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Castelli risk indexes 1 and 2 are higher in major depression but other characteristics of the metabolic syndrome are not specific to mood disorders.

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Abstract.

Aims: This study examined whether Castelli risk indexes 1 (total / high-density lipoprotein (HDL) cholesterol) and 2 (low density lipoprotein (LDL) / HDL cholesterol) and other shared metabolic disorders might underpin the pathophysiology of the metabolic syndrome, major depression or bipolar disorder.

Material and Methods: This cross-sectional study examined 92 major depressed, 49 bipolar depressed and 201 normal controls in whom the Castelli risk indexes 1 and 2 and key characteristics of the metabolic syndrome, i.e. waist / hip circumference, body mass index (BMI); systolic / diastolic blood pressure; total cholesterol, low-density lipoprotein (LDL) and HDL cholesterol, triglycerides; insulin, glucose, hemoglobin A1c (HbA1c); and homocysteine were assessed.

Key findings: Castelli risk indexes 1 and 2 were significantly higher in major depressed patients than in bipolar disorder patients and controls. There were no significant differences in waist or hip circumference, total and LDL cholesterol, triglycerides, plasma glucose, insulin, homocysteine and HbA1c between depression and bipolar patients and controls. Bipolar patients had a significantly higher BMI than major depressed patients and normal controls.

Significance: Major depression is accompanied by increased Castelli risk indexes 1 and 2, which may be risk factors for cardiovascular disease. Other key characteristics of the metabolic syndrome, either metabolic biomarkers or central obesity, are not necessarily specific to major depression or bipolar disorder.

Keywords: Metabolic syndrome; bipolar disorder; depression; cholesterol; HDL; inflammation; oxidative stress; antioxidants

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Introduction

In the 1930s, Ernst Kretchmer developed a new classification system relating body constitution to personality traits and psychopathology. Kretchmer described that individuals with a pyknic (obese) constitution are more predisposed to develop bipolar disorder than leptosomic (thin) individuals who are more prone to develop schizophrenia. Studies in the early 1990s were unable to observe significant relationships between depression and anthropometric measurements, including body mass index (BMI), and triceps skinfold thickness, a measure of subcutaneous fat [1]. More recent studies report that major depression and bipolar disorder may be associated with obesity and the metabolic syndrome and that the association between the metabolic syndrome and depression may be bidirectional [2-4].

The metabolic syndrome is characterized by abdominal obesity, dyslipidemia, hyperglycaemia and hypertension and is a significant risk factor for type 2 diabetes and cardiovascular disease [5-8]. The pathophysiology comprises a cluster of metabolic abnormalities which were thought to be attributable to insulin resistance with an excessive flux of fatty acids that produce an increased production of glucose, triglycerides and secretion of very low density lipoproteins (LDL) [9]. However, it is now conceptualized that obesity and increased leptin protect non-adipose organs against the toxic effects of excess dietary calories and lipid spillover [10]. Associated lipid / lipoprotein abnormalities include reductions in high density lipoprotein (HDL) cholesterol and increased total cholesterol, LDL and triglyceride levels [8]. Some, but not all studies, reported increased homocysteine levels in the metabolic syndrome [11], and homocysteine is a putative biomarker for depression and bipolar disorder [12,13].

The metabolic syndrome and associated metabolic biomarkers may therefore be associated with mood disorders, including depression [14-18]. The high co-

occurrence between mood disorders and the metabolic syndrome suggests a pathophysiological overlap. Bipolar disorder and major depression are associated with increased risk for cardiovascular disease, diabetes mellitus and obesity [16,19,20].

Biochemical characteristics of the metabolic syndrome are also detected in depression, e.g. decreased HDL cholesterol and insulin resistance [14,21,22]. As such, depression and the metabolic syndrome may share metabolic biomarkers which are related to the pathophysiology of depressive disorder and metabolic syndrome. To the best of our knowledge, no research has examined whether the Castelli risk index 1 computed as total / HDL cholesterol and Castelli risk index 2 computed as LDL / HDL cholesterol are associated with unipolar depression or bipolar disorder. Both ratios are significant vascular risk indicators, the predictive value of which is greater than the isolated parameters [23].

The purpose of this study was to delineate a) whether increased Castelli risk indexes 1 and 2 are biomarkers of major depression or bipolar disorder; and b) whether the biomarkers of the metabolic syndrome, i.e. the specific lipid profile, and increased insulin, glucose, and hemoglobin A1c (HbA1c) values are also characteristics for major depression or bipolar disorder.

2. Methods

2.1. Study Population

This cross-sectional study examined participants with major depression (n=92), bipolar disorder (n=49) and normal controls (n=201) recruited from staff at the Londrina State University (UEL) and an outpatient ambulatory of smoking cessation, UEL, Paraná, Brazil. All participants were men and women aged 18-60 and all ethnicities were accepted for this study. The study was conducted from March 2011 to

July 2012. All subjects gave written informed consent to participate in the study after the approval of this research by the Ethics Research Committee at UEL (number 250/2010). We excluded any subjects (controls or depressed patients) with a) abnormal blood values on the following laboratory tests: hemogram, aspartate transaminase (AST), alanine transaminase (ALT), urea and creatinine; b) other actual and life-time axis-I diagnoses (including schizophrenia, psycho-organic syndromes, anxiety disorders, etc) and additionally a diagnosis of depression or bipolar disorder for the controls; c) medical illness, including (auto)immune disorders, diabetes type 1 and type 2, etc.; d) immunomodulatory drugs, e.g. glucocorticoids.

2.2. Diagnostic procedures and measurements

The diagnoses of major depressive disorder and bipolar disorder were made at interview by a trained clinician using the semi-structured DSM-IV interview (SCID), using a validated Portuguese translation [24]. A translated and validated version of the Hamilton Depression Rating Scale, adapted to the Brazilian cultural context and Portuguese language [25] was used to measure the severity of depression in study participants who had been diagnosed with major depressive disorder, bipolar depression, and controls. The diagnosis of nicotine dependence was made using the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2000). We collected patient-reported socio-demographic data and clinical characteristics using a semi-structured interview performed by senior psychiatrists.

We used the International Diabetes Federation diagnostic criteria to make a “metabolic syndrome” diagnosis, i.e. at least three out of the following five criteria should be present: 1) abdominal obesity using population and country specific

definitions, 2) hypertriglyceridemia: ≥ 150 mg/dl or on hypolipidemic agent, 3) low HDL cholesterol: ≤ 40 mg/dl in men and ≤ 50 mg/dl in women or on hypolipidemic agent, 4) average blood pressure $\geq 130/85$ mm Hg or currently taking antihypertensive medication, 5) elevated fasting glucose ≥ 100 mg/dL or on oral antidiabetic medication [6,7].

In order to assess physical activity / mobility we used a patient-reported physical activity (but not validated) questionnaire, i.e. “How would you best describe your mobility?”, 1) very active: moves, walks and works energetically, participants in vigorous exercise; 2) active: walks at brisk pace, does normal housework or other work, engages in light exercise; 3) sedentary: walk reasonable distances, does light housework, shopping or equivalent; normal activities of day-a-day living, but no appreciable exercise.

2.3. Anthropometric and blood pressure measurements

BMI was calculated as weight (Kg) divided by square of height (m^2). Waist circumference was measured in the standing relaxed position, during expiration, at the midline between the lower costal margins and the iliac crest parallel to the floor. Different waist circumference thresholds for abdominal obesity are currently recommended in several different populations and ethnic groups, i.e. waist circumference ≥ 90 cm for men and ≥ 80 cm for women in South Asian and South Americans [6,26] and waist circumference ≥ 94.0 cm for men and ≥ 80.0 cm for women in individuals from European origin [6,7]. Hip circumference was measured over light clothing at the widest girth of the hip. Systolic and diastolic blood pressures were measured by mercury sphygmomanometer on the right arm with the subject in

sitting position after 10 min of rest; the average of two measurements 5 min apart was used.

2.3. Laboratory Assessments

Peripheral blood samples were collected from all participants after 12 to 14 hours overnight fasting. Cholesterol was determined by an automated method in a clinical chemistry system, Dimension® RXL (Siemens Healthcare Diagnostics Inc, Newark, DE, USA). This reaction is based on cholesterol oxidase method. HDL cholesterol was determined by an automated method in a clinical chemistry system, Dimension® RXL (Siemens Healthcare Diagnostics Inc, Newark, DE, USA). This method measures HDL cholesterol levels directly, without the need for sample pretreatment or specialized centrifugation steps. Triglycerides determination was performed by automated method in a clinical chemistry system, Dimension® RXL (Siemens Healthcare Diagnostics Inc, Newark, DE, USA). This method is based on an enzymatic procedure, in which combinations of enzymes are employed to the measurement of serum triglycerides. LDL cholesterol was calculated by Friedewald's equation, i.e. $\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \text{triglycerides} / 5.0$ (mg/dL). Consequently, we computed Castelli risk index 1, i.e. $\text{total} / \text{HDL cholesterol}$, and Castelli risk index 2, i.e. $\text{LDL} / \text{HDL cholesterol}$.

Glucose assays are performed by automated method in a clinical chemistry system, Dimension® RXL (Siemens Healthcare Diagnostics Inc, Newark, DE, USA). This reaction is based on hexokinase-glucose-6-phosphate dehydrogenase method. Plasma insulin levels were determined by MEIA (AXSYM, Abbott® Laboratory, Germany). Hemoglobin A1c (HbA1c) determination was performed by automated method in a clinical chemistry system, Dimension® RXL (Siemens Healthcare

Diagnostics Inc, Newark, DE, USA). This method measures both HbA1c and total hemoglobin. HbA1c measurement is based on a turbidimetric inhibition immunoassay principle and the measurement of total hemoglobin is based on a modification of the alkaline hematin reaction. Total plasma homocysteine levels were measured by chemiluminescent immunoassay (Immulite 2000 Homocysteine, Diagnostic Procedures Corporation, Los Angeles, CA, USA). The inter-assay coefficients of variability for all analytes were less than 5.0%.

2.4. Statistical analyses

Contrasts between groups, i.e. subjects with unipolar and bipolar depression versus those without, were ascertained by analyses of variance (ANOVAs). When significant, we used Fishers protected least significant difference (LSD) to examine planned comparisons between controls and UP / BP depression and between UP and BP depression. Factorial design analyses of covariance (ANCOVA) were used to compare the biomarkers between the groups divided into unipolar and bipolar depression and controls while adjusting for relevant covariates and either depression or metabolic syndrome. Analysis of contingency Tables (Chi-square test) or Fisher's exact probability test were used to ascertain the distribution of socio-demographic and clinical measurements in individuals with unipolar and bipolar depression versus those without. Univariate comparisons were initially conducted and then variables that were statistically significant were included in multivariate analyses. Binary logistic regression analyses were carried out using patients with unipolar and bipolar depression compared to controls as the dependent variable. Normality of distribution was checked with the Kolmogorov-Smirnov goodness-of-fit test. All analyses were performed using

SPSS (Version 20). All tests were 2-tailed and a p-value of 0.05 was used for statistical significance.

3. Results

3.1. Demographic characteristics

Socio-demographic characteristics are outlined in Table 1. Analysis of contingency Tables showed that there was a significant association between mood disorders and female gender. There were significant differences between subjects with depression and bipolar disorder and controls in smoking and physical activity. There were no significant differences between the three study groups in age, years of education, ethnicity, marital status or use of statins. There was no significant difference in the incidence of the metabolic syndrome between depression and bipolar disorder and normal volunteers although there was a trend toward a higher prevalence in bipolar disorder.

Insert table 1 here

3.2. Castelli risk indexes 1 and 2 and other metabolic characteristics in mood disorders

Table 2 summarizes the measurements of the metabolic data in normal controls, depressed and bipolar patients. ANOVAs followed by post hoc analyses (LSD) showed that patients with bipolar disorder had a significantly higher BMI as compared with control subjects ($p < 0.01$) and individuals with major depression ($p < 0.01$). There were no significant differences in systolic and diastolic blood pressure and waist and hip circumference between the three study groups.

Plasma glucose, insulin and HbA1c were not significantly different between the three study samples. There were no significant differences in total and LDL cholesterol and triglycerides between the three study samples. HDL cholesterol was significantly lower in bipolar patients than in normal controls ($p<0.05$), while there were no significant differences between bipolar and depressed patients and between major depression and controls. Castelli risk indexes 1 and 2 were significantly higher in major depression ($p<0.05$) and bipolar disorder ($p<0.05$) than in controls, while there were no significant differences between major depression and bipolar disorder.

Insert Table 2 here

3.3. Multivariate analysis of Castelli risk indexes 1 and 2 and other metabolic characteristics in mood disorders and metabolic syndrome

Table 3 shows the results of factorial design ANCOVAs which considered the metabolic syndrome (and the interaction metabolic syndrome x depression) as a second factor and which were adjusted for possible effects of gender, age and smoking (employed as covariates). BMI was significantly higher in bipolar patients than in controls and depressed patients. Systolic blood pressure and insulin were significantly lower in bipolar patients than in controls and major depressed patients. HDL cholesterol was significantly lower in unipolar depressed patients than in controls. Castelli risk indexes 1 and 2 were significantly higher in unipolar depression than in bipolar disorder and normal controls. There were no significant differences in the other variables between the three study groups.

Table 3 shows also the differences in the same parameters between subjects with and without the metabolic syndrome. ANCOVAs adjusting for gender, age and

smoking and controlling out the effects of depression showed highly significant differences between the two study groups in all variables, except homocysteine.

Insert table 3 here

3.4. Logistic regression of odds of major depression compared to normal controls

Table 4 presents the results of logistic regression analysis with depression and normal controls as dependent variable and metabolic biomarkers, including Castelli risk index 1, insulin, age, sex, physical activity smoking, metabolic syndrome, BMI and Hamilton Depression Rating scale as explanatory variables. In this logistic regression model comparing depressed patients and controls, we have omitted bipolar cases. An increased Castelli risk index 1 significantly predicted depression after considering the effects of all other explanatory variables

Insert table 4 here

3.5. Logistic regression of odds of bipolar disorder compared to normal controls

A similar logistic regression analysis was performed with bipolar disorder and normal controls as dependent variables. In this logistic regression model comparing bipolar patients with controls the unipolar patients were omitted. After considering the effects of all other explanatory variables we found that insulin was a significant predictor variable for bipolar disorder, whereas the Castelli risk index 1 was not significant.

Insert table 5 here

4. Discussion

The first major finding of this study is that major depression, but not bipolar disorder, is characterized by increased Castelli risk indexes 1 and 2, which are more powerful coronary risk predictors than total, LDL and HDL cholesterol used separately [23]. As such, major depression, but not bipolar disorder, may increase atherogenic risk. The increased Castelli risk indexes 1 and 2 in major depression are therefore other factors underpinning the comorbidity between depression and cardiovascular disorder [27].

Our results show that data on cholesterol, HDL, LDL and triglycerides in depression cannot be interpreted without considering the effects of the metabolic syndrome. Thus, without considering the latter effects we found that bipolar disorder is accompanied by lower HDL cholesterol, whereas after adjusting statistically for the effects of the metabolic syndrome it appeared that major depression but not bipolar disorder was accompanied by lowered HDL cholesterol. Since most studies on lipid profiles in depression did not control for the metabolic syndrome previous results are often hard to interpret. The findings of our study that HDL is decreased in unipolar depression are in agreement with those of a previous publication [22] and with findings that depression is accompanied by disorders in the reverse cholesterol transport [23]. Low serum HDL cholesterol was found to be associated with long-term depression [26] and with major depression [29,30]. Van Reedt Dortland et al. [31] reported that current major depression and not remitted depression is associated with lowered HDL cholesterol and increased triglyceride levels. Lieberman et al. [32] reported that lower LDL and increased HDL cholesterol were associated with negative affect in female subjects. Another study detected an U-shaped association between serum LDL

cholesterol and depression among a male household population [33]. Ancelin et al. [34] found that men with low LDL cholesterol had an increased risk towards depression, whereas in women low HDL cholesterol was associated with an increased risk. In parturients, postnatal depression was significantly associated with increased total, HDL and LDL cholesterol levels [35]. Other authors reported a mild inverse association between depressive symptoms and LDL cholesterol in young adult women [36].

The second major finding of this study is that the patients with major depression and bipolar disorder included here did not show the typical risk factors that characterize the metabolic syndrome, i.e. the specific lipid profile and increased blood pressure, blood glucose and insulin levels and central obesity [6]. Thus, the key characteristics of the metabolic syndrome are not necessarily specific to major depression or bipolar disorder. The findings of our study do not fully corroborate previous results that waist circumference or abdominal obesity was associated with an increased likelihood of having major or moderate-to-severe depressive symptoms [37]. The patients in that study met components of metabolic syndrome including abdominal obesity, use of hypolipidemic agents, and low HDL cholesterol. On the other hand, our results that the BMI is higher in patients with bipolar disorder are in agreement with the results of previous studies showing that obesity is more prevalent in a representative sample of adults with mood disorders versus adults without mood disorders [38]. Some hypotheses have been postulated to explain these associations, e.g. the effects of less physical activity and atypical depressive symptoms, such as hyperphagia, hypersomnia, anergia, and carbohydrate craving, which confer increased risk of weight gain, and that most bipolar specific medications are associated with weight gain [39]. Instead of the expected increases in insulin levels, we found lowered insulin levels in bipolar disorder, but not in major depression. Centrally, insulin inhibits norepinephrine reuptake,

modulates catecholamine turnover in the hypothalamus, stimulates phosphoinositol turnover in the hippocampus, and regulates norepinephrine and dopamine transporter mRNA concentration [38]. Insulin signaling pathways may mediate anti-depressant and mood-stabilizing effects of some commonly used psychotropic agents [41].

It should be underscored, however, that both unipolar and bipolar depression and the metabolic syndrome are associated with activation of immune-inflammatory, oxidative and nitrosative (O&NS) stress pathways and dysregulation of mitochondria [42-48]. Adipocytes and monocyte-derived macrophages also enhance secretion of pro-inflammatory cytokines [9]. Moreover, nutritional factors operating in adulthood and development, including overall diet quality and specific nutrients such as ω 3 polyunsaturated fatty acids and the folate shuttle, may be other links between metabolic syndrome and depression [4,49-54]. In the present study, however, we were unable to find any differences in homocysteine levels between subjects with and without mood disorders or the metabolic syndrome. All in all, immune-inflammatory, O&NS pathways, and dietary factors rather than shared disturbances in lipid and glucose metabolism or central obesity could explain the comorbidity between the metabolic syndrome and mood disorders.

We have statistically adjusted our results for possible effects of lifestyle factors, such as sedentary life style and smoking, showing that all abovementioned associations are independently from those environmental factors. Indeed, it is known that the relationships between the metabolic syndrome and bipolar and unipolar depression may be mediated by these lifestyle factors [38,41,55]. Lower physical activity may lead to increased risks of depression and obesity or the metabolic syndrome [56-58]. Sedentary behavior and cigarette smoking can also produce changes associated with insulin resistance [9]. Current smoking is associated with development of both depression and

the metabolic syndrome and smoking cessation reduces the risk [59,60]. Patients with bipolar disorders have high rates of current and life-time cigarette smoking (nearly 68.8% and 82.5%, respectively) while the rates among patients with major depression were 36% and 39%, respectively [61].

Some limitations of our study are discussed in the following. First, this study did not include information regarding the effects of long-term use of psychotropic medications on the BMI or metabolic syndrome. A confounding factor is that some medications used as treatments in bipolar disorder and major depression are associated with weight gain and the onset of the metabolic syndrome. Nevertheless, our results were adjusted for BMI and we took into account the effects of metabolic syndrome when examining the metabolic changes in depression. Second, this study is limited by absence of specific scales for measurement of dietary factors and a validated scale to measure patient-reported physical activity. Despite these limitations, this study shows that the key characteristics of the metabolic syndrome, either metabolic biomarkers or central obesity, are not germane to major depression or bipolar disorder, and that depression but not bipolar disorder is characterized by increased Castelli risk indexes 1 and 2 independently of age, sex, physical activity, nicotine dependence, BMI, the metabolic syndrome and severity of depression.

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All authors contributed equally to the writing up of this paper.

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Table 1 Socio-demographic characteristics of healthy controls, major depression (MDD) and bipolar disorder (BD) patients included in this study

Characteristics	Healthy controls (a) (n=201)		MDD (b) (n=92)		BD (c) (n=49)		Total (n=342)		p-value ¹
	n	%	n	%	n	%	n	%	
Gender									0.006
Female	119	(59.2)	70	(76.1) ^a	37	(75.5)	226	(66.1)	
Male	82	(40.8)	22	(23.9) ^a	12	(24.5)	116	(33.9)	
Age									0.766
18-29	10	(5.0)	3	(3.3)	4	(8.2)	17	(5.0)	
30-39	26	(12.9)	11	(12.0)	9	(18.4)	46	(13.5)	
40-49	92	(45.8)	42	(45.7)	21	(42.9)	155	(45.3)	
50-60	73	(36.3)	36	(39.1)	15	(30.6)	124	(36.3)	
Race									0.207
Caucasian	137	(68.2)	68	(73.9)	29	(59.2)	234	(68.4)	
Black	22	(10.9)	8	(8.7)	6	(12.2)	36	(10.5)	
Yellow	13	(6.5)	2	(2.2)	1	(2.0)	16	(4.7)	
Mixed	29	(14.4)	14	(15.2)	13	(26.5)	56	(16.4)	
Marital status									0.807
Single	28	(13.9)	14	(15.2)	9	(18.4)	51	(14.9)	
Stable relationship	137	(68.2)	59	(64.1)	30	(61.2)	226	(66.1)	
Divorced/seperated	31	(15.4)	16	(17.4)	10	(20.4)	57	(16.7)	
Widow	5	(2.5)	3	(3.3)	0	(.0)	8	(2.3)	
Years of education									0.165
≤ 12 years	86	(43.2)	35	(39.8)	26	(56.5)	147	(44.1)	
≥ 13 years	113	(56.8)	53	(60.2)	20	(43.5)	186	(55.9)	
Smoking									0.000
Yes	78	(38.8)	38	(41.3)	35	(71.4) ^{ab}	151	(44.2)	
Physical Activity									0.045
Very active	47	(24.7)	25	(29.1)	7	(17.1)	79	(24.9)	
Medium activities	30	(15.8)	8	(9.3)	1	(2.4)	39	(12.3)	
Sedentary	113	(59.5)	53	(61.6)	33	(80.5) ^a	199	(62.8)	
Statins									0.269
Yes	16	(8.3)	9	(10.3)	1	(2.3)	26	(8.0)	
Metabolic syndrome									0.087
Yes	55	(27.4)	25	(27.2)	21	(42.9)	101	(29.5)	

¹ The p-value tests the association between the socio-demographic characteristics and the three groups and is based on χ^2 -tests.

a, b & c in a row indicate that the mean values are statistically significant different at $p < 0.05$ (Fishers protected least significant difference) from the means of the categories labelled as a, b or c

Table 2 Metabolic characteristics in major depression (MDD) and bipolar disorder (BD) patients and normal controls.

	Healthy controls (a)		MDD (b)		BD (c)		Total		p- value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
BMI (Kg/m ²)	26.9	(4.8)c	26.3	(4.4)c	29.2	(6.7)ab	27.0	(5.1)	0.003
Systolic (mmHg)	123.4	(19.7)	120.9	(18.1)	120.9	(14.9)	122.4	(18.7)	0.483
Diastolic (mmHg)	79.6	(12.9)	77.5	(12.1)	79.8	(12.8)	79.0	(12.6)	0.396
Waist (cm)	90.9	(13.6)	89.2	(11.0)	93.9	(12.2)	90.8	(12.8)	0.151
Hip (cm)	104.9	(11.8)	104.0	(10.1)	106.6	(11.6)	104.9	(11.3)	0.475
Glucose (mg/dL)	90.7	(19.2)	89.3	(11.5)	90.5	(11.1)	90.3	(16.4)	0.788
Insulin (μU/mL)	9.5	(6.0)	9.4	(5.1)	8.7	(3.6)	9.4	(5.5)	0.707
Hba1c (%)	5.5	(.6)	5.7	(1.3)	5.5	(.4)	5.6	(.8)	0.222
Total (mg/dL)	193.7	(36.1)	196.7	(45.8)	200.1	(47.2)	195.4	(40.5)	0.579
HDL (mg/dL)	49.2	(14.7)c	45.9	(14.9)	43.9	(11.2)a	47.5	(14.4)	0.034
LDL (mg/dL)	119.9	(31.8)	124.3	(41.5)	125.5	(43.8)	121.8	(36.4)	0.486
Castelli risk index 1	4.2	(1.4)bc	4.7	(1.7)a	4.8	(1.8)a	4.4	(1.5)	0.011
Castelli risk index 2	2.6	(1.1)bc	3.0	(1.4)a	3.0	(1.3)a	2.8	(1.2)	0.028
Triglycerides (mg/dL)	123.0	(74.6)	130.7	(79.0)	151.4	(91.6)	129.1	(78.8)	0.075
Homocysteine (μM)	13.1	(5.1)	13.0	(3.7)	13.8	(4.9)	13.2	(4.7)	0.617

All results are shown as mean ±SD;

a, b & c in a row indicate that the mean values are statistically significant different at $p < 0.05$ (Fishers protected least significant difference) from the means of the categories labelled as a, b or c

All results of analyses of variance performed on the three diagnostic subgroups. See text for a description of the results of multiple comparisons among treatment means.

Systolic and diastolic: indicate blood pressure

Waist and hip: indicate circumference

Total, HDL and LDL: total, HDL and LDL cholesterol

Table 3 Multivariate analysis of metabolic characteristics of mood disorders versus metabolic syndrome

Characteristics	Estimated Marginal Means ¹ and SE						
	Diagnosis ²				Metabolic Syndrome ³		
	Healthy controls (a)	MDD (b)	BD (c)	p-value	No	Yes	p-value
BMI (Kg/m ²)	27.7 (0.37) c	26.3 (0.56) c	29.4 (0.70) ab	0.002	25.8 (0.39)	29.9 (0.51)	<0.000
Systolic (mmHg)	127.5 (1.40) c	125.3 (2.08) c	120.1 (2.63) a	0.046	116.2 (1.53)	132.4 (1.87)	<0.000
Diastolic (mmHg)	81.7 (0.99)	79.9 (1.48)	80.7 (1.87)	0.597	78.6 (1.09)	85.0 (1.32)	<0.000
Waist (cm)	93.6 (0.98)	90.9 (1.52) c	96.4 (2.07) b	0.072	88.1 (1.23)	99.2 (1.35)	<0.000
Hip (cm)	106.8 (0.98)	104.0 (1.51)	108.8 (2.08)	0.111	103.7 (1.22)	109.4 (1.36)	0.001
Glucose (mg/dL)	94.7 (1.21)	91.6 (1.85)	92.3 (2.26)	0.313	86.9 (1.26)	98.7 (1.68)	<0.000
Insulin (μU/mL)	10.8 (0.41) c	10.1 (0.64) c	8.5 (0.81) a	0.045	7.8 (0.44)	11.9 (0.59)	<0.000
Hba1c (%)	6.0 (0.07)	5.8 (0.10)	5.5 (0.13)	0.137	5.4 (0.07)	5.9 (0.09)	<0.000
Total (mg/dL)	196.1 (3.18)	204.2 (4.81)	199.6 (5.97)	0.358	191.8 (3.33)	208.1 (4.39)	0.003
HDL (mg/dL)	45.3 (1.00) b	40.7 (1.51) a	42.5 (1.91)	0.032	48.0 (1.07)	37.6 (1.38)	<0.000
LDL (mg/dL)	123.0 (2.91)	131.5 (4.44)	125.0 (5.43)	0.264	119.3 (3.01)	133.6 (4.05)	0.004
Castelli risk index 1	4.7 (0.10) b	5.4 (0.15) ac	5.0 (0.19) b	0.001	4.3 (0.11)	5.7 (0.14)	<0.000
Castelli risk index 2	3.0 (0.09) b	3.5 (0.13) ac	3.1 (0.16) b	0.004	2.7 (0.09)	3.7 (0.12)	<0.000
Triglycerides (mg/dL)	145.7 (5.24)	164.7 (7.94)	159.9 (9.86)	0.100	117.3 (5.50)	196.2 (7.26)	<0.000
Homocysteine (μM)	13.4 (0.35)	13.7 (0.53)	14.7 (0.66)	0.223	14.3 (0.37)	13.6 (0.49)	0.218

¹ Based on ANCOVA and adjusted for gender, age and smoking status; figures in parentheses indicate the standard error;

a, b & c in a row indicate that the mean values are statistically significant different at p<0.05 (Fishers protected least significant difference) from the means of the categories labelled as a, b or c

² Adjusted for metabolic syndrome and the interaction between diagnosis (controls versus MDD + BD) and metabolic syndrome

³ Adjusted for diagnosis and the interaction between diagnosis and metabolic syndrome

Systolic and diastolic: indicate blood pressure

Waist and hip: indicate circumference

MDD: major depression; BD: bipolar disorder

Total, HDL and LDL: total, HDL and LDL cholesterol

Table 4 Logistic regression of odds of major depression compared to normal controls

Variables	OR	95% C.I.		p-value
Gender, Male	0.59	0.27	1.31	0.195
Age	1.00	0.96	1.04	0.929
Physical activity				
<i>Medium activities</i>	0.29	0.09	0.94	0.039
<i>Sedentary</i>	0.89	0.40	1.94	0.765
Smoking, yes	0.13	0.05	0.34	0.000
Metabolic risk, yes	0.63	0.25	1.60	0.332
BMI	1.00	0.92	1.09	0.991
Hamilton scale	1.34	1.23	1.46	0.000
Insulin	0.98	0.91	1.05	0.572
Castelli risk index 1	1.53	1.14	2.05	0.005

Reference categories: Gender – Female; Physical activity – Very active; Smoking – non-smoker; metabolic risk – no

Table 5 Logistic regression of odds of bipolar disorder compared to normal controls

Variables	OR	95% C.I.		p-value
Gender, Male	0.87	0.21	3.62	0.847
Age	1.00	0.94	1.07	0.897
Physical activity				
<i>Medium activities</i>	0.00	0.00	13.08	0.185
<i>Sedentary</i>	1.72	0.45	6.66	0.430
Smoking, yes	0.18	0.04	0.83	0.028
Metabolic risk, yes	2.43	0.54	10.93	0.247
BMI	1.08	0.96	1.21	0.193
Hamilton scale	1.40	1.23	1.59	0.000
Insulin	0.80	0.67	0.97	0.020
Castelli risk index 1	1.19	0.71	1.98	0.509

Reference categories: Gender – Female; Physical activity – Very active; Smoking – non-smoker; metabolic risk – no

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