Medline, Embase and PsycInfo resulted in 457 articles. After the duplicate articles were excluded, 70 titles and abstracts were evaluated for pertinence. This process resulted in 39 references that were relevant to the present literature review. The search chart is shown in Figure 1, and the data extracted from these studies is available online as Supplementary Information.

Quality of studies

None of the studies reached the maximum quality rating of 5 points, mainly due to the lack of a structured BD diagnostic measure, the lack of a control group or general population comparison, or a sample size of less than 100 BD subjects.

Prevalence and demographic features

The prevalence of MS in BD patients was distributed according to different criteria, as presented in Table 1.

Patients with BD had a slightly higher rate of MS compared to the general population, but this difference failed to reach significance.[9-12] However, when compared to a control group, the prevalence of MS was significantly higher in BD patients.[12-16]

BD patients with MS were significantly older than BD patients without MS.[14,17-21] The risk of MS increased more than 3 times in BD subjects over 30 years old[12,19] when compared to a control group.[15,16] However, one study showed no association of MS with age.[9] There were no significant differences in MS rates according to gender.[6,9,10,14-17,20-31]

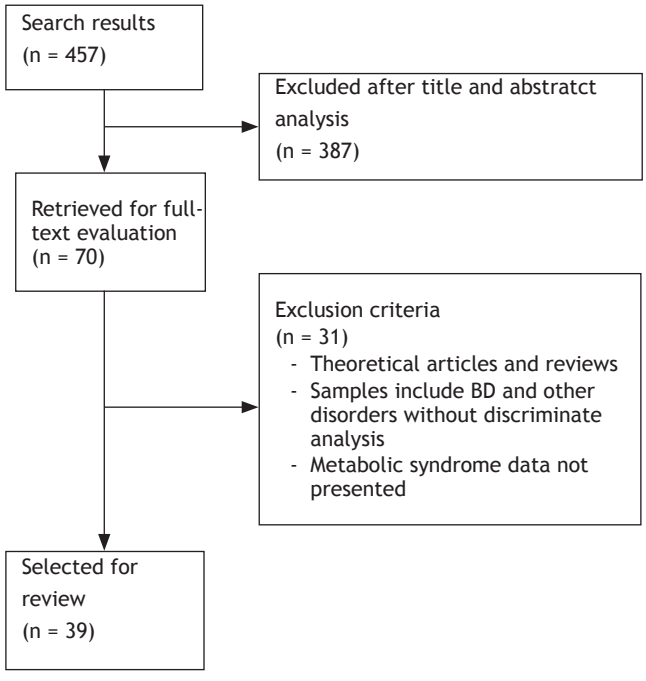


Figure 1 Flowchart of methods.

Table 1 Prevalence of metabolic syndrome in bipolar disorder in each criterion definition.

Criterion	Prevalence	References
NCEP ATP III	16.7%-50.0%	10; 12; 14-17; 19; 20; 22; 23; 25; 26; 28-32; 34; 36; 52; 53
IDF	25.7%-67.0%	12; 19; 20; 39; 51

NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel
IDF: International Diabetes Federation.

Course of disorder and clinical outcomes

Two studies of BD patients reported no significant differences in the age of onset of the first episode in BD patients with MS compared to those without MS.[6,20] However, Guan et al.[13] found that BD patients with MS had a significantly older mean age of onset of the first episode compared to BD patients without MS. Other studies showed that BD patients with MS had a significantly later age of first treatment for depression and mania,[6] a significantly longer illness duration[20] and a significantly greater number of psychiatric hospitalizations,[6] compared to those without MS.

Several studies found no association between psychotropic drug use or treatment strategy and elevated rates of MS.[10,12,14,22,32-34] However, more of the subjects taking olanzapine, clozapine, or lithium met criteria for MS than those who did not take these drugs.[17,35] Patients taking only antipsychotics had higher MS rates than patients taking only mood stabilizers.[24]

The rates of psychiatric comorbidity were not significantly different between BD patients with and without MS,[6,20] but BD patients did have significantly higher rates of psychiatric comorbidities compared with healthy controls.[16] Some studies showed no significant difference in the lifetime history of suicide attempts between BD patients with and without MS,[6,9,23,36] whereas others found that this was significantly higher in BD patients with MS.[36,37]

With regards to clinical comorbidities, BD patients had higher overall comorbidity rates than healthy controls.[15,16] BD patients with MS had significantly increased rates of diabetes and cardiovascular disease compared to both BD patients without MS[14,18,22] and to the general population.[11] These patients also had a significantly greater risk of cardiovascular mortality and coronary heart disease when compared to patients without MS.[38] Smoking was not associated with the presence[14,20] or risk of MS,[39] except when compared to controls or the general population.[11,16] Bipolar patients with MS had significantly higher rates of alcoholism than patients without MS,[14] but they had similar alcoholism rates as controls[16] and significantly lower alcoholism rates than other diagnostic criteria.[35]

Subcomponents of metabolic syndrome

In the analysis of MS subcomponents, the findings on abdominal obesity were inconclusive.

Although some previous studies have found significantly higher obesity rates in BD patients compared to the general population[11] or healthy controls,[12] others have found a significant difference only in women[10] or no difference at all.[33] Data on the differences in gender prevalence are similarly conflicting; in two studies, female patients had significantly higher prevalence rates of abdominal obesity when compared to men,[21,22] whereas another study showed no such difference.[6]

BD patients had significant higher rates of hypertriglyceridemia than controls.[12,14-16,33] When compared to the general population, there was no significant difference.[10] Male BD patients had significantly higher rates of hypertriglyceridemia when compared to female BD patients.[6,22]

Some studies presented significantly higher prevalence rates of low HDL-c in BD patients when compared to controls,[14-16,33] contrary to other reports that showed no significant difference.[11,12] The prevalence of low HDL-c was lower in BD patients compared to the general population, but that was not significantly different.[10] Women had higher rates of low HDL-c than did men, but this was not statistically significant.[6,22] Women did have significantly higher HDL-c ratios when compared to men.[40]

Data on hypertension were also contradictory. Although one study showed similar prevalence rates in patients with BD and the general population,[10] another showed significant higher prevalence in patients.[11] When compared to controls, one study presented significantly higher rates of hypertension in patients,[14] whereas others reported similar prevalence rates.[12,15,16] Among BD patients, men had significantly higher rates of hypertension than women,[6,22] with significantly higher systolic blood pressures as well.[40]

Despite the selectivity of the criteria used, hyperglycemia rates were significantly higher in patients with BD when compared to the general population.[10] However, when compared to controls, patients had a similar prevalence of hyperglycemia.[12,14-16,33] Men and women had similar rates of hyperglycemia.[6,22]

Obesity was higher in patients with BD than controls[12,15,16] and the general population[9,11] (except in one study that found similar prevalence rates in both groups[10]). BD patients were also reported to be more overweight than controls, both significantly[14] and non-significantly,[12] and they were significantly more overweight than the general population.[11] Patients with MS had significantly higher body mass index (BMI) values than those without MS,[18] and it was found that BMI was significantly associated with MS in a logistic regression analysis.[19]

Discussion

Despite finding some contradictory results, we report on a body of evidence that shows a higher prevalence of MS and its subcomponents in bipolar patients. MS was associated with a poor course of illness and prognosis in bipolar individuals, suggesting that this is still an important issue in clinical and psychiatric practice.

The variance in results could be explained by differences in the sample or could reflect differences in the prevalence of MS in the general population due to cultural differences in dietary habits, levels of physical activity and genetic backgrounds. These factors may have influenced the analysis of the subcomponents as well. Indeed, the heterogeneity of the criteria is a significant concern regarding MS diagnosis[41] and could have affected the prevalence rates in the reviewed studies. The criteria by the NCEP ATP III and the IDF are the most widely used to diagnose MS, but there are some differences between them (Table 2). Moreover, there is a large cluster of criteria modifications that makes clinical diagnosis and research analysis challenging.

Although the use of psychotropic drugs provides a common-sense explanation of some of the components of MS, studies that do not find this association show that medications are not a simple explanation. Most BD patients reported polypharmaceutical drug use or had used different types of medication during the course of their disease. Because antipsychotic polytherapy increases the prevalence of MS compared to monotherapy,[42] the use of multiple medications could aggravate the course of MS, resulting in a worse outcome.[35] However, the co-occurrence of BD with obesity and changes in glucose metabolism are observed even before the existence of these medications.[11] A study with first-episode psychotic patients showed increasing rates of obesity, hyperglycemia and dyslipidemia after using atypical antipsychotics.[43] Studies with first-episode or drug-free BD patients are required to clarify the role of medication in this association.

Mechanisms linking MS and bipolar disorder have been largely unidentified. Hypotheses have emerged positing that both negative health behaviors, such as smoking, poor diet, overeating, and a sedentary lifestyle,[44] and biological factors of MS, such as hypothalamic-pituitary-adrenocortical (HPA) axis and sympathoadrenal hyperactivity, and abnormalities of the immunologic system,[45] such as increased proinflammatory cytokines,[46] are correlated with BD.

Negative outcomes such as psychiatric and physical comorbidities could also be explained by the concept of allostatic load (AL). AL results from an overload in the allostatic processes due to the chronic overactivity or inactivity of the physiological systems (such as the hypothalamic-pituitary-adrenal axis) that are involved in the capacity to achieve stability through adaptation to internal and external demands (i.e., allostasis). Patients with a higher AL were found to have an increased risk of incidental cardiovascular disease and all-cause mortality, which is in accordance with the increased prevalence in found in BD patients of medical conditions such as diabetes, hypertension, ischemic heart disease and stroke.[47] All of those correlated factors, such as neuroendocrinal and inflammatory abnormalities, the use of psychotropic drugs and negative health behaviors, act like allostatic components that reinforce the role of AL in BD-MS association.

Several limitations were noted during the review of the cited articles in the current study. First, differing experimental designs and sampling methodologies make formal comparison between studies difficult. Different criteria used to diagnose MS and the lack of a structured diagnostic interview to confirm a bipolar diagnosis did not allow for standardization of the results. Additionally, most of the studies were cross-sectional. Because of this limitation, a causal relationship between bipolar disorder and metabolic syndrome could not be established. The medication treatment regimen may also be a liability, evoking the need for longitudinal studies.

In conclusion, the association between MS and BD, although not clear, is important to consider, as BD patients have other risks factors for MS, such as increased rates of cardiovascular disease and diabetes. Because cardiovascular risk is increased in bipolar patients, and because of the negative impact of MS on general physical and psychological well-being and functioning, MS could contribute to a worse prognosis for BD and vice-versa. Therefore, psychiatrists should be aware of the risk factors involved in MS and should intervene as soon as possible to prevent metabolic

Table 2 NCEP and IDF definitions for metabolic syndrome.

Risk factors	NCEP levels (2002)	NCEP III modified (2005)	IDF levels (2006)
Abdominal obesity	WC > 102 for men WC > 88 for women	WC > 102 for men WC > 88 for women	WC ≥ 94 cm for men (Europe) WC ≥ 80 cm for women or BMI > 30 kg/m^2
Triglycerides	≥ 150 mg/dL	≥ 150 mg/dL (1.7 mmol/L)	≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
HDL-cholesterol	< 40 mg/dL for men < 50 mg/dL for women	< 40 mg/dL (1.03 mmol/L in men < 50 mg/dL (1.29 mmol/L) in women	< 40 mg/dL (1.03 mmol/L in men < 50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality
Blood pressure	≥ 130/85 mmHg	≥130/85 mmHg or current use of antihypertensive drugs	≥130/85 mmHg or treatment of previously diagnosed hypertension
Fasting glucose	≥ 110 mg/dL	≥ 100 mg/dL (5.6 mmol/L)	≥ 100 mg/dL (5.6 mmol/L) or previous diagnosis of type 2 diabetes

NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel; IDF: International Diabetes Federation; WC: waist circumference; BMI: body mass index.

abnormalities that could influence the prognosis of bipolar disorder. Such strategies include monitoring the patient's lifestyle, eating habits and exercise routine.

Disclosures

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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

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Supplementary Information Prevalence of metabolic syndrome and its subcomponents in patients with bipolar disorder described in 39 publications

Study	Sample (Mean Age ± SD/ % Male)	Country	Study Design	BD Diagnostic Measure	MS criteria (Prevalence rate)	Results	Quality Score
1 Grover et al.[28]	200 outpatients with BD (38.96 ± 13.10 / 70%) BD Type not specified Mood state not specified	India	Cross-sectional	Clinical Diagnosis	NCEP ATP III (41.0%) IDF (40.0%)	Abnormal WC - 70.5% 3Hypertriglyceridemia - 42.0% FBG levels ≥ 100 mg% - 24.0% FBG levels ≥ 110 mg% - 14.5% Abnormal SBP - 38.5% Abnormal DBP - 33.5%	3
2 Salvi et al.[30]	70 patients with BD type I, II, NOS or cyclothymia (51.2 ± 14.4 / 35.7%) 31.4% BD type I 68.6 BD type II Mood state not specified	Italy	2-year follow-up	SCID-I	NCEP ATP III (24.17%)	Baseline vs. 2-year follow-up: MS prevalence - 28.6% vs. 44.3%, p = .027 Abnormal WC - 52.9% vs. 64.3%, p = .096 Low HDL-c - 25.4% vs. 35.7%, p = .189 Hypertriglyceridemia - 30.0% vs. 30.4%, p = 1.000 Hyperglycemia - 14.3% vs. 31.4%, p = .004 Abnormal BP - 48.6% vs. 52.9%, p = .664	3
3 D'Ambrosio et al.[25]	211 inpatients with BD (49.0 ± 15.7 / 39.5%) 38.3% BD type I 58.6% BD type II 3.1% BD NOS 55.9% depressed 11.4% hypomanic/manic 6.8% mixed 25.9% euthymic	Italy	Cross-sectional	SCID-I	NCEP ATP III (24.17%)		*4*
4 Ezzaher et al.[26]	130 patients with BD type I (37.9 ± 12.1 / 65.38%) 16.15% depressed 27.7% manic 56.15% euthymic	Tunisia	Cross-sectional	Clinical Diagnosis	NCEP ATP III (26.1%) WC substituted by BMI ≥ 28.8	Low HDL-c - 59.2% Hypertriglyceridemia - 53.1% Hyperglycemia - 16.1% Abnormal BP - 5.4% BMI ≥ 28.8 - 33.8% No differences between gender, illness episode or medications	1
5 Khatana et al.[29]	822 patients with BD (55.7 ± 12.8 / 91.4%) BD Type not specified Mood state not specified	USA	Chart Review Study	Clinical Criteria	NCEP ATP III (57.1%) WC substituted by BMI ≥ 30		1
6 Vuksan-Cusa et al.[31]	36 euthymic inpatients with BD (44.9 ± 15.8 / 63.9%) BD Type not specified	Croatia	Cross-sectional	SCID-I	NCEP ATP III (30.6%)	Abnormal WC - 36.1% Low HDL-c - 25.5% Hypertriglyceridemia - 47.2% Hyperglycemia - 25.7% Abnormal Blood Pressure - 41.7%	3

Study	Sample (Mean Age ± SD/ % Male)	Country	Study Design	BD Diagnostic Measure	MS criteria (Prevalence rate)	Results	Quality Score
7 Baptista et al.[10]	1627 outpatients, 182 with BD (42.7 ± 14.2/ 34.1%) BD Type not specified Mood state not specified	Venezuela	Cross-sectional	Clinical Diagnosis	NCEP ATP III (28.6%)	BD vs. GP: MS prevalence - 28.6% vs. 26.6%, OR 1.06 (.69-1.6) Abnormal WC - male: 35.5% vs. 22.7%, OR 2.5 (.7-8.4); female: 52.1% vs. 36.2%, OR 2.3 (1.1-4.9)* Low HDL-c - male: 55.9% vs. 81.4%, OR .3 (.1-.7); female: 66.1% vs. 86.2%, OR .3 (.2-.6) Hypertriglyceridemia - 33.1% vs. 39.9%; OR .8 (.5-1.3) Hyperglycemia - 11.7% vs. 6.3%; OR 2.6 (1.2-5.8)* Abnormal SBP - 26.3% vs. 24.0; OR 1.1 (.6-1.8) Abnormal DBP - 32.0% vs. 28.0%; OR 1.0 (.6-1.6) Obesity -28.0% vs. 24.4%; OR 1.2 (.7-1.9)	4
8 Salvi et al.[21]	200 outpatients or inpatients with BD (50.9 ± 15.5/ 40%) 28.1% BD Type I Mood state not specified	Italy	Cross-sectional	SCID-I	NCEP ATP III modified [fasting glucose ≥ 100 mg/dL] (26.5%)	Men vs. Women: Hypertension - 67.5% vs. 43.3%; x^2 = 11.254, d.f. = 1, p = .001; OR .37 (.20-.617)* Hypertriglyceridemia - 48.8% vs. 24.4%; x^2 = 12.641, d.f. = 1, p < .001; OR .34 (.19-.62)* Abdominal obesity - 37.5% vs. 53.3%; x^2 = 4.831, d.f. = 1, p = .028; OR 1.91 (1.07-3.39)* Low HDL-c - 25.7% vs. 33.9%, p = .241; OR 1.48 (.77-2.87) Hyperglycemia - 6.2% vs. 13.4%, p = .105; OR 2.33 (.82-6.64) MS - 32.5% vs. 22.5%, p = .116, OR .60 (.32-1.14)	4
9 Correll et al.[48]	10084 voluntary outpatients with mental illness, 3923 with BD (1093 with full data) BD Type not specified Mood state not specified	USA	Cross-sectional	Self-reported	NCEP ATP III modified [fasting glucose ≥ 100 mg/dL] (54%)	Overweight - 27% Obesity - 55% Hypertension - 51% Hypertriglyceridemia - 48% Hyperglycemia - 31% Low HDL-c - 61%	2
10 Guan et al.[13]	*148 patients with BD [113 at month 6] (30.93 ± 12.36/47.3%) 70.27% type I 69.6% in depression 18.2% in mania 12.2% in mixed states*	*China*	*6-month*	*Clinical Diagnosis*	*CDS (11.5%)*	At baseline, BD vs. control: Prevalence - 11.5% vs. 1.6%, x^2 = 5.777; p = .015* Low HDL-c - 15.5% vs. 0%, x^2=11.324; p = .0001* Hypertriglyceridemia - 29.1% vs. 15.4%, x^2=4.515; p = .039* Hyperglycemia - 5.4% vs. 0%; x^2=3.651; p = .110 Hypertension - 14.9% vs. 3.1%; x^2=6.277; p = .010* Overweight - 34.5% vs. 10.8%; x^2=12.792; p = .0001*	*3*
11 Garcia-Portilla et al.[38]	194 outpatients with BD (46.6 ± 13.9/ 49.2%) BD Type not specified Mood state not specified	Spain	Cross-sectional	Clinical Diagnosis	NNHANES (22.4%), AHA (35.6%)	Abnormal WC - 36.1% Low HDL-c - 25.5% Hypertriglyceridemia - 47.2% Hyperglycemia - 25.7% Abnormal Blood Pressure - 41.7%	2

Study	Sample (Mean Age ± SD/ % Male)	Country	Study Design	BD Diagnostic Measure	MS criteria (Prevalence rate)	Results	Quality Score
12 Lee et al.[12]	152 outpatients with BD (36.3 ± 12.3/ 46.7%) BD Type not specified Mood state not specified	Korea	Cross-sectional	Clinical Diagnosis	NCEP ATP-III (25.0%), AHA (27.0%), IDF (25.7%) + KSSO criteria for WC (≥90 cm for men and ≥85 for women)	BD vs. GP: AHA – 27.0% vs. 23.1%; OR 1.48 (1.02-1.93) ATP III – 25.0% vs. 20.4%; OR 1.54 (1.05-2.03) IDF – 25.7% vs. 16.1%; OR 1.98 (1.36-2.60) BD vs. control: AHA – 27.0% vs. 13.2%; OR 2.44 (1.35-4.40)* ATP III – 25.0% vs. 11.8%; OR 2.48 (1.34-4.59)* IDF – 25.7% vs. 11.8%; OR 2.57 (1.40-4.74)* Abnormal WC - 47.4% vs. 25.7%, OR 2.61 (1.61-4.23)* Hypertriglyceridemia - 32.9% vs. 21.7%; OR 1.77 (1.06-2.95)* Low HDL-c - 32.9% vs. 19.1%; OR 1.08 (1.23-3.52) Hyperglycemia - ≥110: 15.1% vs. 11.2%, OR 1.42 (.72-1.77); ≥100: 5.3% vs. 4.6%; OR 1.15 (.41-3.26) Hypertension – 25.7% vs. 27.0%; OR .93 (.56-1.56) Abnormal SBP - 23.7% vs. 24.3%; OR .97 (.57-1.63) Abnormal DBP - 13.8% vs. 12.5%; OR 1.12 (.58-2.18) Overweight – 40.8% vs. 28.3%; OR 1.75 (1.08-2.82) Obesity – 9.9% vs. 5.3%; OR 1.97 (.81-4.80)	4
13 Kemp et al.[33]	125 patients with BD Type I in acute mixed or manic episode (44.2 ± 1.42/ 27%)	Argentina, Mexico and USA	Placebo-controlled trial, *post-hoc* analysis	SCID or MINI	NCEP ATP III modified [fasting glucose ≥100 mg/dL] (36.0%)		3
14 Khatana et al.[29]	1,401 inpatients or outpatients included in VISTA electronic medical record system, 822 with BD (55.7 ± 12.8/ 91.4%) BD Type not specified Mood state not specified	USA	Cross-sectional	Clinical Diagnosis	NCEP ATP III modified [fasting glucose ≥100 mg/dL] (57.1%/ Age-adjusted 46.6%)		2
15 McIntyre et al.[53]	99 euthymic outpatients with BD (38 ± 11.15/ 48.5%) 76.8% type I	Canada	Cross-sectional	Clinical Diagnosis and MINI	NCEP ATP III (32.6%)	(Total) Men vs. Women: MS – (32.6%), 35.4% vs. 29.8%, p = NS Abdominal Obesity – (41.1%), 33.3% vs. 48.9%, p = NS Hypertriglyceridemia – (38.8%), 50% vs. 27.9%, p = .037* Elevated SBP – (29.7%), 42.5% vs. 17%, p = .007* Elevated DBP – (27.6%), 42.5% vs. 12.7%, p = .001* Low HDL-c – (36.4%), 35.7% vs. 37.2%, p = NS Hyperglycemia – (6.1%), 5.1% vs. 6.9%, p = NS	3
16 Taylor et al.[49]	54 patients, 20 with BD at baseline (N.I./ N.I.) BD Type not specified Mood state not specified	Canada	Cohort	SCID	NCEP ATP III modified [fasting glucose ≥100 mg/dL] (5%-15%)		3

Study	Sample (Mean Age ± SD/ % Male)	Country	Study Design	BD Diagnostic Measure	MS criteria (Prevalence rate)	Results	Quality Score
17 Vuksan-Ćusa et al.[22]	181 euthymic patients, 60 with BD (40.76 ± 12.19/ 53.33%) BD Type not specified	Croatia	Cross-sectional	Clinical Diagnosis	NCEP ATP III (31%)		1
18 Almeida et al.[9]	84 outpatients with BD (41.6 ± 11.6/ 34.5%) 92.9% type I Mood state not specified	Brazil	Cross-sectional	SCID	AHA (28.6%), NHANES (20.2%)	Abdominal obesity – 46.4% Hypertriglyceridemia – 44% Low HDL-c – 26.2% Hypertension – 45.2% Hyperglycemia – ≥100: 20.2%; ≥110: 10.7%	4
19 Centorrino et al.[50]	28531 inpatients or outpatients with BD (N.I./ 35.7%) 53.8% type I Mood state not specified	USA	Cohort	Clinical Diagnosis	Clinical Diagnosis (.4%)	BD vs. control: MS prevalence – .4% vs. .2%, p < .0001*	2
20 Chang et al.[39]	117 outpatients with BD (34.1 ± 10.7/ 41.9%) 46.2% type I Mood state not specified	Taiwan	Cross-sectional	Clinical Diagnosis and SAS	IDF (33.9%)	Hyperglycemia – 13.7% Hypertriglyceridemia – 36.8% Low HDL-c – 53.0% Hypertension – 18.6% Abdominal obesity – 61.0%% Men vs. Women: Waist-to-hip ratio – .89 ± .41 vs. .86 ± .51, p = .031* HDL-c – 42.0 ± 9.2 vs. 48.7 ± 11.7 mg/dL, p = .001* SBP – 117.8 ± 12.1 vs. 108.6 ± 12.1 mm Hg, p = .004*	3
21 Elmslie et al.[32]	60 overweight outpatients with BD (42 ± 11/ 18.33%) 66.67% type I Mood state not specified	New Zealand	Cross-sectional	SCID	NCEP ATP III (50%)	BD vs. controls: MS prevalence – 50% vs. 32%, p= .06 Abnormal WC – 85% vs. 80%, p = .63 Hypertriglyceridemia – 40% vs. 30%, p = .34* Low HDL-c – 63% vs. 28, p = .006* Hypertension – 50% vs. 52%, p = 1.0 Hyperglycemia – 6% vs. 3%, p = .68	4
22 Garcia-Portilla et al.[37]	194 outpatients with BD (46.6 ± 13.2/ 49.2%) BD Type not specified 46% euthymic 16.8% depressed 11.5% hypomanic 11% manic with psychotic symptoms	Spain	Cross-sectional	Clinical Diagnosis	NHANES (22.4%), AHA (35.6%)(5%-15%)	(Total) Men vs. Women: Diabetes – (6.5%), 5.4% vs. 7.7%, p = .525 Hyperglycemia – (9.5%), 5.3% vs. 13.8%, p < .05* Low HDL-c – (49.3%), 53.8% vs. 44.6%, p = .254 Abnormal SBP – (19.8%), 24.7% vs. 15.1%, p = .098 Abnormal DBP – (26.0%), 19.4% vs. 12.9%, p = .232	2

Study	Sample (Mean Age ± SD/ % Male)	Country	Study Design	BD Diagnostic Measure	MS criteria (Prevalence rate)	Results	Quality Score
23 John et al.[51]	203 inpatients or outpatients with SMI, 39 with BD (N.I./N.I.) BD Type not specified Mood state not specified	Australia	Cross-sectional	Clinical Diagnosis	NCEP ATP III (N.I.), AHA (N.I.), IDF (67%)		1
24 Vuksan-Cusa et al.[52]	40 patients with BD (N.I./100%) BD Type not specified Mood state not specified	Croatia	Cross-sectional	Clinical Diagnosis	NCEP ATP III (27.5%)		1
25 Cardenas et al.[16]	98 patients with BD (N.I./ 91.83%) BD Type not specified Mood state not specified	USA	Cross-sectional	Clinical Diagnosis	NCEP ATP III (49%)		1
26 Correl et al.[24]	1185 inpatients, 74 with BD (44.4 ± 16.4/ 48.6%) BD Type not specified Mood state not specified	USA	Cross-sectional	Clinical Diagnosis	NCEP ATP III (43.2%), modified (54.0%)	BD vs. SCHIZ: MS – 54.0% vs. 54.0%, p = 1.00 Abdominal obesity – 33.8% vs. 39.6%, p = .42 Hypertriglyceridemia – 46.6% vs. 47.7%, p = .88 Hyperglycemia – ≥110: 15.1% vs. 11.7%, p = .52; ≥100: 32.4% vs.28.2%, p = .54 Hypertension – 54.0% vs. 59.5%, p = .55 Low HDL-c – 67.6% vs. 63.2%, p = .53	1
27 Fagiolini et al.[35]	441 patients with BD (44.4 ± 15.3/ N.I.) 72.78% type I Mood state not specified	N.I.	Cross-sectional	N.I.	AHA (40%)		2
28 Fiedorowicz et al.[27]	217 outpatients with BD (46.3 ± 15 / 37%) 59% BD type I 34% BD type II 7% BD NOS Mood state not specified	USA	Retrospective Chart Review Study	Clinical Records	NCEP ATP III (36%)	Hypertriglyceridemia – 48% Low HDL-c – 27% Hypertension – 63% Hyperglycemia – 28% = .232	2
29 Garcia-Portilla et al.[18]	194 patients with BD (46.6 ± 13.9/ 49.2%) BD Type not specified 46.5% euthymic 16.8% depressed 11.5% hypomanic 11% manic with psychotic symptoms	Spain	Cross-sectional	Clinical Diagnosis	NHANES (22.4%)	(Total), Men vs. Women: MS – (22.4%), 19.3% vs. 25.9%, p = .302 Abdominal obesity – (53.8%), 41.8% vs. 65.3%, p = .001* Hypertriglyceridemia – (36.1%), 34.8% vs. 31.1%, p = .598 Low HDL-c – (38.2%), 30.8% vs. 45.9%, p = .054 Hypertension – (20.9%), 21.5% vs. 17.2%, p = .458 Hyperglycemia – (12.2%), 7.4% vs. 15.1%, p = .099	3

Study	Sample (Mean Age ± SD/ % Male)	Country	Study Design	BD Diagnostic Measure	MS criteria (Prevalence rate)	Results	Quality Score
30 Salvi et al.[19]	108 (99 with complete data) inpatients or outpatients with BD (51.7 ± 13.9/ 40.7%) 35.2% type I Mood state not specified	Italy	Cross-sectional	SCID	NCEP ATP III (25.3%), IDF (30%)	Abdominal obesity – 50% Hypertriglyceridemia – 34.7% Low HDL-c – 32.3% Hypertension – 40% Hyperglycemia – 11% BD with MS vs. without MS: Obesity – 52% vs. 12.7%, p = .001*	3
31 Sicras-Mainar et al.[14]	742 medical records of outpatients receiving ATPs, 128 with BD [51.8 ± 6.3/ 47.7%) BD Type not specified Mood state not specified	Spain	Cross-sectional	Clinical Diagnosis	NCEP ATP III modified [BMI > 28.8 kg/m^2] (25.8%)	BD vs. control: MS prevalence – 25.8%, OR 1.56 (1.01-2.41), p = .047* Obesity – 38.3%, OR 2.42 (1.65-3.55), p < .001* Hypertension – 32.8%, OR 1.03 (.67-1.59), p = .886 Hypertriglyceridemia – 22.7%, OR 1.93 (1.26-2.96), p = .003* Hyperglycemia – 18%, OR 1.50 (.92-2.44), p = .101 Low HDL-c – 52.3%, OR 2.28 (1.57-3.31), p < .001*	4
32 Sicras et al.[15]	178 medical records of outpatients with BD [45.5 ± 17.8/ 45.5%] BD Type not specified Mood state not specified	Spain	Cross-sectional	Clinical Diagnosis	NCEP ATP III modified [BMI > 28.8 kg/m^2] (24.7%)	BD vs. control:MS prevalence – 24.7% vs. 14.4%, OR 1.65 (1.11-2.44), p = .013* Obesity – 33.1% vs. 17.9%, OR 2.05 (1.46-2.87), p < .001* Hypertension – 29.8% vs. 24.4%, OR 1.00 (.68-1.49), p = .987 Hypertriglyceridemia – 23.0% vs. 11.3%, OR 2.09 (1.45-3.02), p < .001* Hyperglycemia – 16.9% vs. 9.8%, OR 1.55 (1.00-2.41), p = .53 Low HDL-c – 54.5% vs. 29.4%, OR 2.77 (2.02-3.80), p < .001*	4
33 Van Winkel et al.[20]	60 patients with BD [45.3 ± 13.0/ 43.3%] BD Type not specified Mood state not specified	Belgium	Cross-sectional	Clinical Diagnosis	NCEP ATP III (16.7%), NCEP ATP III modified [fasting glucose ≥ 100 mg/dL] (18.3%), IDF (30.0%)	(total) Men vs. Women: Abdominal obesity – ATP-III: (30%), 15.4% vs. 41.4%, p = .03; IDF: (60%), 30.6% vs. 69.4%, p = .01 Hypertension – (48.3%), 61.5% vs. 38.2%, p = NS Low HDL-c – (21.7%), 19.2% vs. 23.5%, p = NS Hypertriglyceridemia – (26.7%), 38.4% vs. 17.6%, p = NS Hyperglycemia – ATP-III: (13.3%), 15.1% vs. 11.8%, p = NS; IDF: (28.3%), 23.1% vs. 32.4%, p = NS	1
34 Van Winkel et al.[20]	707 patients with SMI, 112 with BD [44.3 ± 12.2/ 40.2%] BD Type not specified Mood state not specified	Belgium	Cross-sectional	Clinical Diagnosis	NCEP ATP III modified [fasting glucose ≥ 100 mg/dL] (23.2%)	Abdominal obesity – 33.9% Hypertension – 50.9% HDL-c – 25.0% Hypertriglyceridemia – 32.1% Hyperglycemia – 23.2%	2
35 Birkenaes et al.[11]	273 outpatients, 110 with BD [38.7 ± 11.9/ 39.1%] 56.36% type I Mood state not specified	Norway	Cross-sectional	SCID	NCEP ATP III modified [fasting glucose ≥ 100 mg/dL] (21.5%)	BD vs. GP: Abdominal obesity: 54.2% vs. 16.0%, p < .001* Overweight: 62.6% vs. 52.0%, p = .027* Obesity: 24.9% vs. 14.1%, p = .001* Hypertension: 60.8% vs. 43.0%, p < .001* Low HDL-c: 23.2% vs. 21.4%, p = .655 Diabetes mellitus – 5.5% vs. 2.2%, p = .026*	4

Study	Sample (Mean Age ± SD/ % Male)	Country	Study Design	BD Diagnostic Measure	MS criteria (Prevalence rate)	Results	Quality Score
36 Teixeira and Rocha[34]	170 psychiatric inpatients, 47 with BD [N.I./ 11.3%] BD Type not specified Mood state not specified	Brazil	Cross-sectional	Clinical Diagnosis	NCEP ATP III (38.3%)		1
37 Yumru et al.[23]	125 outpatients with BD Type I [34.52 ± 9.86/ 62.4%] Mood state not specified	Turkey	Cross-sectional	Clinical Diagnosis	NCEP ATP III (32%)		2
38 Correll et al.[17]	367 psychiatric inpatients treated with SGAs, 76 with BD [N.I./ N.I.] BD Type not specified Mood state not specified	USA	Cross-sectional	Clinical Diagnosis	NCEP ATP III (43.42%)		1
39 Fagiolini et al.[36]	171 patients with BD [46.9 ± 16.5/ 39%] 71% type I Mood state not specified	USA	Cross-sectional	SCID	NCEP ATP III (30%)	(Total) Men vs. Women: MS – (30%), 31% vs. 29% Abdominal obesity – (49%), 42% vs. 53% Hypertriglyceridemia – (48%), 62% vs. 39% Low HDL-c – (23%), 27% vs. 20% Hypertension – (39%), 40% vs. 38% Hyperglycemia – (8%), 6% vs. 9%	3

AHA, American Heart Association; BD, bipolar disorder; CDS, Chinese Medical Association Diabetes Branch; CHD, Coronary Heart Disease; CMR, Cardiovascular Mortality Risk; GP, general population; KSSO, Korean Society for the Study of Obesity; MINI, MiniInternational Neuropsychiatric Interview; MS, metabolic syndrome; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; SAS, Schedule for Affective and Schizophrenia - Lifetime Chinese version; SCID, Structured Clinical Interview for DSM; SGA, Second-generation antipsychotics; SMI, Severe mental illness; VISTA, Veterans Health Information Systems and Technology Architecture; WC, waist circumference.